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Editorial

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Sodium oxybate—a new horizon for symptomatic treatment of RBD?

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In patients with rapid eye movement (REM) sleep behavior disorder (RBD), complex and violent behaviors reflecting dream enactment are responsible for the high risk of injuries, ranging from 37.8% to 58.6% for self-injuries and from 16.7% to 21.1% for injuries to the bed partner [1, 2]. Severity of injuries varies, but some are potentially lethal [3]. Milder RBD-related dream enactment may result in sleep disruption. Therefore, having effective symptomatic treatments for RBD is a large unmet need. Few available symptomatic treatment options are available, clonazepam and melatonin being the mainstay treatment. Randomized double-blind placebo-controlled trials of these agents are scarce, with two recent trials failing to demonstrate their effectiveness likely due to methodological limitations in measuring therapeutic effects in RBD [4, 5]. Clinical trials that employed objective outcome measurements are rare [6, 7] The clinical trial of sodium oxybate as a symptomatic RBD treatment by During et al. [8] is a significant contribution to the therapeutic landscape of RBD. In this randomized, double-blind, placebo-controlled, parallel group trial 24 participants received sodium oxybate or placebo nightly with a 1:1 ratio for a 4-week stable dosing period, after a titration of at least 4 weeks. The primary endpoint was the change in number of self-reported RBD episodes. Secondary endpoints included PSG objective measures such as RBD behaviors observed in the video and audio recordings, and REM sleep without atonia.

Several mechanisms may underlie a potential beneficial effect of sodium oxybate on RBD symptoms. Sodium oxybate is the sodium salt of γ-hydroxybutyric acid, which is a normal metabolite of γ-aminobutyric acid (GABA). It interacts with the $GABA_B$ receptor, acting as a $GABA_B$ agonist. One of the initial studies investigating the effects of sodium oxybate on sleep dates back 20 years and reported an increase in slow-wave sleep and a decrease in REM sleep [9]. A reduction in RBD episodes could therefore be secondary to the decrease in REM sleep, which may be applicable to the study by During et al. [8]. In fact, the authors report a significant median reduction in total RBD movements, but not in movement per 10 minutes of REM sleep with sodium oxybate compared to placebo. While additional mechanisms may be responsible for the reported effect, the small sample size could explain the lack of significance when assessing movements per 10 minutes of REM sleep. Few case reports previously suggested that sodium oxybate may be effective for RBD symptoms in adults with isolated RBD [10, 11] or RBD secondary to Parkinson's disease [12], whereas in narcolepsy type 1 an effect on muscle tone but not on motor episodes during REM sleep has been reported [13, 14]. GABAergic neurons are involved in the complex regulation of REM sleep and muscle atonia during REM sleep, and it is reasonable to hypothesize that sodium oxybate may promote muscle atonia during REM sleep. For example, REM-ON GABAergic neurons in the medulla inhibit the ventrolateral peri-aqueductal gray activity, releasing the sublaterodorsal and caudal lateral dorsal tegmental nucleus from inhibition, in turn triggering the atonia of REM sleep [15]. REM sleep regulation is however complex; there are two subpopulations of GABAergic neurons in the ventrolateral peri-aqueductal gray region, which are REM-active and REM-inhibiting [16, 17]. Thus, how sodium oxybate may regulate REM sleep and REM sleep atonia still needs to be further clarified. Of note, above mentioned data about the two subpopulations of GABAergic neurons [16, 17] may provide the pathophysiological background for reports that sodium oxybate can induce REM sleep and even sleep paralysis or cataplexy (e.g. in the presence of normal levels of orexin) and that sodium oxybate may have opposite immediate (induction of REM sleep and even cataplexy) and long-term effects (reduction of REM sleep and suppression of cataplexy), likely also due to its interactions with the cholinergic system [18].

The investigation of sodium oxybate in the RBD population highlights additional interesting aspects. Sodium oxybate has been suggested to be an antioxidant and to improve cell energy [18]. Based on these observations, a neuroprotective effect of sodium oxybate has been postulated [19]. The increase in slow-wave sleep with sodium oxybate could contribute to this due to its relevance for proper function of the glymphatic system. However, these are only hypotheses thus far, which highlighting potential direction for future studies.

Notwithstanding a still unclear mechanism of action of sodium oxybate and caution needed in case of combination with other

hypnotics or alcohol, as well as in patients with sleep apnea, the study by During et al. [8].shows promising preliminary results of a medication with complex effects on REM sleep regulation and muscle atonia during REM sleep. This first double-blind placebo-controlled clinical trial of sodium oxybate was needed, considering that RBD symptomatic treatment is essential and available treatment options are very limited. Despite drawbacks such as a mixed cohort of definite isolated RBD and "probable RBD" in patients with Parkinson's disease, the small sample size, and the inclusion of only treatment-resistant RBD patients, this study has important strengths, including the sound methodology, application of the video-polysomnography guidelines for the diagnosis of RBD by the International RBD Study Group [20] and the use of objective endpoints (although as secondary outcomes). As underlined by the authors, the inconsistency in self-reported responses and the large placebo effect underpins the need for objective endpoints in clinical trials assessing symptomatic treatment for RBD. With this study, During et al. [8] provided an important basis for future larger clinical trials on sodium oxybate for the treatment of RBD symptoms. Main pitfalls of symptomatic RBD trials such as difficulties in measuring RBD events reliably and challenges in assessing possible fluctuation of these events within the different phases of the trial need to be considered in future studies.

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