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Title: A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: Time for more and larger randomized placebo-controlled trials.

Authors: Moran Gilat PhD[1], Nathaniel S Marshall PhD[2], Dries Testelmans MD PhD[3], Bertien Buyse MD PhD[3], Simon JG Lewis MBBCh MD[4]

Affiliations:
1 - Neurorehabilitation Research Group (eNRGy), Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
2 - Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia
3 – Leuven University Centre for Sleep and wake disorders (LUCS), Department of Pneumology, UZ Leuven, Leuven, Belgium
4 - Forefront Parkinson's Disease Research Clinic, Brain and Mind Centre, School of Medical Sciences, University of Sydney, Sydney, Australia.

Corresponding author:
Dr Moran Gilat PhD
Neurorehabiliation Research Group (eNRGy)
Department of Rehabilitation Sciences, KU Leuven
Tervuursevest 101, box 1501
3001, Leuven, Belgium
Email: moran.gilat@kuleuven.be
Tel: +32 16 32 94 27

Supplementary materials:
- Supplementary Tables S1-S28
- Supplementary materials: Description of alternative treatments
- Supplementary materials: WHO clinical trial registrations

Abstract

Rapid Eye Movement sleep behavior disorder (RBD) is a parasomnia causing sufferers to physically act out their dreams. These behaviors can disrupt sleep and sometimes lead to injuries in patients and their bed-partners. Clonazepam and melatonin are the first-line pharmacological treatment options for RBD based on direct uncontrolled clinical observations and very limited double-blind placebo-controlled trials. Given the risk for adverse outcomes, especially in older adults, it is of great importance to assess the existing level of evidence for the use of these treatments. In this update, we therefore critically review the clinical and scientific evidence on the pharmacological management of RBD in people aged over 50. We focus on the first-line treatments, and provide an overview of all other alternative pharmacological agents trialed for RBD we could locate as supplementary materials. By amalgamating all clinical observations, our update shows that 66.7% of 1,026 RBD patients reported improvements from clonazepam and 32.9% of 137 RBD patients reported improvements from melatonin treatment on various outcome measures in published accounts. Recently, however, three relatively small randomized placebo-controlled trials did not find these agents to be superior to placebo. Given clonazepam and melatonin are clinically assumed to majorly modify or eliminate RBD in nearly all patients - there is an urgent need to test whether this magnitude of treatment effect remains intact in larger placebo-controlled trials.

Key words

Pharmacotherapy; drugs; Parkinson's disease; Lewy Body Dementia; Multiple System Atrophy; Benzodiazepines; Circadin.

1 - Introduction

Rapid Eye Movement (REM) sleep behavior disorder (RBD) is a parasomnia, in which a loss of physiological muscle atonia during REM sleep leads to dream enactment behaviors (DEB) [1]. A clinical history of DEB together with video-polysomnography (PSG) confirmed REM sleep without atonia (RWA), or a combination of RWA and dream-enactment behaviors documented with PSG, are mandatory for a clinical diagnosis of RBD according to the International Classification of Sleep Disorders-III. Although RBD symptoms can be seen in several disorders, such as narcolepsy-cataplexy and parasomnia overlap disorder, and may be precipitated by certain drugs, such as selective serotonin reuptake inhibitors [1], its isolated presence in the general adult population is closely linked with alpha synuclein neuropathology and a future diagnosis of either Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB) or Multiple System Atrophy (MSA) [2, 3]. In the general population around 1% of people have clinically isolated RBD, whereas the proportion is much higher in PD (20-50%) and over 80% of DLB and MSA patients report RBD [1, 3]. People with severe obstructive sleep apnea (OSA) frequently experience OSA-induced arousals that may result in movements during REM sleep mimicking RBD symptoms. Importantly, however, people with OSA can indeed have true RBD, which should be confirmed with PSG after treating the OSA [4].

Although patients may not be aware of mild symptoms [5], treating RBD can often be necessary as it can cause frequent and sometimes life-threatening injuries to patients and their bed partners [1, 6]. The current guidelines for RBD treatment include counseling, modification of the bedroom environment to reduce the risk of injury and two main pharmacological agents, namely clonazepam and melatonin [1, 7]. Such information is also presented to patients via reputable online sources, such as sleepfoundation.org and websites of specialized sleep clinics.

Clonazepam has been the recommended treatment since the first clinical description of RBD by Schenck and colleagues back in 1986 [8]. Indeed,

subsequent case series and open-label studies have reported a clinical efficacy rate of up to 90% [9]. Clonazepam is a benzodiazepine, which enhances inhibitory γ-aminobutyric acid (GABA) activity in the central nervous system leading to anticonvulsant, anxiolytic and skeletal muscle relaxation effects. It has been suggested that clonazepam may be efficacious by suppressing phasic bursts of muscle activity during REM sleep [10]. However, the true mechanisms of action of clonazepam for reducing RBD remain unknown [11, 12]. Significantly, clonazepam is a long acting benzodiazepine with a half-life of 30-40 hours that should be used with caution, especially in older adults, as it can lead to dependence along with frequent and sometimes serious side effects, including confusion, morning sedation, cognitive impairment and falls [7]. Clonazepam may also induce [13] or possibly worsen obstructive sleep apnoea (OSA) symptoms [1, 7]. It is therefore critical to systematically assess whether the existing evidence supports the use of clonazepam to treat RBD, especially in the older population who are known to have the highest prevalence of RBD and in whom the adverse outcomes, such as falls, may be most impactful, particularly in patients with a neurodegenerative disorder such as PD or DLB [5].

When compared to clonazepam, melatonin has a much safer profile with no reports of dependence, along with fewer and milder side effects, which include headache and morning sleepiness [1, 7]. Melatonin has therefore been proposed as a preferable treatment for RBD, especially for older patients and/or those who have OSA, neurodegenerative conditions, are at higher risk of experiencing side effects, or are considered refractory to the effects of clonazepam [1, 7, 14-18].

Melatonin is a natural hormone that is predominantly synthesized in the pineal gland and promotes sleep propensity across the brain [19]. Endogenous melatonin secretion is tightly regulated by photic cues received by the hypothalamic suprachiasmatic nucleus, which is the major circadian oscillator [19]. Melatonin secretion reduces with ageing and thus, low dosages (0.3-1mg) of exogenous melatonin may help to coordinate circadian rhythms when administered in a specifically timed manner [19, 20]. This may be of particular interest to people with PD, who experience circadian dysregulation [21] and

have altered peak melatonin concentration levels [22, 23]. The soporific effect of acutely administering higher dosages (2-25mg) of melatonin at night-time has further been shown to improve sleep efficiency and may help reduce secondary sleep disorders, including RBD, whereby its chronobiotic effect may correct the timing, amount, and quality of REM sleep when administration is timed correctly [19, 20]. There is also indication of melatonin reducing the amount of RWA in patients with RBD [20]. Melatonin has a short (30-50 minute) elimination half-life, which lessens 'hang-over' effects the following morning [19]. Due to its short half-life, however, the effectiveness of melatonin might be suboptimal for the majority of REM sleep periods that occur in the second part of the night. A prolonged release formulation that releases melatonin gradually over 8-10 hours (Neurim Pharmaceuticals Inc.: Circadin) has therefore been proposed for treating RBD [17].

Despite the widespread use of both clonazepam and melatonin for treating RBD, until recently there was a lack of good quality trial data [24]. Current international guidelines are still based on evidence from mainly small case-series and open-label studies [25], which are at high risk of bias and have demonstrated inconsistencies in the clinical effectiveness levels reported. In fact, many patients with RBD were considered refractory to these first-line treatment options, which led clinicians to trial a multitude of other pharmacological agents off-label [26-29]. Past reviews have not consistently accounted for such reports when calculating the number of responders for these commonly prescribed treatments [25, 30], or were conducted more than ten years ago [7]. Thus, there is a need to re-assess whether the existing evidence supports the current recommended guidelines for the pharmacological management of RBD.

The purpose of this update is to provide a semi-systematic overview of all clinical and scientific evidence published to date on the pharmacological management of RBD. We focus on the middle- to older (50 years and above) adult population, which has the highest prevalence of RBD as well as being at the greatest risk for adverse outcomes [5]. Doing so, we set out to provide an update on the total number of adults with isolated or secondary RBD who were clinically

followed to assess the efficacy of any pharmacological compound given to treat their RBD symptoms. We also assessed the level of evidence based on the study design, as depicted in *Box 1*. This review specifically investigates the divide between clinical expectancy and the actual evidence for the effectiveness of the common drugs being recommended for managing RBD. We also seek to provide future directions on how this field could move to a more rigorous evidence-base.

Box 1: Level of evidence (I-V) and limitations (*in italic*) per type of study design

I-A: Randomized double-blind placebo controlled trial of sufficient size and consistency:
- *Maximal control for risk of bias, especially when multi-centered*

I-B: Randomized double-blind placebo controlled trial of possibly insufficient size and/or consistency:
- *Possibly underpowered or too inconsistent to detect treatment effects*

II-A: Non-randomized single arm open-label prospective observation studies without a control (e.g. placebo) intervention of sufficient size and quality and with a fixed treatment period:
- *No control for placebo effect*
- *Lack of randomization and concealment creates risk for preferential allocation*
- *Lack of randomization creates risk for unmatched groups at baseline*
- *Subjects, therapist, and assessors not blinded to treatment allocation*

II-B: Non-randomized single arm open-label prospective observation studies without a control (e.g. placebo) intervention of possibly insufficient size and quality or without a fixed treatment period:
- *All risks as per II-A*
- *Possibly underpowered or too inconsistent to detect true treatment effects*
- *Treatment dosage and/or treatment duration often not standardized across subjects*

III-A: Retrospective reports from medical histories with cross-sectional or longitudinal comparison (e.g. treatment vs. no-treatment condition):
- *All risks as per II-B*
- *Selection bias as subjects not prospectively recruited to assess eligibility criteria*
- *Selection bias as often only subjects with complete datasets included*
- *Treatment dosage and/or treatment duration often not standardized across subjects*
- *Risk for missing data and limited control over data quality*
- *Difficult to assess adherence to treatment*
- *Difficult to assess dropout as a result of treatment allocation*
- *Often many different therapist and/or assessors involved*
- *Often covering long periods of time during which many elements of the study could have changed, including diagnostic criteria, equipment, procedures, data quality, etc.*
- *Other treatments could have been tried without mentioning leading to a risk for biased observations and publication bias*

III-B: Retrospective reports from medical histories without cross-sectional or longitudinal comparison (e.g. clinical observations/opinions):
- *All risks as per III-A*
- *Lack of statistical hypothesis testing*
- *No comparison group to test effect of treatment against*

IV: Case series describing >1 subjects:
- *All risks as per III-B*
- *High risk for publication bias, whereby only interesting cases are published*
- *Small sample size resulting in limited translation to wider clinical population*

V: Case report of a single subject:
- *All risks as per IV*
- *No between-subject variability greatly limits translation to wider clinical population*

2 - Search syntax and screening

Literature was searched in PubMed, EMBASE, MEDLINE Ovid, and Web of Science core collection from conception until the 17th April 2020. The following terms were used to search in all fields, namely: ((REM sleep behavior disorder OR REM behavior disorder OR RBD); AND (medication OR drug OR treatment OR therapy OR pharmacotherapy OR pharmacological OR intervention); AND (clonazepam OR melatonin OR temazepam OR lorazepam OR zolpidem OR zopiclone OR pramipexole OR donepezil OR ramelteon OR agomelatine OR cannabinoid OR sodium oxybate OR dopamine agonist OR levodopa)).

A total of 607 non-duplicate citations were identified by the search strategy and an additional eight citations, of which five eligible [31-35], were identified from the reference list of a previous review on the best practice guides for RBD [7] (*Figure 1*). Two reviewers (MG, DT) then screened the abstracts and remaining full-texts according to the following inclusion criteria: i) Any type of study containing original data on a change in RBD symptom severity following any type of pharmacological intervention administered with the purpose of reducing RBD in any type of disorder or isolated RBD; ii) Intervention administered for more than 1 week; iii) RBD severity assessed as an outcome of the intervention, including surrogate measures, such as RWA, and clinical opinions; iv) The mean or median age of the RBD group investigated was >50 years, or the age of the persons with RBD in case report series were >50 years at the time of the assessment; v) Written in English language; vi) Published in a peer-reviewed scientific journal, and; vii) Evidence based on human subjects. The following exclusion criteria were additionally applied to assess final eligibility of remaining full-texts: i) Review of the literature with or without meta-analysis; ii) Conference abstract; iii) Intervention outcome on RBD not reported.

3 - Risk of bias assessment

To aid interpretation of intervention outcomes, the study quality assessment tool for controlled intervention studies by the NIH, National Heart, Lung, and Blood Institute (nhlbi.nih.gov) was used to assess risk of bias for each of the RCT's performed. This tool assesses 14 criteria to help evaluate internal validity and

detect possible flaws in study design. The risk of bias assessment was conducted by MG and controlled for accuracy by DT.

