



Editorial

Melatonin in rapid eye movement sleep behavior disorder: why does it work?

“Most sleep experts are frankly puzzled why melatonin has any effect on RBD” [1]. Why is it that no hypnotic other than melatonin improves the symptoms of rapid eye movement (REM) sleep behavior disorder (RBD)? The answer is quite simple: because melatonin is not a hypnotic. After all, rats and bats also secrete melatonin, but this secretion happens at night when they are most active. As a hormone, melatonin only promotes whatever a species is meant to do during the night. As a drug, melatonin is a chronobiotic with highly time-dependent effects [2]. These insights are not new [3,4], and yet the general view on melatonin has not changed. Indeed melatonin is still being sold in the United States and Europe as a hypnotic, creating false expectations. Moreover, most studies examining the effects of melatonin have been designed like those used to test hypnotics, measuring the increase in total sleep and reduction of wakefulness after sleep onset and using a crossover design [5–7]. A hypnotic is defined as a substance that induces sleep after intake, independently of time of day or whether or not it is administered to healthy subjects or patients.

Melatonin clearly does not fit these criteria; in healthy subjects, melatonin has no effect when administered in the evening [2]. When I started to treat patients with melatonin in the mid 1990s, a patient who had been on melatonin for four weeks said, “Doc, melatonin isn’t a hypnotic.” I asked, “Why?” The patient replied, “Because I sleep less.” I asked, “Okay, so do you want to stop taking it?” The patient then replied, “No, I feel better during the day now.” In short, when administered properly melatonin normalizes sleep; sometimes it is lengthened and sometimes it is shortened, but its quality is improved either way.

I had just presented data at a meeting in 1996 on six RBD patients treated with melatonin. At the end of the session I took the chance to ask the chair of the session, who was editor of a highly respected sleep journal at the time, what the chances were to publish the data in his journal. “They’ll shoot you! They’ll crucify you! Why, after treating your first patient, didn’t you conduct a placebo-controlled trial?” I am so glad that we have continued to perform open-label trials, as they lead to important insights.

In our first RBD patient treated with melatonin, the clinical symptoms improved over a period of several weeks. Repeated polysomnography showed gradual improvements over the course of months. After melatonin administration was stopped, the clinical symptoms gradually returned over the course of months but did not reach their previous severity. This finding implied subacute effects that could be due to the mechanisms of a circadian clock [8]. In the series of six RBD patients that we followed, melatonin improved the clinical symptoms and REM sleep muscle atonia in five of the individuals. Only one patient did not respond. It took

us some time to find the clue; she was a medical assistant in her mid-twenties who liked to party on the weekends. Therefore, although she followed rule number 1: “Take melatonin 30 minutes before bedtime”, she did not follow rule number 2: “Always take the melatonin at the same time each day”. On Fridays and Saturdays, she took melatonin between 3:00 and 5:00 am. On Sunday evenings, she was exhausted from her weekend adventures and took it at 8:00 pm. During the week she took it between 10:00 and 11:00 pm. In short she was mimicking a business traveler flying from Berlin to New York on Friday, returning to Moscow for a short Sunday rendezvous, and flying back to Berlin to live there during the week. The permanent jetlag resulting from this regime will only reduce the amplitude of circadian rhythms, weakening the strength of the clock.

As a chronobiotic, melatonin predominantly influences the circadian components of the sleep-wake cycle. Of course, REM sleep is the stage of sleep most strongly regulated or modulated by the circadian timing system. The timing and amount of REM sleep within the sleep cycle, the REM sleep polarity, and the quality of REM sleep all depend on the proper functioning of the circadian timing system [9–11]. Suppressing melatonin with β blockers is accompanied in healthy subjects by specific changes in REM sleep; however, these changes can be reversed by simultaneously administering evening melatonin [12]. Similarly the reduced individual capability of the pineal gland to produce melatonin is associated with similar changes in REM sleep [13], which can be normalized by the adequately timed administration of melatonin [14]. Such changes in REM sleep through melatonin are paralleled by an increase in nighttime temperature variation—a marker of the clock’s strength [14].

In this issue, the International RBD Study Group proposes a study design to evaluate the effects of melatonin vs clonazepam in RBD patients [15]. Perhaps this design can be improved if the specific mode of action of melatonin is more clearly recognized.

First, it is well known that withdrawal of clonazepam is followed by an immediate return of symptoms [1]. However, melatonin has an outlasting effect [14,16]. A physician who is aware of these mechanisms therefore will become unblinded in cases in which study participants on clonazepam are not compliant with their regimens. Furthermore, patients in the clonazepam group are more likely to remain compliant in the first place; as a result, compliance may favor a particular outcome.

Second, the timing of melatonin administration needs to be fixed at a set point every evening [6]. The common instruction to “take one tablet 30 minutes before bedtime” is not sufficient. Irregular bedtimes mean irregular timing of administration, and this

will preclude any response to melatonin. In cases in which patients forget or are unable to take melatonin at the scheduled time, melatonin should be skipped. One solution in cases in which the time of melatonin administration is inappropriate would be to administer a substitute (i.e., a placebo). In contrast, the substitute would be clonazepam in the clonazepam group. The effective time of administration should always be monitored.

Third, it has been suggested that patients treated with melatonin or clonazepam prior to the study could nevertheless be included after a washout period. As described above, melatonin has an outlasting effect that would extend beyond a typical washout period, sometimes even by months.

Lastly, the most fascinating aspect of the upcoming trials comparing clonazepam with melatonin in RBD patients is the conversion rate. Early recognition of RBD and its effective treatment may make it possible to lengthen the symptom-free period in the early phase of developing neurodegenerative disorders [17]. RBD patients treated with clonazepam appeared to have an approximate 80% conversion rate over 25 years [18]. Melatonin restores muscle atonia and has an outlasting effect, suggesting that it may act at a more basic level of the disorder than clonazepam [8,14,16,19]. Moreover, melatonin has proved effective when administered to patients suffering from nighttime agitation in Alzheimer's disease [20]. Therefore, I recommend long-term treatment studies comparing the effect of clonazepam vs melatonin on the conversion rate.

I have one last thought. Although controlled studies are the gold standard to prove hypotheses, the basis for controlled studies is clinical research; this type of research involves observing and listening to patients. These clinical observations are one of the greatest resources we have. Let us publish more case studies and then let us actually read them!

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2013.05.004>.

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