https://doi.org/10.5664/jcsm.8566

JCSM | Journal of Clinical Sleep Medicine

LETTERS TO THE EDITOR

Use of clonazepam in REM sleep behavior disorder is not associated with fall-related injuries

Response to Dokkedal-Silva V, Kim LJ, Morelhão PK, Galduróz JCF, Tufik S, Andersen ML. Use of clonazepam in REM sleep behavior disorder: association with fall-related injuries and alternative treatments. *J Clin Sleep Med.* 2020;16(4):655–656. doi:10.5664/jcsm.8308

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The recent letter by Dokkedal-Silva et al[1] contains some inaccurate and misleading statements that need clarification, beginning with the worrisome phrase in the title "fall-related injuries." This phrase, in fact, pertains much more to REM sleep behavior disorder (RBD) than to its therapy. RBD is known to frequently manifest with major and even life-threatening injuries.[2–5] Many of the injuries related to RBD are due to falls—falling out of bed or from falling while running, for example. The mainstay of therapy for decades has been nightly use of clonazepam, and the published benefit-risk ratio with clonazepam therapy of RBD has been reassuring. Clonazepam is a level B therapy (with "modifying the sleep environment" as level A therapy) in the American Academy of Sleep Medicine best practice guide for the treatment of RBD,[6] which the authors of the letter[1] did not cite. Also, reassuring efficacy and safety data were published on the long-term therapy of RBD with nightly clonazepam therapy in 49 RBD patients (and 58 patients with non-REM [NREM] parasomnias), without any significant dose increase (by paired *t* test) from the start of therapy until the latest follow-up (mean > 3 years).[7] Complete/substantial control of RBD/NREM parasomnias was achieved in > 85% of patients, and notably only 8% had adverse effects (none with falls) requiring medication changes. In another study of 39 RBD patients treated with clonazepam with follow-up at a mean 29 months, none reported any falls, and 6 stopped clonazepam due to daytime somnolence.[8]

Two polysomnography (PSG) studies by Ferri et al.[9,10] of clonazepam-treated RBD patients documented various objective beneficial effects on NREM sleep. In the first study, 42 unmedicated RBD patients were compared with 15 clonazepam-treated patients.[9] The clonazepam-treated patients showed a lower rate of sleep stage shifts, higher sleep efficiency, lower percentage of wakefulness after sleep onset, and lower N1 sleep, with an increased percentage of N2 sleep. Longitudinal follow up PSG analysis in 13 of 15 clonazepam-treated patients showed moderately increased total sleep time, sleep efficiency, N2 sleep, and N3 sleep, and decreased wakefulness after sleep onset and N1 sleep. The second study documented significant decreases in NREM sleep (N1, N2) instability in clonazepam-treated RBD patients.[10] In a third study, Ferri et al[11] also reported a subtle but significant increase in REM sleep electroencephalogram instability in RBD patients that was counteracted by clonazepam. A major thrust from these three studies is that clonazepam confers multiple objective benefits on the sleep of clonazepam-treated RBD patients, beyond its impressive control of injurious RBD behaviors.

We disagree with the authors' undocumented statement that "The overlap between the side effects of clonazepam and the diurnal symptoms of patients with RBD could lead to episodes of falling and consequent hip fractures." RBD patients are not sleepy, unless they have comorbid narcolepsy, or are experiencing advancing Parkinson disease. Melatonin (not mentioned by the authors) is another level B therapy[6] that is an alternative therapy to clonazepam in RBD patients who have already developed an alpha-synucleinopathy and are at increased risk for falls and daytime somnolence.

The authors acknowledged the well documented high risk of RBD being a herald of alpha-synucleinopathy neurodegeneration, including Parkinson disease, but unfortunately they confused the therapy of RBD with neuroprotective interventions—most notably exercise. The authors urged, without documentation, the "practice of physical activity to improve RBD symptoms." This is a false and misleading statement. There are no published data on exercise as therapy of RBD, and so we disagree with the authors that exercise is an "alternative treatment option" in RBD. Exercise is *not* a therapy for RBD and its injurious nocturnal behaviors.

However, there is an emerging literature on exercise, along with physical therapy and occupational therapy, as potential useful interventions in RBD patients who are in the process of developing overt Parkinson disease,[12] with research in this area being encouraged.[13] We agree with the authors "that the practice of physical activity in older adults [with RBD can] improve…balance to prevent falls."

The authors stated that "lower levels of physical activity were also identified as a risk factor for the development of RBD". The cited study used an RBD screening questionnaire, and not PSG. It is now standard practice in publications to use the term "probable RBD" (pRBD) when PSG is not performed, which unfortunately the authors of the letter did not do, nor did the authors of the cited study (Lerche et al[14]). PSG is required for the objective diagnosis of RBD.[15] Therefore, we urge all authors of future publications to make the important distinction between RBD and pRBD.

CITATION

Schenck CH, Zucconi M, Ferri R. Use of clonazepam in REM sleep behavior disorder is not associated with fall-related injuries. *J Clin Sleep Med*. 2020;16(8):1399–1400.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication April 24, 2020
Submitted in final revised form May 2, 2020
Accepted for publication May 4, 2020
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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The work was done at the institutions of all 3 authors. Carlos H. Schenck, MD is a consultant for Axovant Sciences (not relevant to this manuscript). Marco Zucconi, MD, and Raffaele Ferri, MD, report no conflict of interest.