4 - Publication bias assessment

To assess for possible publication bias, another search was conducted on 20 November 2020 in the International Clinical Trials Registry Platform of the World Health Organisation (apps.who.com), which encompasses many of the trial registries around the work, including ClinicalTrials.gov. We used the search terms ('REM sleep behavior disorder' OR 'RBD'), which led to a total of 77 listed trials that were screened according to the same inclusion criteria as described above, except criteria v and vi. A total of 17 trials were deemed eligible and assessed for possible publication bias.

5 - Literature search results

A total of 92 articles were deemed eligible for inclusion in the review (*Figure 1*).

Suggested position Figure 1

6 - Study designs

As shown in *Figure 2*, the large majority of included studies were case reports (CR, n=51) or retrospective accounts based on medical histories (RMH, n=21). Only 7 studies had a single-centered randomized placebo-controlled trial (RCT) design and 13 were prospectively planned single arm open-label (i.e. without a control intervention) cohort studies (POS). Overall, the bulk of evidence that currently exists on the pharmacological management of RBD in the adult population is therefore considered to be of poor scientific quality (*Box 1*).

Suggested position Figure 2

7 - Overview of results

The included papers were divided into supposedly prospectively planned studies (i.e. noted by the author as being prospective, but not necessarily pre-registered; n=20) and retrospective studies or case reports (n=72). *Table 1* presents the full

systematic overview of the prospective studies per drug class and type including the level of evidence as per *Box 1*. *Table 2* presents an overview of the risk of bias for each of the RCT's. Given the intrinsically high risk of bias for POS, and especially RMH and CR (see *Box 1*), no quality assessment was conducted on those studies.

Suggested position Tables 1 & 2

Table 3 presents a summary report of the updated total number of responders per pharmacological intervention trialed for treating RBD. Patients were considered full responders if the authors reported clear and sustained improvements for the duration of the trial without troublesome side effects or classified the patients as full responders, often because of >50% symptom reduction (Clinical Global Impression-Improvement (CGI-I) score = (very) much improved); as partial responders if the authors reported improvements, but with some RBD symptoms remaining or some minimally troublesome side-effects occurring (CGI-I score=minimally improved); and as non-responders if the authors reported no sustained improvements for the duration of the trial, classified the patients as non-responders, or the treatment had to be discontinued due to troublesome side-effects (CGI-I score=no change, or worse). An overview of the data underlying *Table 3* listing all clinical interpretations on the efficacy for each drug and dosage used to treat RBD in the adult population per study is presented in *Supplementary Tables S1-S28*. A description of the existing evidence for clonazepam and melatonin as the current first-line treatment options is provided below, and a description of the evidence for all other alternative drugs trialed to treat RBD off-label is provided in the *Supplementary materials*.

Suggested position Table 3

8 - First-line treatment options

8.1 Clonazepam

Amalgamating all clinical accounts suggested that 684 (66.7%) out of a total of 1,026 RBD patients (regardless of aetiology) reported clear benefits following

clonazepam mono-therapy with no troublesome side effects noted by the authors for the duration of the trial. A further 159 (15.5%) reported partial improvements with some residual RBD symptoms or manageable side effects occurring, while a total of 183 (17.8%) of RBD patients were considered refractory, experiencing intolerable side effects or showing no sustained reduction of their RBD for the duration of the trial. This update is based on the clinical reports from 1 RCT [36], 3 prospective observational studies (POS), 16 retrospective medical histories (RMH), and 31 case reports (CR). The patients across these studies represented a mixture of iRBD and secondary RBD with comorbid conditions (*Table S1*).

When clonazepam mono-therapy proved ineffective, clinicians often resolved to trial in their case series a combination of clonazepam with one or multiple other pharmacological agents, as the second treatment option. A total of 13 RBD patients were reported to receive a combination of clonazepam plus melatonin treatment, with 3 (23.1%) experiencing clear improvements, 6 (46.1%) partial improvements and 4 (30.8%) reporting no benefits (*Table S2*). Out of a total 69 RBD patients treated with clonazepam plus add-on therapies other than melatonin, such as carbamazepine, pramipexole, etc., 41 (59.4%) reported clear benefits, 3 (4.4%) partial benefits whilst 25 (36.2%) experienced no benefits (*Table S3*).

Given the strong clinical effectiveness reported for clonazepam there may have been little equipoise to demand comparative studies. Indeed, only a very limited number of prospective comparative studies have been conducted to assess the efficacy of clonazepam to reduce RBD (*Table 1*). To date, only one RCT (level I-B) tested the efficacy of clonazepam. In this recent study, Shin et al. (2019) compared the clinical effects of 0.5mg clonazepam treatment to 0.5mg matched placebo taken before sleep for 4 weeks in a prospectively registered, double-blinded RCT on 20 (active arm) and 20 (placebo arm) PD patients with probable RBD [36]. One patient in the active arm withdrew consent prior to receiving the allocated intervention. The primary outcome was the CGI impression-improvement (CGI-I) score, which is a 7-point ordinal scale, compared between

groups at the end of the intervention. Partners, who were instructed to sleep beside the patient for every night of the intervention and record any observed RBD events, were interviewed to assess the CGI-I. Importantly, no differences between groups were found (p=0.253), with subjective RBD severity tending to improve in both groups equally. Also no improvements following clonazepam were noted on any of the secondary subjective sleep severity outcomes as compared to placebo. The combination of a small sample size and a 7-point ordinal outcome measure that is prone to what seems to be powerful placebo effects makes it difficult to confirm the presumed effectiveness of clonazepam for reducing RBD using the outcomes of this single RCT only. The study also lacked PSG recordings to confirm the RBD diagnosis and to objectively assess RWA or DEB severity as a trial outcome [36].

In a recent POS study, Li et al. (2016) prospectively followed 39 iRBD patients taking clonazepam 0.125-3mg for a mean duration of 28.8 months [37]. The treatment duration was not fixed and only 27 patients remained on the original dosage, while 10 had their prescriptions changed, and 2 were lost to follow-up. There was no control group to compare the treatment effects against and the study was not randomized, nor blinded (*Table 1*). Interestingly, although a subjective improvement was noted by 26 (66.7%) of the patients, the objective RWA actually worsened over time and no reduction in DEB were noted on PSG [37]. Earlier, Lapierre et al. (1992) prospectively followed 5 iRBD patients, one of whom presented with mild cerebellar signs, taking 0.5-2mg clonazepam for 2 months [38]. All patients had PSG confirmed RBD and the primary outcomes were phasic and tonic chin EMG activity and DEB during REM sleep recorded with PSG. As a case series it did not employ randomization, blinding, or a control group. The five patients subjectively reported partial improvement of their RBD (*Table 1*). A reduction in DEB and phasic chin EMG activity during REM sleep was noted, although no reduction in tonic RWA was found [38]. Finally, Iranzo et al. (2005) prospectively followed a group of 39 iRBD, 45 PD, and 26 MSA patients with PSG confirmed RBD who were administered clonazepam, if clinically required, with dosages titrated up until clinical resolution or tolerability [39]. The treatment duration was not fixed with the average follow-up duration being

26.9 months. There was no control group and the study was not randomized, nor blinded. Most patients reported subjective improvements, though no objective outcomes of RBD were compared pre- and post intervention [39].

Two retrospective studies by Ferri et al. (2013A, 2013B) were eligible for inclusion, but as the authors did not report the exact number of clinical responders, this data could not be included in *Table 2* and *Table S1* [11, 12]. Ferri et al. (2013A) first compared the PSG's of 13 iRBD patients before and after they took 0.5-1mg clonazepam for an average duration of 2.6±1.1 years [11]. The primary outcome was the RBD severity scale (RBDSS), which rates RBD severity based on the DEB recorded by PSG [40], along with the RWA and CGI. No differences were found longitudinally in these patients, indicating that long-term clonazepam administration did not reduce clinical RBD severity. In a second study, Ferri et al. (2013B) retrospectively compared the same outcome measures in a group of 15 iRBD patients assessed before and after taking 0.125-1mg clonazepam for 2.8±1.6 years. Again, clonazepam was not found to significantly reduce objective or subjective RBD severity [12]. These studies put the presumed magnitude of the clinical effectiveness of clonazepam in doubt. A limitation across these studies is that the data was retrospectively analyzed and that no control intervention was administered to compare the treatment effects against.

8.2 Melatonin

The clinical outcome of melatonin mono-therapy was reported for a total of 137 RBD patients, of whom 45 (32.9%) experienced clear benefits, 37 (27.0%) partial benefits and 55 (40.1%) no benefits (*Table S7*). This update is based on the clinical outcomes of 3 RCT's [16, 41, 42], 2 POS, 7 RMH, and 10 CR's. Of these, 100 patients were administered immediate release melatonin, with 34% reporting clear benefits, 31% partial benefits and 35% no benefits. A total of 37 patients were administered a prolonged-released formulation of melatonin (Circadin), with 11 (29.7%) reporting clear benefits, 6 (16.2%) partial benefits, and 20 (54.1%) no benefits. Most patients across these studies had secondary diagnoses besides RBD. A combination of melatonin plus an adjunctive therapy

other than clonazepam was trialed in just three patients. One patient with iRBD plus palatal tremor with ataxia received melatonin plus ropinirole, which mildly improved RBD [43], and another patient with iRBD received melatonin plus pramipexole, which was unsuccessful until sodium oxybate was added leading to partial resolution of RBD [26] (*Table S8*). One other iRBD patient received melatonin plus gabapentin, but the effectiveness was not reported [44].

Recently, two double-blinded RCT's (level I-B) with a parallel group design evaluating melatonin were published, one in PD and one in iRBD patients (*Table 1*). Our trial, Gilat et al. (2019), compared the effects of 4mg (2x2mg) prolonged-release melatonin (PR-melatonin) to 4mg (2x2mg) of matched placebo taken 1 hour before bedtime for 8 weeks in 30 PD patients (15 per group) with PSG confirmed RBD [42]. The study also had a 4-week extension phase without treatment to test whether melatonin is effective even after you stop taking it as has been previously reported [16]. A patient-centered primary outcome was used, whereby patients and/or bed-partners (if applicable) recorded the frequency and severity of RBD events for each night on a weekly RBD event diary, which they had been trained on for 4 weeks prior to randomization. Importantly, we observed that patients completed their dream enactment diaries on 99% of days. The primary endpoint was the number of documented RBD events per week observed across the last 4 weeks of the treatment period and compared between the groups. Secondary outcomes were the severity of documented RBD events, RWA on PSG, several RBD-related questionnaires including the RBD Questionnaire-Hong Kong (RBDQ-HK), the CGI, as well as one week of actigraphy and several other sleep-quality related measures assessed before and during the last 4 weeks of the intervention period. No significant differences were found between the PR-melatonin and placebo groups on any of the RBD-related outcome measures, with both groups improving markedly. Post-hoc analyses revealed that there was no difference in bedtime variability between the groups, suggesting differences in sleep hygiene did not impact on the presumed circadian effectiveness of melatonin. Moreover, sleep onset latencies measured with actigraphy did improve in the melatonin group compared to placebo, in line with the known effects of melatonin [45]. During the

4 week extension phase both the patients originally on melatonin and those on placebo continued to have markedly reduced RBD events compared to baseline and of very similar severity to when they were in the double-blind parts of the study. Limitations of this study were the relatively small groups and that the secondary RWA outcome could only be assessed in a subgroup of the total sample constituting just 14 patients [42].

Around the same time, Jun et al (2019) published their double-blinded RCT (level I-B) using PR-melatonin in adults with PSG confirmed iRBD [41]. They compared three parallel groups, one (n=9) receiving 6mg (3x2mg) PR-melatonin, one (n=7) receiving 2mg (1x2mg) PR-melatonin plus 4mg (2x2mg) matched placebo, and the final arm (n=9) receiving 6mg (3x2mg) matched placebo, for 4 weeks of treatment. The primary outcomes were the CGI-I and the Korean version of the RBDQ-HK (RBDQ-KR) compared across groups at the end of treatment. Secondary outcomes included an RBD diary (the outcomes of which were not reported) and subjective sleep quality scales. Again, no significant differences were found between PR-melatonin and placebo groups on subjective RBD or any of the secondary outcomes. There were also no significant improvements observed in any of the groups on the RBDQ-KR or secondary outcomes following the intervention as compared to baseline. Limitations of the study were the small groups and that no objective RBD measures were obtained as an outcome [41]. These two recent RCT's thereby add to the small body of scientific evidence indicating that the presumed clinical effectiveness of first-line RBD treatments may in fact be driven by placebo.

Kunz & Mahlberg (2010) conducted a cross-over RCT in eight patients comparing the effects of 4 weeks of 3mg melatonin to the effects of 4 weeks of 3mg matched placebo across all subjects, with the order of treatment being randomized [16]. Commonly, RBD patients are instructed to take melatonin 1-hour before bedtime, regardless of how variable bedtimes are across nights. A key difference with other trials is that Kunz & Mahlberg (2010) instructed their patients to take melatonin at set times between 22.00-23.00h and to go to bed 30 minutes after, with the idea that this regime facilitates the chronobiotic effects of

melatonin that might lead to reduced RBD [16, 20]. Unfortunately, their trial had to be cut short due to administrative changes in the department and as a result, only eight patients were randomized and completed the study, five of whom had iRBD, one had PD and two had RBD and narcolepsy plus periodic limb movements (PLMS) [16]. The primary outcomes were the number of 3-second mini-epochs of RWA on PSG assessed in a double-blind manner and the CGI compared between treatments at the end of the intervention and for each treatment compared to baseline. Clinically, the authors reported that all, but one patient, reported clear benefits from the melatonin treatment, though the possible benefits following placebo were not reported in a similar vein. When comparing the primary outcomes, the authors noted significant improvements in the number of RWA epochs and the CGI severity score (CGI-S) after melatonin treatment compared to baseline. In addition, the CGI improvement score (CGI-I) was significantly different between groups and judged by the authors to indicate a significant improvement due to melatonin. However, the mean CGI-I after melatonin was 3.3±1.2 and 4.5±0.8 after placebo, whereby a score of 3 on the CGI-I indicates 'minimal improvement' and a score of 4 indicates 'no change', which might be interpreted as a minor improvement after melatonin compared to placebo. Moreover, when directly comparing the two groups, no significant differences were found for either the number of REM epochs with RWA or CGI-S. Sleep onset latency also significantly improved after both melatonin and placebo [16].

An interesting observation made by the authors was that in the patients receiving the placebo second (n=5), the number of RWA epochs was also significantly lower after placebo as compared to baseline. Based on the idea that the effects of melatonin may outlast the treatment period and the finding that no such improvement was seen in the group receiving placebo first (n=3), the authors interpreted this finding as confirmatory for long-lasting effects of melatonin that carried-over into the second placebo period [16]. However, the comparison done in the group receiving placebo first was severely underpowered (n=3). Furthermore, the 4-week extension period in our own trial [42] indicated that RBD kept improving not only after melatonin, but also after

placebo [16]. Future larger RCT's aimed at assessing the efficacy of melatonin for reducing RBD should consider adopting observation periods lasting beyond the intervention period to robustly test this interesting observation.

Two open-label POS studies also assessed the effect of melatonin. Takeuchi et al. (2001) classified 13 out of a total of 15 RBD patients receiving 3-9mg of melatonin as partial responders, though three of them responded remarkably (75% less RBD), while the other 10 indeed responded moderately (50% less RBD) or mildly (25% less RBD) [46]. The treatment duration, and whether the patients had comorbid diagnoses besides their RBD, was not reported. Objectively, melatonin significantly reduced tonic EMG during REM sleep as compared to baseline [46]. During the second PSG on melatonin treatment, blood melatonin concentration levels were sampled every three hours. The authors reported that melatonin concentration was increased in a subset of the patients (exact number not reported) who had low baseline melatonin levels (values not reported) [46]. Kunz and Bes (1999) further reported that 3mg of melatonin for 6 weeks led to substantial clinical improvements in five out of six patients with mixed diagnoses besides their RBD (*Table 1*) [15]. These clinical effects were considered long-lasting, with clinical responsiveness remaining after treatment cessation, even for as long as 22 months in one patient. Also on PSG, there was a reduction in RWA observed on melatonin as compared to baseline [15]. Given the lack of a control intervention, the outcomes of these open-label studies should be interpreted with caution.

Taken together, to date only three relatively small RCT's and two POS studies have been conducted to test the efficacy of melatonin for reducing RBD. Two of the parallel-group RCT's showed no improvements after melatonin [41, 42] and the third cross-over study, showed partial improvements compared to placebo [16]. These studies thereby highlight the importance of a double-blinded assessment to preclude a seemingly strong placebo effect influencing both the patients and assessors. Importantly, there are much fewer concerns regarding side effects with melatonin compared to clonazepam and for that reason, melatonin is almost certainly a safer first-line treatment option for RBD,

especially in the elderly. Based on the current scientific evidence, however, our prior assumption that melatonin has a marked clinical effect should be tempered by the observation of marked placebo and/or regression to the mean effects in placebo-controlled trials. Adequately powered RCT's will provide more precise estimates of the true treatment effect size, if any.

9 - Alternative treatments for RBD

Eleven other prospective studies were identified that tested the effect of alternative treatments for RBD (see *Table 1*), including two RCT's on a cholinesterase inhibitor (rivastigmine) [27, 28], one RCT on a glutamatergic antagonist (memantine) [47], two open-label studies on a melatonin-agonist (ramelteon) [48, 49], five open-label studies on dopamine-agonists (pramipexole, ropinirole, and rotigotine) [50-54], and one open-label study on a selective serotonin reuptake inhibitor (paroxetine) [33]. The existing evidence for all other alternative drugs trialed to reduce RBD is based solely on retrospective accounts and case reports (see *Table 3*). The evidence on the effectiveness of all the alternative treatments for RBD is described in the S*upplementary materials*. Given the lack of robust evidence, to date none of these pharmacological agents can be recommended as first-line treatment options for RBD.

10 - Publication bias evaluation

A separate search was conducted in the International Clinical Trials Registry Platform of the World Health Organisation to assess for possible publication bias, resulting in 17 eligible trials. Details on each of these trials are tabulated in the Supplementary Materials. The outcomes of three completed RCT's (Registration Identifiers: NCT02836743, NCT02312908 and ACTRN12613000648729), including our own, were published in a peer-reviewed scientific journal and included in the present review [36, 41, 42]. Another trial registration containing limited information (EUCTR-2009-012071-10) is possibly linked to two included publications as they have the same study sponsor and assess the same intervention (4.6mg rivastigmine patch) [27, 55]. The investigators, however, do not refer to the trial registration in their publications, and some inconsistencies

are apparent between the registration and the publications, such as the sample size and primary outcome. Moreover, six recently registered trials are likely still ongoing (i.e. status listed as 'recruiting' or 'not yet recruiting') and as such could not be assessed for possible publication bias at this time (see Supplementary Table for trial identifiers).

Three listed trials were terminated before the target samples were reached. One RCT on the effects of 8mg ramelteon compared to placebo was terminated after enrolling only three subjects due to low recruitment rates (NCT00745030), and another open-label trial on the effect of 20-80mg nelotanserin, a serotonin receptor inverse agonist, was terminated early after changes were made to the overall development program for the study drug (NCT02871427). Our own trial on the effect of 4mg of PR-melatonin compared to placebo in patients with isolated RBD was also terminated early after enrolling just 6 subjects due to low recruitment rates (ACTRN12613000647730). None of these terminated trials posted any outcome data on the trial registries. Another RCT on the combined effect of clonazepam and melatonin PR with December 2019 as the estimated completion date also has no results listed and has not yet been published (NCT02789592), though the recruitment status of that trial is listed as 'unknown', and as such it might still be ongoing. Similarly, a double-blinded trial comparing the effect of melatonin to clonazepam on RBD in PD is listed as 'completed', whilst the results have not been posted nor published (IRCT20170821035819N3). However, that trial was only completed recently in 02/2020, and so the investigators might still be in the process of publishing their findings. Of note is that the registration text, which was posted before the study end date, appears to un-blind the trial investigators.

Importantly, the outcomes of two RCT's that have been completed for over two years have also not been published, indicative of possible publication bias. One RCT completed in 2011 tested the effect of 8mg ramelteon compared to a placebo over 30 nights, but to our knowledge the investigators have not posted nor published the trial results (NCT01401413). Another RCT completed in 2018 on the effect of 40-80mg nelotanserin compared to placebo over 28 nights in

RBD patients with dementia (DLB or PD) has also not been published in a peer-review journal, though the investigators of that trial did disseminate part of the results on the trial registry (NCT02708186). A total of 16 patients (all male) were randomized to receive nelotanserin, and 18 patients (13males) were randomized to receive matched placebo for 28 days. Two patients in each group dropped-out. The primary outcome was the change in the number RBD events observed on a single night of PSG compared between baseline and post-treatment. Based on an intention-to-treat analysis, the least mean squares (standard error) for the nelotanserin group was -1.47 (1.006) RBD events and for the Placebo group -0.26 (1.027). It is not reported whether this finding represents a statistically significant effect. Nelotanserin was also associated with several adverse events. Given the limited amount of evidence, no recommendation can be made for the use of nelotanserin to treat RBD in patients with dementia. Taken together, there is some indication of possible publication bias for pharmacological interventions for RBD.

11 - Outcomes used

Choosing a primary outcome measure for RBD is challenging [30]. The large majority of studies identified by this literature review relied on subjective recollections from the patient and/or their bed partners to assess the effectiveness of RBD treatments. The 7-point ordinal CGI scale was the most frequently used measure of a clinically evident effect and in some cases a customized scale was devised, such as a three- [33, 53] or four-point [51, 54] ordinal RBD severity rating based on clinical opinion or a VAS scale completed by the bed-partners [48]. However, baseline expectations on the presumed effectiveness of the intervention, as would be the case for first-line treatment options for RBD, create a high risk for bias. Clinical opinions are also at high risk of being influenced by placebo effects, if not controlled for in a double-blinded manner. Furthermore, retrospective recollections of symptom severity can be heavily driven by the occurrence of a single severe event, which may have been an 'oddball', rather than an average of all events. Biased recollection may be exacerbated in those RBD patients with memory difficulties, such as those with DLB and PD dementia. People may also struggle to remember whether the RBD

events occurred during or outside of the intervention period. Finally, patients with other symptoms besides RBD, for example such as is the case for PD and DLB patients, may report benefits to their clinician after receiving treatment for their RBD, as at that time their desire to resolve RBD may be overshadowed by the desire to resolve some other symptom that may still go untreated. Importantly, all RCT's conducted to date on first-line treatments for RBD included the CGI as either the primary [16, 36, 41] or as a secondary outcome [42]. This ordinal scale makes it difficult to show differences in the small samples that have been studied. Indeed, only one of the RCT's could report a minor improvement on the CGI following the active intervention [16], whereas the three other double-blinded RCT's showed no benefits compared to placebo [36, 41, 42]. Whilst RBD-related questionnaires are useful to screen for the presence of probable RBD, of the questionnaires used by the included RCT's and POS studies only the RBDQ-HK and its Korean version (RBD-KR) were developed to assess RBD severity [56]. As such, the RBDQ-HK or RBDQ-KR was used as either a primary [37, 50] or secondary outcome [42] in three prospective intervention studies. However, RBD-related questionnaires, such as the RBDQ-HK, also rely on subjective retrospective recollections of RBD severity by patients and their bed-partners, questioning their accuracy. Taken together, we would not recommend the exclusive use of subjective retrospective accounts for assessing the efficacy of any RBD intervention in routine clinical practice. The use of CGI should be coupled with sufficient sample sizes to detect meaningful differences in ordinal data and a good randomized double-blinded control (probably placebo at this point).

Two of the recent RCT's on PR-melatonin implemented an RBD event diary as either the primary [42] or as a secondary but unreported outcome [41]. Such patient-centered measures of RBD frequency and severity might be good outcome measures in symptomatic RCTs as long as the subjects are fully blinded to the treatment allocation, and by filling out the diary each morning, there is presumably a reduced risk for recollection error. Diary outcomes measured continuously may thus provide a more sensitive representation of RBD clinical severity (i.e. severe enough and memorable enough to motivate a patient to

actually seek clinical help), especially when the entries can be complemented by a bed-partner. We have found the diary seems to have good 'face' validity with patients accepting that it looks like it captures patient and bed partners' complaints [42]. However, the patients themselves are asleep and often the bed-partners are too when RBD occurs, and as such, RBD events may be missed. Moreover, if RBD becomes disruptive of sleep and/or forms a risk for injuries, the bed-partners will often resolve to sleep in a separate room and many RBD patients do not have a bed-partner. Excluding subjects without a bed-partner sleeping in the same room will thus lead to a non-representative sample of the population. Finally, there is no way to control whether the entries provided are accurate. Based on our experience we recommend a training period for patients to learn to adequately complete such an outcome prior to randomization and provide patients with frequent reminders to keep filling out the diary as adequately as possible to prevent missing entries. In our trial such an approach resulted in 99% adherence for completing the primary outcome, ensuring adequate statistical power in the analysis [42].

12 - Future directions

Our interpretation of the totality of treatment evidence in RBD is that the presumed effectiveness of the two mainstay treatments may be largely or wholly attributable to the non-specific effects of good clinical care, placebo effects, and regression to the mean. As such, it should be a pressing priority in the field today to ascertain how effective the mainstay treatments for symptomatic alleviation truly are. It is time to conduct robustly designed and properly powered and blinded, placebo-controlled parallel group RCT's using outcome measures that are free from interpretation bias.

One of the challenges has been the development of an accurate primary outcome measure of true RBD burden that is specific to RBD and free from subjective interpretation [30]. Actigraphy outcomes have been proposed as an objective outcome for RBD [57, 58], but with actigraphy alone it is impossible to ascertain whether the patient is truly in REM sleep when movements are detected. Similarly, automated 3D video analysis of leg movements during REM sleep, in

particular short jerks of 0.1-2.0 seconds, as captured with a Microsoft Kinect v2 sensor using infrared camera's was recently shown to be able to accurately (90.4%) distinguish iRBD patients from prodromal RBD and patients with other sleep disorders and leg movements [59]. The number of leg jerks documented with this automated system during REM sleep correlated strongly with RWA and visually scored leg movements. PSG, however, was still required to score REM sleep, in particular as low classification accuracies were reported for non-REM sleep periods [59]. In effect, currently only PSG can objectively detect the presence, frequency and severity of RBD. To date, several RCT's and prospective open-label studies already rated dream enactment behaviors and/or RWA on PSG as an outcome of their intervention [15, 16, 27, 37, 38, 41, 42, 46, 48, 50, 53, 54] with many of these showing no differences (*Table 1*). However, gold-standard PSG requires an overnight stay in a sleep laboratory, which is costly and involves travel for the patient. A laboratory environment may also be an unfavorable setting for patients to achieve typical sleep, possibly having an impact on the amount of REM sleep. Finally, RBD can be highly variable across nights [40]. As a result, a single night of laboratory PSG may not provide an adequate representation of RBD frequency and severity and this may have precluded past studies from detecting a favorable treatment effect.

Home-based PSG devices (HB-PSG) are now able to collect the same signals as laboratory PSG (i.e. EEG, EOG, nasal flow, thermistor, and importantly EMG), therefore offering new possibilities for sleep evaluation over multiple nights in the subject's own homes [60, 61]. Combined with an infrared camera and microphone, such ambulatory PSG devices could, in the near future, offer the same DEB, RBDSS and RWA outcomes as laboratory PSG [60]. They could be conducted without overnight supervision, or trained staff could supervise via remote monitoring [62]. Importantly, the feasibility and validity of HB-PSG has already been demonstrated for the diagnosis and treatment of obstructive sleep apnea (OSA) with surprisingly low failure rates [60, 63]. Specifically, 79% of OSA patients preferred HB-PSG and achieved greater sleep-quality, -efficiency and -duration than during laboratory PSG [61, 63]. The amount of REM sleep was also increased at home compared to laboratory PSG in several studies [61]. Such

benefits are of even greater significance in patients with a neurodegenerative disease, such as PD and DLB, who suffer from impaired mobility and heightened sleep sensitivity, especially as multiple testing nights will be required. As such, HB-PSG may serve as a new objective endpoint for future clinical trials for RBD. Thus a next step for the field is to validate HB-PSG by comparing the RBD outcomes to those obtained with laboratory PSG and to determine the natural variability and minimally detectable change of HB-PSG derived RBD outcomes [25].

Of interest is that a home-based screening device was previously evaluated for assessing OSA in PD, showing greater discrepancy in diagnostic accuracy of OSA compared to laboratory PSG [64]. However, PD patients in that study were required to place the sensors on themselves, leading to high failure rates and reduced data quality. In fact, >15% of subjects declined to participate because they were not confident about their ability to correctly wear the device [64]. It is therefore advised that trained study staff should apply the sensors and conduct system calibration and impedance testing in future HB-PSG studies [60]. Remote monitoring may further help reduce signal loss [62]. Future HB-PSG devices may require fewer sensors and be made easier for patients to apply. Moreover, we recommend incorporating a lead-in period whereby the HB-PSG is applied during one or preferably several nights to get subjects accustomed to wearing the device and knowledge of being monitored, prior to the randomization, in order to prevent a regression towards the mean due to a familiarization effect. In addition, care should be taken to prevent weekend-effects, whereby a change in sleep schedule during the weekend may impact on the amount of REM sleep, especially in the working population [65].

High accuracy for detecting the primary outcome measure, such as RWA, short limb jerks, DEB or RBDSS averaged over multiple nights [3, 40, 59] can be ensured through HB-PSG with each RBD event scored on video and confirmed by RWA without OSA-induced arousal. Thereby, HB-PSG systems will provide an objective measure of RBD frequency and severity, which can be obtained in any patient, with- or without- a bed partner, and over multiple nights in the patient's

own homes to maximize the representation of true RBD severity in daily life. Given that complex DEB can be highly variable across nights, perhaps capturing the number of short limb jerks during REM sleep would prove to be a more reliable outcome of overt RBD [3, 59]. Clearly, the costs of such a HB-PSG system and the time needed for trained staff to apply the device and monitor data acquisition represents a potential limitation of this suggested approach.

Another important consideration for future studies is the timing of patient enrollment. Indeed, patients are often enrolled upon first referral to the sleep clinic after they have experienced a period with troublesome RBD symptoms. Given the variability of RBD over time [40], enrollment into a clinical trial during such a period of high RBD severity might result in a regression towards the mean over time, unrelated to the treatment effect. As such, and if clinically ethical to temporarily withhold possibly effective treatment, we recommend future studies to implement an observation period prior to randomization in order to assess the natural variability in RBD symptom severity, resulting in better statistical power.

A possible limitation of the present review is that we included studies that assessed patients with probable RBD, whose diagnoses were not confirmed by PSG. We also interpreted the clinical effects across all patients with RBD. Future work is needed to determine whether pharmacological effects differ across patient populations, for instance secondary versus isolated RBD.

13 - Conclusion

The best current evidence base for pharmacotherapies for RDB could charitably be described as being of an I-b level (*Box 1*). Based on lower levels of evidence, the traditionally claimed effectiveness of the two first-line therapies for RBD (melatonin and clonazepam) may be greatly overestimated. The clinically observed effectiveness of these interventions may have been driven by strong placebo effects, regression towards the mean, and the non-specific but laudable effects of good clinical practice in RBD, such as behavioral advice. Concerns continue to exist about the ability of any outcome measure to accurately and

objectively capture RBD severity in an unbiased manner. Thus there is a clear need to conduct more robustly designed and adequately powered double-blind placebo-controlled RCT's using better outcome measures on appropriately selected patient groups. Patient-centered diary outcomes are currently recommended for larger phase 3 trials and following validation, objective RBD as measured by home-based PSG over multiple nights is suggested as the most promising primary endpoint for future earlier phase RCT's on RBD.

14. Declarations

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14.2 Competing interests

The authors declare to have no competing interests.

14.3 Availability of data and material

Not applicable

14.4 Code availability

Not applicable

14.5 Author's contributions

MG devised the concept, conducted the systematic search, screening, performed risk of bias assessments and wrote the original draft of the manuscript; DT

performed risk of bias assessments; NM, DT, BB and SJGL contributed to the writing of the manuscript draft and all authors critically reviewed the manuscript.

Figures

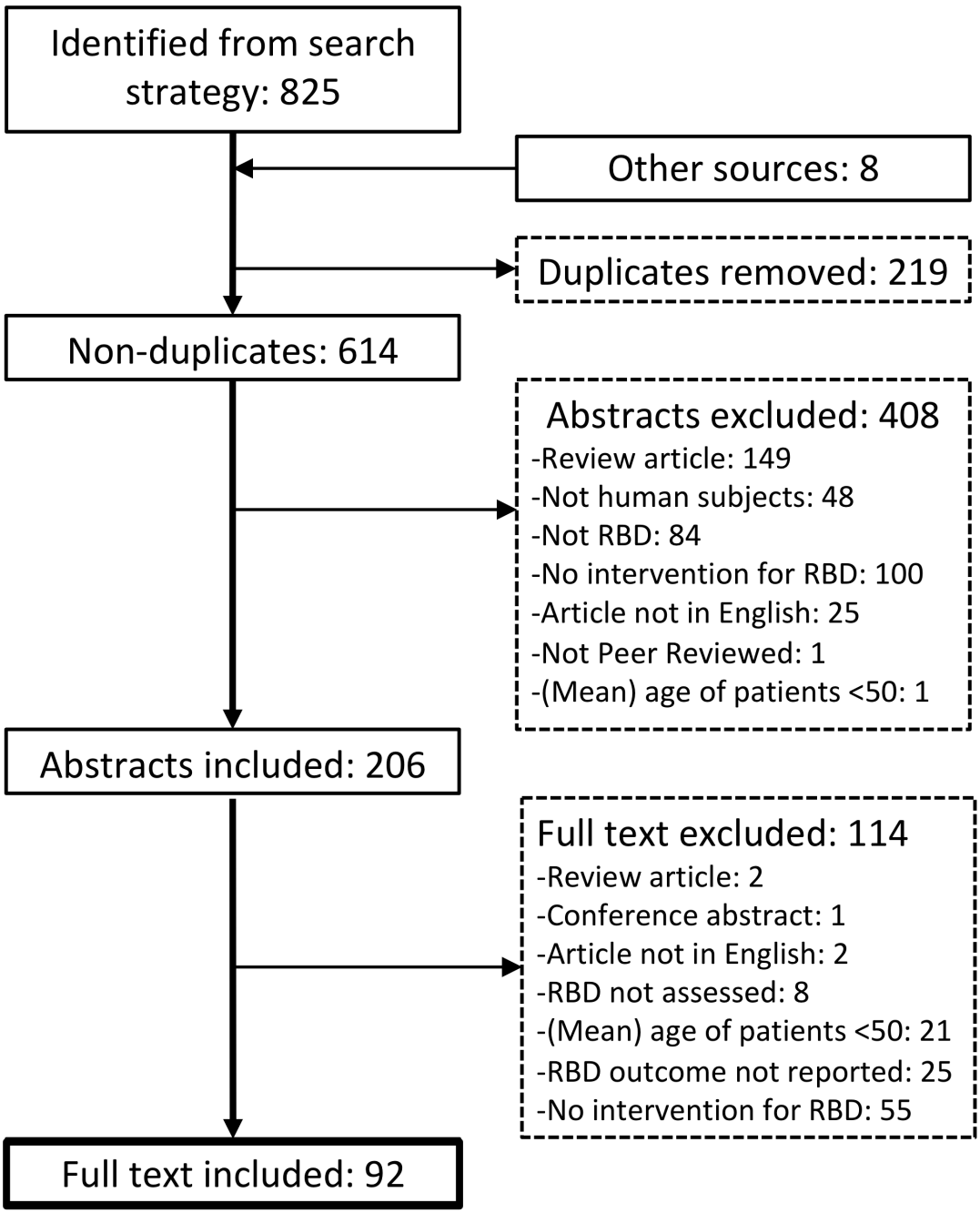

Figure 1: Flowchart of search results and screening.

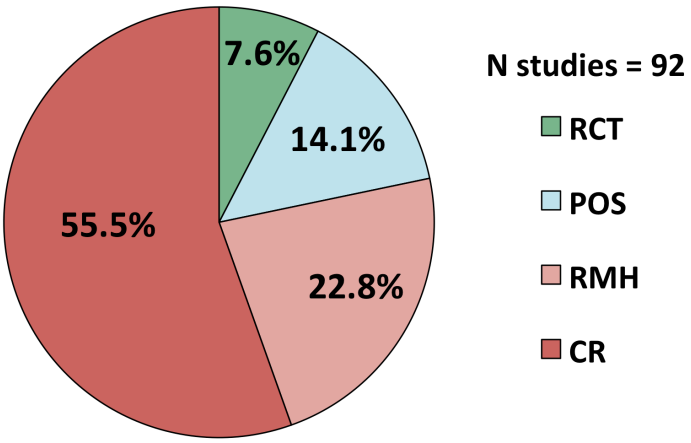

Figure 2: Overview of study designs used to test pharmacological interventions for treating RBD in the adult population. Abbreviations: RCT=Randomized controlled trial; POS=Prospective single arm open-label cohort study; RMH=Retrospective study based on medical history; CR=Case report.

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Title: A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: Time for more and larger randomized placebo-controlled trials.

Authors: Moran Gilat PhD, Nathaniel Marshall PhD, Dries Testelmans MD PhD, Bertien Buyse MD PhD, Simon JG Lewis MD PhD

Corresponding author:
Dr Moran Gilat PhD
Email: moran.gilat@kuleuven.be

Table 1: Systematic overview of all prospective observational studies on the pharmacological management of RBD

Study Design	Study (First author, year)	Clinical population	Treatment (Daily dosage)	Groups (n subjects) [Age in years]	RBD screening method	RBD outcome measure(s)	Main results on RBD	Level of evidence (*Box 1*)
Clonazepam								
DB-RCT	Shin, 2019 [34]	Parkinson	A) Clonazepam (0.5mg) daily for 4 weeks B) Matched placebo (0.5mg) daily for 4 weeks	A) Active (n=19) [66, 48-73]* B) Placebo (n=20) [70, 56-77]	RBD single screening question	1) CGI	Non-effective. No other outcomes of RBD assessed.	I-B
POS	Li, 2016 [35]	iRBD	Clonazepam (0.125-1.0mg) at baseline and (0.125-3.0mg) at follow up 28.8 ± 13.3 months later. *Treatment duration not fixed.*	Active (n=39). [68.3 ± 7.8] -27 remained on therapy -10 had prescription changed -2 were not on therapy at follow-up *No control group*	PSG	1) RWA on PSG 2) Movements during sleep on PSG 3) RBDQ-HK modified to cover past 3 months	Worse RWA and no reduction in movements during sleep on PSG. Subjective improvement reported in 66.7% of subjects	II-B

POS	Iranzo, 2005 [37]	iRBD, Parkinson, and MSA	If clinically required, clonazepam (0.25-0.5mg) was started at diagnosis and titrated up in 0.25-0.5mg increments to clinical response and tolerability. Mean follow-up across all subjects was 26.9 ± 21.3 months later. *Treatment duration not fixed.*	Active -iRBD (n=39) taking mean dose of 0.89 (0.55) mg/day [68.4 ± 5.9] -Parkinson (n=45) taking mean dose of 0.72 (0.42) mg/day [64.8 ± 7.8] -MSA (n=26) taking mean dose of 0.63 (0.22) mg/day [62.0 ± 7.1] *No control group*	PSG	1) Clinical response to clonazepam (Substantial, partial, no response, in %)	Subjective improvement (substantial or partial) reported in almost all subjects, except 3.1% of the iRBD cases. No side effects in Parkinson, whereas 11.1% of MSA and 25% of iRBD reported side effects, mainly somnolence.	II-B
POS	Lappiere, 1992 [36]	iRBD, with one case presenting soft cerebellar signs on MRI	Clonazepam (0.5-2.0mg) for a duration of 2 months	-Active (n=5) [58.6, 44-65]* *No control group*	PSG	1) RBD episodes on PSG 2) Phasic EMG density on PSG at REM 3) RSWA on PSG	1) Subjective improvements reported though occasional sleep-talking and limb-jerking observed 2) Reduction in phasic EMG density at REM 3) No reduction in RSWA	II-B
Melatonin								

DB-RCT	Gilat, 2020 [40]	Parkinson	A) PR-melatonin (Circadin, 2x2mg) for 8 weeks B) Matched placebo (2x2mg) for 8 weeks	A) Active (n=15) [65.3 ± 6.9] B) Placebo (n=15) [67.9 ± 5.3]	PSG	1) Frequency of RBD in 2nd month of treatment based on self-report diary entries 2) RWA on PSG in a subset of n=8 on melatonin and n=6 on placebo 3) Several RBD questionnaires 4) CGI-I	Non-effective. Also no group differences seen for RWA on PSG, the CGI, or any of the RBD Questionnaires.	I-B
DB-RCT	Jun, 2019 [39]	i-RBD	A) PR-melatonin (Circadin, 1x2mg) + matched placebo (2x2mg) for 4 weeks B) PR-melatonin (Circadin, 3x2mg) for 4 weeks C) Matched placebo (3x2mg) for 4 weeks	A) Active 1 (n=7) [68.1 ± 9.1] B) Active 2 (n=9) [64.7 ± 8.3] C) Placebo (n=9) [66.4 ± 8.5]	PSG	1) CGI-I 2) RBDQ-KR questionnaire after 4 weeks of treatment 3) DEB frequency recorded by patients on daily diary	Non-effective on either primary- or any secondary outcomes on RBD, including diary entries. RWA on PSG not assessed post-treatment.	I-B
DB-RCT	Kunz, 2010 [14]	Mixed diagnoses (5 iRBD, 1 Parkinson, 2 Narcolepsy + PLMS)	A) Melatonin (3mg) for 4 weeks B) Placebo for 4 weeks	Subjects (n=8) entered in cross-over study and randomized to first receive melatonin or placebo therapy for 4 weeks and switch treatments	PSG	1) Number of REM epochs without RWA on PSG 2) CGI severity	Compared to baseline, melatonin significantly reduced number of REM epochs with RWA and improved CGI, whereas the	I-B

				after 3-5 days of washout period. [53.8, 26-67]* *Two subjects were 26 and 37 years old, respectively.*			improvement seen during placebo did not reach significance. No differences were found for RWA or CGI severity scores when comparing melatonin to placebo.	
POS	Takeuchi, 2001 [44]	RBD, idiopathic or with unknown concomitant diagnoses (not reported)	Melatonin (3mg) that in some subjects was titrated up to 9mg according to degree of clinical RBD symptoms *Treatment duration not fixed and not reported.*	Total of 15 subjects with RBD assessed at baseline and at a non-specified point in time during therapy 'when their clinical symptoms were improved or stable' [63.5, SD or range not reported]	PSG	1) Clinical opinion 2) % Tonic/Phasic REM activity on PSG 3) Melatonin blood concentration levels at 3hour intervals	Remarkable improvement noted in 3/15 and partial improvement in 10/15 patients. Significant reduction in tonic REM EMG activity on PSG. Melatonin concentration increased in a subset of patients with low baseline melatonin levels.	II-B
POS	Kunz, 1999 [13]	Mixed diagnoses	Melatonin (3mg) for 6 weeks	Total of 6 subjects assessed before and after therapy	PSG	1) Clinical opinion 2) Number of REM	Subjective improvements in 5/6 patients	II-B

		(2PD, 2 iRBD, 1 RBD with hypertension, 1 RBD with sympathetic dysautonomia)		[54, 26-71]*		epochs without RWA on PSG 3) Movement time in bed based on actigraphy data	with presumed long-term effects lasting weeks or even up to 22 months in one subject. Reduced REM epochs without muscle atonia on PSG seen after 6weeks of melatonin compared to baseline	
Ramelteon								
POS	Esaki, 2016 [46]	iRBD	Ramelteon (8mg) for 8.3±6.8 weeks *Treatment duration not fixed*	Active (n=12) [70.9, 52-81] *No control group*	PSG	A) RWA on PSG B) RBDSS on PSG C) VAS-scale for subjective RBD severity rated by partner	Non-effective on PSG or VAS-scale, though subjective severity trended towards a significant improvement. Some subjects with worsening RWA reported subjective improvements	II-B
POS	Kashihara, 2016 [47]	Parkinson	Ramelteon (8mg) for 12 weeks	Active (n=35) -24 screened	RBDSQ (Japanese	RBDSQ (Japanese version)	Significant improvement in	II-B

				positive for probable RBD -6 stopped therapy due to adverse events -3 were lost to follow-up [69.1 ± 11.1] *No control group*	version)		13 patients with probable RBD, but also in 11 patients without probable RBD	
Dopamine-agonists								
POS	Sasai, 2012 [49]	iRBD with PLMS	Pramipexole (0.21± 0.09 mg) for 9.1 ± 7.1 months. *Treatment duration not fixed.*	Total of 15 subjects assessed before and after treatment period [66.5, 57-75]	PSG	1) Four-point severity scale based on clinical opinion 2) Subjective frequency of nightmares 3) RSWA on PSG	Subjective partial improvements were noted for 12/15 patients	II-B
POS	Kumru, 2008 [51]	Parkinson	Pramipexole (0.54mg) divided in 3 dosages with last dosage taken one hour before bedtime, for 3 months.	Total of 11 PD with untreated RBD on levodopa monotherapy at study entry assessed before and after 3 months of pramipexole therapy [62.1 ± 8.0]	PSG	1) Three point severity scale on subjective frequency of RBD by patient and bed-partner 2) Subjective frequency of unpleasant dreams by patients and bed-partners 3) RWA on PSG 4) % of time spent	Non-effective on both subjective and objective PSG measures.	II-B

						with DEB during REM sleep 4) Three point severity scale of DEB on PSG by blinded assessors		
POS	Fantini, 2003 [52]	iRBD	Pramipexole (0.125mg/24hr) titrated up by 0.125mg every 3 days until a mean final dosage of 0.78 ± 25mg/24hr, 1-9 months later *Treatment duration not fixed.*	Total of 8 subjects with iRBD assessed before and after 4.5 (range 1-9.5) months of therapy [66 ± 6.8]	PSG	1) Four point subjective severity rating based on patient and bed partner self-report of RBD severity on 2) RWA on PSG 3) DEB on PSG	Subjective sustained improvement in 5/8 patients and reduced simple DEB on PSG, though RWA on PSG worsened on therapy compared to baseline	II-B
POS	Wang, 2016 [48]	Parkinson	Rotigotine (2mg/24hr) titrated up to 16mg over 8 weeks followed by 12-20 weeks of dose-maintenance *Treatment duration not fixed*	Active (n=11) [66.27 ± 8.47]	PSG	A) RWA on PSG B) DEB on PSG C) RBDQ-HK	Non-effective on PSG measures. Subjective improvement reported in 63.64% of subjects.	II-B

POS	Dušek, 2010 [50]	Parkinson	PR-ropinirole for 5-13 weeks at the dosage closest to the dosage of immediate release ropinorole already taken by the subjects at study entry for past 3.4±1 years. *Treatment duration not fixed*	Total of 35 PD, of whom only 5 had RBD, taking immediate release ropinorole 2-5 times daily at study entry who were switched to a similar dose (17.2±6mg) of PR-ropinorole and followed-up 5-13 weeks later. [62.5, 44-75]*	PSG	RBDSQ	Non-effective in subset of 5 PD with RBD at study entry.	II-B
Acetylcholinesterase inhibitors								
SB-RCT	Brunetti, 2014 [26]	iRBD with MCI	A) Rivastigmine patch (4.6mg/24hr) for 30 days B) Placebo patch for 30 days	Subjects (n=25) deemed refractory to melatonin or clonazepam therapy entered in cross-over study and randomized to first receive rivastigmine or placebo therapy for 30 days and switch treatments after 7 days of washout period. [63.0, 49-81]*	PSG	A) RBD frequency recorded on diary by bed-partners *PSG not performed post-therapy*	Improvement in subjective RBD frequency on rivastigmine compared to placebo.	I-B

DB-RCT	Di Giacopo, 2012 [25]	Parkinson	A) Rivastigmine patch (4.6mg/24hr) for 3 weeks B) Placebo patch for 3 weeks	Subjects (n=12) deemed refractory to melatonin or clonazepam therapy entered in cross-over study and randomized to first receive rivastigmine or placebo therapy for 3 weeks and switch treatments after 7 days of washout period. Two dropped out. [66.7 ± 7.3]	PSG	A) RBD frequency recorded on diary by bed-partners B) RWA on PSG in subset of 4 subjects	Significantly lower frequency of RBD on diary during rivastigmine, but not placebo. No change on PSG in subset of 4 subjects.	I-B
NMDA antagonist								
DB-RCT	Larsson, 2010 [45]	Parkinson with dementia (PDD) or DLB	A) Memantine (5mg) for 24 weeks titrated up to 20mg at week 4 of therapy B) Placebo *Secondary analysis from previously published DB-RCT, which was not focused on RBD.*	A) Active (n=25) [76.4 ± 6.5] B) Placebo (n=22) [76.3 ± 5.0]	Probable RBD based on subjective rating on a single item of the Stavanger Sleep Questionnaire (SSQ): "Is the patient physically active	Four-point subjective severity rating on a single item of the SSQ regarding physical activity during sleep, which may or may not have occurred during REM sleep. The baseline frequency of patients with probably RBD was 54% and equally distributed between	Probable RBD severity decreased significantly following memantine compared to placebo, though careful interpretation is warranted due to possible non-RBD specificity of outcome measure.	I-B

					during sleep?"	the two groups.		
SSRI								
POS	Yamamoto, 2006 [31]	IRBD	Paroxetine (10-40mg) for an unknown duration. *Treatment duration and dosage not fixed*	A) Active (n=19) [64.7 ± 7.8] *No control group*	PSG	A) Subjective RBD severity rating (Mild, Moderate, Severe)	Subjective RBD improved to a mild state in 11 and to a moderate state in 5 patients, while in 3 patients severe RBD persisted. Treatment was ceased in 2 due to side-effects.	III-B
Notes: Daily dose presented as mean ± SD mg/day; Age in years presented as [mean ± SD], or [mean, range]; *=one or more subjects could be <50 years of age.								
Abbreviations: CGI=Clinical Global Impression scale; DB-RCT=Double-blinded randomized controlled trial; DEB=Dream Enactment Behaviors; (I)RBD=(Idiopathic) REM sleep Behavior Disorder; Parkinson=Parkinson's disease; PLMS=Periodic Limb Movements; POS= Prospective open-label study (i.e. no control intervention); PR=Prolonged Release; PSG=Polysomnography; QA=Quality Assessment; RBDQ-HK= RBD Questionnaire Hong Kong; RBDSQ=RBD Screening Questionnaire; RBDSS=RBD Severity Scale based on PSG; RWA=REM sleep without atonia; SB-RCT= Single-blinded RCT; SSRI=Selective Serotonin Reuptake Inhibitor; VAS=Visual Analogue Scale.								

Table 2 - Quality assessment of the randomized controlled trials assessing the pharmacological management of RBD in adults

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Gilat, 2019	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓	✓	✓	✓
Jun, 2019	✓	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	✗	✓	✗
Shin, 2019	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✓	✓	✗
Brunetti, 2014	✓	✗	✗	✓	✗	✗	✓	✓	✗	✓	✓	✗	✗	✓
Di Giacopo, 2012	✓	✗	✗	✓	✓	✗	✓	✗	✗	✓	✓	✗	✗	✓
Kunz, 2010	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✓
Larsson, 2010	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✓

Summary of items from the NIH quality assessment tool (nhlbi.nih.gov): 1=Randomized; 2=Randomization adequate; 3=Concealed; 4=Blinding subjects; 5=Blinding assessors; 6=Groups matched at baseline; 7=Overall dropout ≤20%; 8=Differential dropout ≤15% between groups; 9=Adherence to intervention; 10=Other interventions avoided; 11=Outcome assessed using valid and reliable measures; 12=Sample size large enough for 80% power; 13=outcomes and analyses pre-specified (registered); 14=All received treatment allocated to. Green background with '✓'=low risk of bias; Red background with '✗' = high or unclear risk of bias.

Table 3 - Update on the total number of responders per drug used to treat RBD as based on clinical interpretation

Drug class	Drug type	N studies	N patients	YES N (%)	PARTIAL N (%)	NO N (%)
Benzodiazepine	Clonazepam[1]	51	1026	684 (66.7)	159 (15.5)	183 (17.8)
	Clonazepam + Melatonin	6	13	3 (23.1)	6 (46.1)	4 (30.8)
	Clonazepam + Adjunctive	10	69	41 (59.4)	3 (4.4)	25 (36.2)
	Temazepam	3	3	1 (33.3)	0 (0)	2 (66.7)
	Zopiclone	4	12	7 (58.3)	0 (0)	5 (41.7)
	Other	6	22	3 (13.6)	0 (0)	19 (86.4)
Melatonin (+agonist)	Melatonin[1]	22	137	45 (32.9)	37 (27.0)	55 (40.1)
	Melatonin + Adjunctive	2	3	0 (0)	2 (66.7)	1 (33.3)
	Ramelteon	3	16	5 (31.3)	1 (6.2)	10 (62.5)
	Agomelatine	1	3	3 (100)	0 (0)	0 (0)
Dopamine (+agonist)	Levodopa	4	45	8 (17.8)	1 (2.2)	36 (80)
	Pramipexole	6	126	71 (56.3)	4 (3.2)	51 (40.5)
	Ropinirole	4	7	0 (0)	1 (14.3)	6 (85.7)
	Rotigotine	1	11	7 (63.6)	0 (0)	4 (36.4)
Anticholinergic	Donepezil	4	56	1 (1.8)	3 (5.4)	52 (92.8)
	Rivastigmine	3	36	25 (69.4)	1 (2.8)	10 (27.8)
NMDA antagonist	Memantine	1	24	NR	NR	NR
Gabapentinoid	Gabapentine	3	16	12 (75)	0 (0)	4 (25)
	Pregabalin	1	3	2 (66.7)	0 (0)	1 (33.3)
Noradrenergic agonist	Clonidine	2	2	1 (50)	0 (0)	1 (50)
Antidepressants (per class)	SSRI	5	24	0 (0)	17 (70.8)	7 (29.2)
	Tricyclic	6	9	1 (11.1)	0 (0)	8 (88.9)
	Other	3	8	0 (0)	0 (0)	8 (100)
Antipsychotics	Mixed types	6	9	3 (33.3)	1 (11.1)	5 (55.6)*
Anticonvulsants	Phenobarbital	1	1	0 (0)	0 (0)	1 (100)
	Lamotrigine	1	1	0 (0)	0 (0)	1 (100)
	Oxcarbazepine	1	1	0 (0)	0 (0)	1 (100)

Gamma-hydroxybutyric acid	Sodium oxybate	4	4	4 (100)	0 (0)	0 (0)
	Sodium oxybate + Pramipexole	1	1	1 (100)	0 (0)	0 (0)
Other	Yi-Gan San	2	18	13 (72.2)	0 (0)	5 (27.8)
	Yi-Gan San + Adjunctive	1	19	4 (21.1)	0 (0)	15 (78.9)
	Cannabidiol	1	4	4 (100)	0 (0)	0 (0)
	Aspirin	1	1	0 (0)	0 (0)	1 (100)
	Metropolol	1	1	0 (0)	0 (0)	1 (100)

NOTES: %=Percentage of total sample per drug type; YES = Full responders, authors reported clear and sustained improvements without side effects; PARTIAL = Partial responders, authors reported improvements, but with some RBD symptoms remaining or some non-troublesome side-effects occurring; NO = Non-responders, authors reported no sustained improvement or the treatment was discontinued due to troublesome side-effects; 1=Currently the first-line treatment options; *= Some of the antipsychotic drugs induced or worsened RBD. Abbreviations: SSRI = Selective Serotonin Reuptake Inhibitor; NMDA=*N*-Methyl-D-aspartate; NR = Not reported.

Supplementary Materials: World Health Organisation Clinical Trial registrations on the pharmacological treatment of RBD

Title: A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: Time for more and larger randomized placebo-controlled trials.

Authors: Moran Gilat PhD, Nathaniel Marshall PhD, Dries Testelmans MD PhD, Bertien Buyse MD PhD, Simon JG Lewis MD PhD

Corresponding author:
Dr Moran Gilat PhD
Email: moran.gilat@kuleuven.be

Supplementary Table: World Health Organisation Clinical Trial registrations on the pharmacological treatment of RBD

Registration ID	Registration Source	Date Registration first posted	Study Start date	(Estimated) Completion Date	Prospective or Retrospective Registration	Public Title	Trial status	Published in peer-review journal?	Results posted on registry?	Notes
NCT01401413	ClinicalTrials.gov	07/2011	01/2008	09/2010	Retrospective	Study to Determine Whether Ramelteon Helps People With REM Sleep Behavior Disorder	**Completed**	No	No	*Possible publication bias.*
NCT00745030	ClinicalTrials.gov	09/2008	06/2008	09/2010	Retrospective	Efficacy and Tolerability of Ramelteon in Patients With Rapid Eye Movement (REM) Behavior Disorder and Parkinsonism	Terminated	No	No (only enrolment numbers)	Terminated after enrolling three subjects due to low recruitment rates.
2009-012071-10	EU Clinical Trials Registry (EUCTR)	29/05/2009	15/06/2009	Not reported	Prospective	Rivastigmine in the treatment of Sleep REM Behaviour Disorder (RBD) and Hallucinations in Parkinsonism: a Clinical and Polysomnographic study	**Completed**	*Possibly*	N.A.	Limited information on trial registration.
ACTRN12613000648729	Australian New Zealand Clinical Trials Registry (ANZCTR)	02/06/2013	01/08/2013	15/01/2018	Prospective	Efficacy of melatonin in rapid eye movement (REM sleep) behaviour disorder with coexisting Parkinsonism	**Completed**	Yes	N.A.	
ACTRN12613000647730	Australian New Zealand Clinical Trials Registry (ANZCTR)	02/06/2013	01/08/2013	15/05/2016	Prospective	Efficacy of melatonin in idiopathic REM sleep behaviour disorder	Terminated	No	No	Terminated after enrolling 6 subjects due to low recruitment rates.

NCT02312908	ClinicalTrials.gov	09/12/2014	01/03/2015	01/03/2016	Prospective	Effect of Clonazepam on REM Sleep Behavior Disorder in Patients With Parkinsonism	**Completed**	Yes	N.A.	
NCT02708186	ClinicalTrials.gov	03/2016	03/2016	05/2018	Prospective	Study Evaluating Nelotanserin for Treatment of REM Sleep Behavior Disorder in Subjects With Dementia (DLB or PDD)	**Completed**	No	Partly	*Possible publication bias.*
NCT02789592	ClinicalTrials.gov	06/2016	07/2016	12/2019	Retrospective	Efficacy and Safety of Melatonin PR and Clonazepam in Patients With REM Sleep Behavior Disorder in Parkinson Disease	**Unknown**	No	No	*Possible publication bias.*
NCT02836743	ClinicalTrials.gov	19/07/2016	01/2016	31/12/2017	Retrospective	Effect of Slow-release Melatonin (Circadin®) Therapy on Idiopathic RBD: a Pilot Study	**Completed**	Yes	N.A.	
NCT02871427	ClinicalTrials.gov	18/08/2016	20/10/2016	17/01/2019	Prospective	Open-label Study of Nelotanserin in Lewy Body Dementia With Visual Hallucinations or REM Sleep Behavior Disorder	Terminated	No	No	Terminated due to changes to study drug development program.
NCT03255642	ClinicalTrials.gov	21/08/2017	09/11/2017	30/12/2019	Prospective	Efficacy and Safety of Melatonin and Clonazepam for IRBD	Recruiting	N.A.	N.A.	Trial ongoing past expected completion date.
RBR-5fwhf7	Brazilian Registry of Clinical trials (REBEC)	22/11/2017	01/08/2017	01/01/2018	Retrospective	Canabidiol in the treatment of sleep disorder associated with Parkinson's Disease	Recruiting	N.A.	N.A.	Trial ongoing past expected completion date.
ChiCTR1800017395	Chinese Clinical Trial Registry (ChiCTR)	28/07/2018	01/09/2018	31/12/2020	Prospective	Clinical research about neuroprotection of idebenone on rapid eye movement sleep behaviour disorder	Recruiting	N.A.	N.A.	Trial ongoing.
UMIN000034492	Japan Primary Registries Network (JPRN)	15/10/2018	15/10/2018 (anticipated)	Not reported	Prospective	The effect of Orexin receptor antagonist Suvorexant on REM sleep behaviour disorder using Escitalopram (2)	Not yet Recruiting	N.A.	N.A.	Trial not yet recruiting as per 10/2018.

NCT04006925	ClinicalTrials.gov	05/07/2019	10/10/2019	01/12/2020	Prospective	Treatment of REM Sleep Behavior Disorder (RBD) With Sodium Oxybate	Recruiting	N.A.	N.A.	Trial ongoing.
KCT0004317	Clinical Research Information Service (CRIS) of Korea	25/09/2019	02/03/2020 (anticipated)	31/12/2025	Prospective	Effects of Donepezil or Rivastigmine in Patients with idiopathic REM Sleep Behavior Disorder Patients	Not yet recruiting	N.A.	N.A.	Trial ongoing.
IRCT20170821035819N3	Iranian Registry of Clinical Trials (IRCT)	16/02/2020	22/06/2019	20/02/2020	Retrospective	Comparison of the effect of Melatonin and Clonazepam on the REM sleep behavior disorder of patients with Parkinson's disease	**Completed**	No	No	Investigators may be in the process of publishing the findings. RBD listed as a secondary outcome.

NOTES: The search was conducted on the International Clinical Trials Registry Platform of the World Health Organisation (apps.who.int) on 20 November 2020 using ("REM sleep behavior disorder" OR "RBD") as search terms. The search resulted in 77 listed trials, of which 23 potentially eligible trials were selected based on title screening. Following full registration screening, a total of 17 trials were deemed eligible for assessment of publication bias and added to this Table. Three trials from Japan (JPRN-UMIN0000/20313/27333/37876) were excluded as the participants only took the investigational drug on a single night, and three trials from China (NCTR0/4152655/4534023 and ChiCTR2000037624) were excluded for not targeting symptomatic RBD.

Supplementary Materials: Brief descriptions of the existing evidence for the alternative treatments trialled to date in older adults to treat RBD

Title: A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: Time for more and larger randomized placebo-controlled trials.

Authors: Moran Gilat PhD, Nathaniel Marshall PhD, Dries Testelmans MD PhD, Bertien Buyse MD PhD, Simon JG Lewis MD PhD

Corresponding author:
Dr Moran Gilat PhD
Email: moran.gilat@kuleuven.be

Table of content

1. Benzodiazepines

1.1 - Temazepam (Table S4)

Temazepam is an intermediate benzodiazepine often prescribed to aid sleep continuity. It has a shorter 10-hour elimination half-life, compared to 40-hours for clonazepam, though this is still longer than the average sleep duration, especially in the elderly [1]. There are three reports of temazepam use for RBD. One patient with iRBD showed clear improvements [2], while one patient with iRBD and major depression (MD) [3], as well as another RBD patient with a possible condition besides RBD [4], reported no benefits. No comparative studies have been performed for temazepam.

1.2 - Zopiclone (Table S5)

Zopiclone is a drug of the cyclopyrrolone class, which has similar effects on GABAergic receptors as benzodiazepine drugs. Zopiclone has a much shorter 5-hour elimination half-life, and has therefore been proposed for RBD in order to limit hangover effects the next morning [4]. The clinical effects of zopiclone were reported for a total of 12 patients, two with iRBD [2, 5], one with iRBD plus MD [3] and 9 with mixed conditions [4]. Of these, 7 (58.3%) reported clear benefits, while 5 (41.7%) reported no benefits (*Table S12*). No comparative studies have been performed for zopiclone.

1.3 - Other benzodiazepines (Table S6)

Anderson et al. (2009) achieved symptom control in one RBD patient who was refractory to different kinds of monotherapy by administering a combination of temazepam plus zopiclone [4]. However, the dosage and duration of the treatment were not reported nor was it reported whether this patient had any other condition besides RBD. Triazolam treatment was trialed by Olson et al. (2000) in two RBD patients refractory to clonazepam and with unknown conditions besides RBD [6]. One of them reported clear benefits whereas the results in the other were uncertain. Fernandez-Acros et al. (2016) reported that 14 patients with mixed conditions besides RBD had no benefit from benzodiazepines other than clonazepam, without reporting which drugs were trialled or for how long [7]. Shinno et al. (2008) reported no benefits in 1 iRBD

patient with either 5mg of nitrazepam or bromazepam treatment [8]. Schenck et al. (1986) reported that two patients with iRBD did not benefit from alprazolam 0.5mg [9]. Finally, Escriba et al. (2016) reported to have effectively treated RBD using benzodiazepines 0.5-2mg in one RBD patient with an unknown condition, though they did not report which drugs were administered and for how long [10]. Out of a total of 22 patients, 86.4% reported no benefits. No comparative studies have been performed.

2. Melatonin agonists

2.1 - Ramelteon (Table S9)

Ramelteon is a melatonin MT_1 and MT_2 receptor agonist with selectivity for MT_3 receptors as well. It gained particular interest in Japan where melatonin is not a formally approved drug, whereas ramelteon got approved for treatment of insomnia [11]. Kashihara et al. (2016) noted a significant reduction on the Japanese version of the RBD screening questionnaire (RBDQ-JP) across 24 PD patients with probable RBD who took 8mg of ramelteon for 12 weeks as compared to baseline, though surprisingly a reduction on the RBDQ-JP was also seen in another 11 PD patients without probable RBD [12]. The exact number of responders was not reported and the study was open-label. Another prospective open-label study further showed that 10 out of 12 patients with iRBD reported no benefits from 8mg ramelteon and also no clear improvements on RSWA or RBSS on PSG were found [11]. The treatment duration was not reported. Two earlier case-reports (*Table S9*) noted beneficial effects from 8mg of ramelteon to reduce RBD in 2 DLB patients [13], one MSA patient, and one PD patient [14]. Across the 16 patients with RBD for whom clinical responsiveness was reported, 5 (31.25%) indicated clear benefits, 1 partial benefits (6.25%), and 10 no benefit (62.5%) (*Table S9*). Only mild adverse effects were noted in 8 out of the 51 patients taking ramelteon (including patients without RBD), rendering it a relatively safe treatment option to trial in patients for whom melatonin is not available, though the effectiveness appears limited and a placebo-controlled RCT is lacking as of yet.

2.2 - Agomelatine (Table S10)

Agomelatine is an atypical antidepressant, which act as a melatonin (MT_1 and MT_2) agonist and a serotonin receptor antagonist. Bonakis et al. (2012) describe three drug-naïve patients with PSG confirmed iRBD who reported to benefit from agomelatine (25-50mg) treatment for up to 6 months of follow-up [15]. Dream content was also reported to have become more pleasant. A repeated PSG after 6 months of treatment revealed a reduction in tonic RSWA in 2 out of the 3 patients, though this could not be statistically compared and there was no control condition [15]. No comparative studies have been performed.

3. Dopamine + agonist

3.1 - Levodopa (Table S11)

Levodopa is the mainstay dopamine replacement treatment for people with PD and highly effective to reduce cardinal motor symptom severity. Evening dose or controlled-release levodopa administration overnight may also reduce nocturnal akinesia, which could indirectly lead to improved sleep quality [16]. It follows that the effect of levodopa on RBD has been mainly tested in PD patients, but so far only in three retrospective studies and 1 case report. Fernandez-Acros et al. (2016) noted that 1 patient with RBD did not benefit from levodopa-carbidopa [7]. The diagnosis of the patient and treatment dosage used were not reported. Bonakis et al. (2009A) reported that 3 patients with PD and 3 patients with iRBD benefited from levodopa treatment, though the dose or duration was not reported [2]. Tan et al. (1996) similarly reported a subjective benefit in 3 PD patients with probable RBD after levodopa, though again the dose and duration were not reported [17]. The largest sample was reported by Özekmeçi et al. (2005), who in contrast to the other reports, noted that levodopa 460±250mg did not prevent the occurrence of RBD in 35 PD patients with probable RBD, 12 of whom were taking levodopa monotherapy and 25 levodopa plus a dopamine-agonist (pergolide, lisuride or bromocriptine) [18]. No objective RBD outcomes were obtained and there was no control condition in any of the studies. Given that the large majority of PD patients are taking levodopa treatment while RBD is still frequently troublesome, makes it unlikely that levodopa mono-therapy is sufficient to treat RBD in these patients. No comparative studies have been performed.

3.2 - Dopamine agonist (Tables S12-S14)

Pramipexole is a dopamine D_2, D_3, and D_4 receptor agonist that is frequently used to treat PD motor symptoms, as well as restless legs syndrome (RLS) and periodic limb movements (PLMS). Sasai et al. (2012) noted a subjective improvement in RBD in 12 out of 15 iRBD patients with PLMS of whom 10 also reported a reduction in disturbed dreaming [19]. No change in RSWA was noted on pramipexole as compared to baseline. The treatment dosage and duration were not fixed and the study was rated to be of poor quality (*Table 1*). Similarly, Fantini et al. (2003) reported that 5 out of 8 iRBD patients benefitted from pramipexole as based on subjective rating [20]. They also noted reduced DEB on PSG, though surprisingly the RSWA was increased on pramipexole treatment compared to baseline. The treatment duration was also not fixed [20]. Fernandez-Acros et al (2016) reported pramipexole (dosage unknown) did not reduce RBD in 1 patient with a possible secondary diagnosis (not reported) [7]. Kumru et al. (2008) further showed that the addition of pramipexole 0.54mg per night for 3 months did not resolve subjective or objective RBD in 11 PD patients with RBD on otherwise levodopa monotherapy [21]. The large majority of patients (n=81) reported to date, however, were iRBD cases who's medical histories were retrospectively studied by Sasai et al. (2013) [22], while one other case study reported the clinical effectiveness of pramipexole of another 10 patients with mixed conditions besides their RBD [23]. Taken together, the clinical effect of pramipexole was reported for a total of 126 patients, with 56.3% reporting clear benefits, 3.2% partial benefits and 40.5% no benefits (*Table S12*).

Ropinirole is another dopamine D_2, D_3, D_4 receptor agonist used to treat PD and RLS. It has been trialed for RBD in just three studies, namely one prospective open-label study whereby 5 PD patients reported no benefit from a prolonged-release formulation [24], one retrospective study reporting that one RBD patient did not benefit (dosage and formulation not reported) [7], and one case report on an iRBD patient plus palatal tremor with ataxia [25] reporting partial benefit from an immediate release formulation (*Table S13*).

A rotigotine patch (12.4±4.3mg) was reported to be clinically effective in 7 out of 11 PD patients in a prospective open-label study, though no differences in DEB or RSWA were noted on PSG [26] (*Table S14*). This open-label level II-B study was also rated to be of poor quality (*Table 1*). Taken together, dopamine agonists have offered mixed results for reducing RBD. No RCT has been conducted for dopamine agonists.

4. Anticholinergic

4.1 - Donepezil (Table S15)

Donepezil is an acetylcholinesterase inhibitor commonly prescribed to support mental functions in people with dementia, such as Alzheimer's disease (AD) or DLB. It gained interest after Ringman et al. (2000) reported three patients, one young adult, one DLB patient and one patient with probable AD, experienced partial improvement of their RBD after taking donepezil 10-15mg [27]. After this, donepezil was trialed in two other case reports on 4 DLB patients of whom 1 reported clear benefit [28], 1 partial benefit [29], and 2 no benefit [28]. Finally, Boeve et al. (2003) provided an anecdotal account that in their clinical experience with over 50 DLB patients, none reported an improvement of RBD after donepezil treatment [30]. As such, only 1.8% of cases published to date reported a clear benefit, 5.4% a partial benefit and 92.8% no benefit from donepezil for reducing RBD. No comparative studies have been performed.

4.2 - Rivastigmine (Table S16)

Rivastigmine is another acetylcholinesterase inhibitor prescribed to support mental functions in people with dementia. Two RCT's and one case report have trialed rivastigmine to treat RBD. Brunetti et al. (2014) conducted a single (patient)-blinded RCT with a cross-over design to assess whether 30 days of 4.6mg rivastigmine per 24hours (patch) would reduce RBD, as compared to a similar period of matched placebo, in 25 patients with mild cognitive impairment and PSG confirmed RBD who were considered refractory to first-line clonazepam and melatonin treatments [31]. No objective outcomes were obtained, though the primary outcome was RBD frequency as recorded on an event diary by the bed-partners. Rivastigmine significantly reduced RBD frequency as compared to

placebo, with 18 patients being considered as responders (≤50% reduction in RBD frequency) [31]. Di Giacopo et al. (2012) conducted a similar, but double-blinded, crossover RCT to assess the effect of 4.6mg rivastigmine per 24 hours (patch) for 3 weeks over a matched placebo for 3 weeks in 12 PD patients with PSG confirmed RBD who were also refractory to first-line treatment options [32]. Two patients dropped-out, so treatment outcomes were reported for a total of 10 patients. The primary outcome was RBD frequency as noted on a dairy by the bed-partners, while objective RSWA on PSG was obtained pre- and post the intervention periods for a subset of 4 patients. A significant reduction in RBD frequency was found on rivastigmine compared to placebo, and the reduction was more consistent in patients with greater RBD frequencies at baseline. No change in RSWA was noted in the subset of 4 patients with repeated PSG's. Seven patients could be considered as responders (>50% reduction), 1 partial responder and 2 non-responders [32]. Importantly, however, a case study by Yeh et al. (2010) reported that rivastigmine might have induced RBD in a patient with AD [33]. Taken together, 69.4% of RBD patients reported benefits, 2.8% partial benefits, and 27.8% no benefit from rivastigmine. However, as there is at least one other report of rivastigmine possibly inducing RBD in a patient with probable AD [34], cholinesterase inhibitors should only be trailed in patients who are refractory to first-line treatments and great care should be taken not to induce or worsen RBD in patients with dementia.

5 - NMDA antagonist *(Memantine)*

Larsson et al. (2010) reported a secondary outcome related to RBD, which was obtained from a previously published double-blinded RCT on the effectiveness of 24 weeks of 5-20mg memantine, a glutamatergic *N*-methyl-D-aspartate receptor antagonist, for treating dementia in people with PD or DLB, as compared to matched placebo [35]. One of the outcomes of that trial was the Stavanger Sleep Questionnaire, which contains a single question addressing probable RBD, namely "*Is the patient physically active during sleep?*" with possible answers being either no, mild, moderate or severe [35]. A total of 27 patients were randomized to memantine, and 30 to placebo. Ten patients dropped-out, leaving 25 in the memantine group and 22 in the placebo at the end of the study. At

baseline, the overall frequency of probable RBD was 54%. The exact number of responders was not reported, though the authors noted that the number of patients reporting no or only mild probable RBD increased over time, while the number of patients reporting moderate probable RBD decreased over time in the memantine group, but not in the placebo group. There was also a significant between-group difference at the end of the intervention, indicating a favorable effect for memantine over placebo [35]. However, it is important to note that this study is based solely on secondary outcomes from a previously published RCT, with the RBD-related outcome being a single questionnaire item on physical activity during sleep, which may, or may not have been specific to RBD [35]. Therefore, no recommendation for memantine can be made based on the outcomes of this study alone.

6. Gabapentinoid *(Tables S17-S18)*

Gabapentin is an anti-epileptic drug used to prevent seizures or treat nerve pain. A case study on a single iRBD patient with MD reported no benefits from gabapentin on RBD [3]. Another patient with a possible condition besides RBD (unreported), and who may have been <50 years of age (unreported), also did not benefit from gabapentin in a retrospective observational study [4]. Neither of these studies reported the dosage used. A retrospective study by Escriba et al. (2016) reported benefits of 300-800mg gabapentin in 12 out of 14 patients with mixed conditions besides RBD, though the other 2 patients reported no benefits [10]. The same authors also reported that 2 out of 3 of their patients with mixed conditions besides RBD benefited from 75-150mg pregabalin, which is another drug of the gabapentinoid class, while the third patient did not benefit [10]. Gabapentinoids have several possibly serious side effects associated to them and their use should therefore be monitored with great care. Taken together, there is insufficient evidence to recommend these drugs for treating RBD, and if trialled, the patient should be monitored carefully.

7. Noradrenergic agonist *(Table S19)*

Clonidine is a selective partial receptor agonist for central and peripheral noradrenaline-releasing neurons, by which clonidine stimulation inhibits

noradrenaline release. It was shown to reduce REM sleep time and phasic EMG activity during REM sleep in healthy adults [5, 36]. It was thus hypothesized that clonidine would directly influence the maintenance of REM sleep muscle atonia via noradrenergic transmission in patients with RBD [5]. Only two cases of clonidine use are reported. Nash et al. (2003) reported one iRBD patient who benefited from a treatment plan of one week with clonidine (100-200μg) interspersed by one week without treatment [5], while Shneerson et al. (2009) noted no benefit from clonidine in a single iRBD patient with MD (dose and duration not reported) [3]. No objective RBD outcomes were assessed and there was no control condition. Importantly, there is a report of mirtazapine, which is an presynaptic receptor antagonist leading to increased noradrenergic neurotransmission, inducing RBD in 4 patients with PD [37], which together with the clinical response of a noradrenergic agonist in at least one iRBD patient may suggest that the noradrenergic circuit is implicated in the pathophysiology of RBD [5]. However, the current body of evidence is too limited to make a risk-benefit assessment for the use of noradrenergic agonists for treating RBD.

8. Antidepressants (per class)

There have been several case reports [38] and retrospective studies [39] indicating that antidepressant drugs are associated with an increased risk-ratio for inducing or aggravating RBD symptoms. The clinical evidence shown below from studies attempting to treat RBD with such drugs should therefore be interpreted with caution.

8.1 - SSRI (Table S20)

The only prospective study conducted to date on any antidepressant or antipsychotic drug tested the effect of paroxetine (10-40mg), a selective serotonin-reuptake inhibitor (SSRI), for reducing RBD in 19 patients with PSG confirmed iRBD presumably by reducing the amount of REM sleep [40]. The study was open-label and there was no control condition (*Table 1*). Sixteen of the iRBD patients reported partial improvements, whereas severe RBD persisted in three patients. Side effects were noted, including nausea, dizziness, and diarrhea, which led to treatment cessation in two patients [40]. Two other case studies

also reported mixed results for paroxetine, with one iRBD patient reporting partial benefits with 10mg [41], whilst another reported no benefits with 20mg [8]. Two case studies further reported that fluvoxamine (50mg) [41] and trazodone (dosage not reported) [5], both SSRI's, did not improve RBD in single iRBD patients. A final case study reported no benefits following sertraline (100-150mg) treatment in an RBD patient with OSA, major depression and mild cognitive impairment [42]. Taken together, across a total of 24 patients with RBD, SSRI's led to partial benefits in 70.8% and no benefits in 29.2%. No comparative studies have been conducted for SSRI's, whilst there are reports of SSRI's aggravating RBD [38], indicating these drugs are not favourable for treating RBD.

8.2 - Tricyclic antidepressants (Table S21)

One case study reported beneficial effects following carbamazepine 100mg reduced RBD in a single iRBD case [43], while a restrospective account on another patient reported no benefit from carbamazepine (dosage not reported) [7]. Fernandez-Acros et al. (2016) further reported that another patient did not benefit from imipramine (dosage not reported) [7]. Yet another case study reported that desipramine (50-250mg) was also not effective in two iRBD patients [9]. No benefits were also reported following amitriptyline in two iRBD patients reported in two case studies, one administering 50 mg [5], and one not reporting the dosage used [9]. Similarly, clomipramine (100mg) was not effective in a single iRBD patient [44] and dothiepin (150mg) did not reduce RBD in a single patient with RBD, MD and MCI [42]. Taken together, 8 out of 9 patients reported no benefits from tricyclic antidepressants. No comparative studies have been conducted.

8.3 - Other antidepressants (Table S22)

One case study reported that nefazodone (dosage not reported), an atypical serotonin antagonist and reuptake inhibitor, was not effective in a single iRBD patient [5]. Similarly, mianserin (10mg) [41], a tetracyclic antidepressant, as well as venlafaxine (dosage not reported) [5], a serotonin-norepinephrine-dopamine reuptake inhibitor, were reported not to be effective in two single iRBD patients.

Critically, tandospirone, an antidepressant drug of the azapirone class, was shown to aggravate RBD symptoms in a single iRBD patient [41], and mirtazapine, a noradrenergic and specific serotonin antagonist (NaSSA) was shown to induce RBD in four PD patients with RBD [37]. Taken together, none of the 8 patients in total reported benefits, while antidepressants can aggravate or induce RBD in some patients. No comparative studies have been conducted.

9. Antipsychotics (*Table S23*)

Clozapine, an atypical antagonist that binds to serotonin and dopamine receptors and may interact with GABA receptors, was reported to be beneficial for RBD in two patients with dementia and partially effective in another patient with RBD and dementia [6, 45]. The dosages and durations of the intervention were not reported. Quetiapine 25mg, another atypical antagonist of serotonin, dopamine and norepinephrine receptors, was reported to be beneficial in one patient with a possible condition besides RBD (not reported) [46], while the same dosage was not effective in two cancer patients with RBD [47]. Haloperidol, a butyrophenone type antipsychotic, was reported not to be effective in three patients, one with RBD and dementia [48], one with RBD and a possible secondary condition (not reported) [7], and one with RBD and cancer [47]. No comparative studies have been conducted for any of the antipsychotics.

10. Anticonvulants (*Table S24*)

A retrospective account by Fernandez-Acros et al. (2016) indicates that 3 patients with RBD did not benefit from anticonvulants, namely phenobarbital, lamotrigine, or oxcarbazepine [7]. The diagnosis of the patients, dosages used, and treatment durations were not reported. No comparative studies exist.

11. Sodium Oxybate *(Table S25))*

Sodium oxybate (SO) influences gamma-aminobutyric acid-B receptors and is used to form gamma-hydroxybutyric acid (GHB). Despite the risk for illicit misuse, SO is a registered drug for treating cataplexy and excessive somnolence in narcolepsy patients [49], possibly by enhancing slow-wave EEG during sleep, though it also leads to hypothermia and hypolocomotion [50] and may alter

dream mentation [49]. In animal models, low dosage of SO inhibits dopamine signalling, while this is increased at higher dosages [50, 51]. To date, five clinical cases have been published whereby SO was administered to treat five patients with mixed conditions besides RBD. One study did not report the dosage used, whilst the dosage in the other 4 patients ranged from 4.5-6mg. SO was considered highly effective in all patients. Mogdaham et al. (2017) treated two iRBD patients, one of whom received melatonin 5mg plus pramipexole 0.45mg plus 4.5mg SO [49]. No worsening in symptom severity occurred after removal of melatonin, and hence the final treatment consisted of pramipexole plus SO. The other patient first received clonazepam 2mg plus melatonin 5mg, and next clonazepam 2mg plus pramipexole 0.36mg, both resulting only in temporal improvement. The patient was thus considered refractory to melatonin and pramipexole, and SO was later added to the clonazepam resulting in a sustained reduction of RBD [49]. Overall, the mechanism of action for SO remains elusive and no comparative studies have been conducted to assess the true efficacy of SO for reducing RBD. Particular care should be taken when attempting to treat PD patients with SO, given the possible influence on dopamine signalling.

11. Other drugs

11.1 - Yi-Gan San /Yokukansan (Table S26)

Yi-Gan San, otherwise known as Yokukansan, is an herbal medicine containing a mixture of herbal ingredients [8]. In Japan, Yi-Gan San is registered for treating insomnia, though its mechanisms of action for modulating sleep remain elusive [8, 52]. Shinno et al. (2008) first reported beneficial effects of 2.5mg Yi-Gan San for treating RBD in a patient with PSG confirmed iRBD [8]. Matsui et al. (2019) then retrospectively analysed the outcomes of Yi-Gan San in 36 iRBD patients, 17 of whom received monotherapy and 19 received add-on clonazepam and/or pramipexole (exact number of patients, treatment schemes and dosages not reported) besides Yi-Gan San [52]. Treatment response was assessed with the CGI scale. The outcomes of their study indicated that 12 out of 17 patients on monotherapy and 4 out of 19 receiving add-on therapy reported clear benefits [52]. Taken together, 45.9% of iRBD patients reported benefits from Yi-Gan San treatment, though no comparative studies exist to date.

11.2 - Cannabidiol (Table S27)

Chagas et al. (2014) published the only case series to date on the use of cannabidiol for treating RBD [53]. They presented the secondary outcomes from an RCT aimed at assessing the effect of cannabidiol to reduce psychosis in PD. After breaking the blind, the authors found that four of the PD patients enrolled in the cannabidiol group had probable RBD, which was confirmed with PSG in two. Three of them received 75mg of cannabidiol and one received 300mg for 6 weeks. RBD severity was clinically assessed by a neurologist specialized in sleep disorders. All four patients reported prompt and substantial improvements in their RBD after cannabidiol treatment [53]. No other comparative study exists and further research into the effectiveness and underlying mechanisms of this seemingly safe treatment option is needed.

11.3 - Cardiac drugs (Table S28)

Schenck et al. (1987) reported that a physician, other than the authors themselves, unsuccessfully attempted to treat RBD in an iRBD patient with metropolol and/or aspirin (dosages not reported) before referring the patient to the sleep clinic [48]. Currently, no indication exists that these drugs would reduce RBD.

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Supplementary Tables S1-S28: Number of clinical responders per drug type trialled to treat RBD in older adults to date.

Title: A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: Time for more and larger randomized placebo-controlled trials.

Authors: Moran Gilat PhD, Nathaniel Marshall PhD, Dries Testelmans MD PhD, Bertien Buyse MD PhD, Simon JG Lewis MD PhD

Corresponding author:
Dr Moran Gilat PhD
Email: moran.gilat@kuleuven.be

Table of content

Benzodiazepines

Table S1: Reports on the clinical effectiveness of *Clonazepam* for treating RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Shin, 2019	1	RCT	PD	19	Clonazepam (0.5)	PSG	10	3	6
Li, 2016	2	POS	IRBD	39	Clonazepam (0.125-3)	PSG	26	0	13
Iranzo, 2005	3	POS	IRBD	39	Clonazepam (0.25-CT)	PSG	32	6	1
Iranzo, 2005	3	POS	PD	45	Clonazepam (0.25-CT)	PSG	38	7	0
Iranzo, 2005	3	POS	MSA	26	Clonazepam (0.25-CT)	PSG	20	6	0
Lapierre, 1992	4	POS	IRBD	5	Clonazepam (0.5 - 2)	PSG	0	5	0
Lee, 2020	5	RMH	Mixed	171	Clonazepam (1 ± 0.5)	PSG	147	0	24
Abenza Abildúa, 2019	6	RMH	Mixed*	22	Clonazepam (NR)	PSG	19	0	3
Fernandez-Acros, 2016	7	RMH	Mixed	183	Clonazepam (0.25-4)	PSG	92 (~)	52 (~)	39
McCarter, 2013	8	RMH	Mixed*	18	Clonazepam (<0.5-3)	PSG	3	11	4
Sasai, 2013	9	RMH	IRBD	17	Clonazepam (0.6 ± 0.3, 0.25-2)	PSG	15	0	2
Anderson, 2009	10	RMH	Mixed*	36	Clonazepam (0.25-4)	PSG	15	0	21
Bonakis, 2009A	11	RMH	Mixed	26	Clonazepam (NR)	PSG	17	0	9
Lin, 2009	12	RMH	Mixed*	44	Clonazepam (0.5-2.0)	PSG	0	41	3
Wing, 2008	13	RMH	Mixed*	71	Clonazepam (1.4 ± 1.4)	Clinical	62	0	9
Özekmekçi, 2005	14	RMH	PD	35	Clonazepam (0.5-1)	Clinical	35	0	0
Boeve, 2003	15	RMH	Mixed*	8	Clonazepam (0.5-1)	PSG	0	0	8
Olson, 2000	16	RMH	Mixed	38	Clonazepam (0.25-1.5)	PSG	21	12	5
Boeve, 1998	17	RMH	DLB	11	Clonazepam (NR)	PSG	10	0	1
Schenck, 2013, 1996[#]	18, 19	RMH	Mixed	27	Clonazepam (NR)	PSG	24	0	3
Schenck, 1993	20	RMH	Mixed*%	67	Clonazepam (NR)	PSG	53	8	6
Schenck, 1991	21	RMH	Mixed[$]	16	Clonazepam (0.25-2.0)	Clinical, some had	12	2	2

						PSG			
Moghadam, 2017	22	CR	IRBD	2	Clonazepam (2)	PSG	0	0	2
Zhou, 2017	23	CR	IRBD with childhood onset POD	1	Clonazepam (0.5)	PSG	1	0	0
Liebenthal, 2016	24	CR	PD with DBS + mild OSA	1	Clonazepam (1)	PSG	0	0	1
Coelho, 2015	25	CR	DLB+OSA	1	Clonazepam (NR)	PSG	1	0	0
Cosentino, 2014	26	CR	Parkinsonism+NT1	1	Clonazepam (0.5)	PSG	1	0	0
Weeks, 2014	27	CR	IRBD	1	Clonazepam (1)	PSG	1	0	0
Nomura, 2013	28	CR	PD	1	Clonazepam (1)	PSG	0	0	1
Di Giacopo, 2012	29	CR	PD	12	Clonazepam (≤2)	PSG	0	0	12
Lo Coco, 2012	30	CR	FTD	1	Clonazepam (1)	PSG	1	0	0
Shinno, 2010	31	CR	Cancer Patients¥	3	Clonazepam (0.5)	PSG	3	0	0
Bonakis, 2009B	32	CR	IRBD+PAPT	1	Clonazepam (0.75)	PSG	0	1	0
Shneerson, 2009	33	CR	IRBD	1	Clonazepam (NR)	PSG	0	0	1
Xi, 2009	34	CR	Pontine stroke	1	Clonazepam (0.25)	PSG	1	0	0
Oguri, 2008	35	CR	IRBD+Parkinsonism	1	Clonazepam (NR)	PSG	1	0	0
Shinno, 2008	36	CR	IRBD	2	Clonazepam (0.5-1)	PSG	0	1	1
Boeve, 2007	37	CR	IRBD	1	Clonazepam (0.5)	PSG	1	0	0
Manni, 2005	38	CR	IRBD	2	Clonazepam (0.5-1)	PSG	2	0	0
Thomas, 2004	39	CR	IRBD	1	Clonazepam (0.5)	Clinical	1	0	0
Iranzo, 2003	40	CR	Spinocerebellar ataxia type 3*	3	Clonazepam (1)	PSG	2	1	0
Massironi, 2003	41	CR	DLB	3	Clonazepam (0.3-0.5)	Clinical	2	0	1
Nash, 2003	42	CR	IRBD	1	Clonazepam (NR)	PSG	0	0	1

Daly, 2002	43	CR	IRBD	2	Clonazepam (1)	Clinical	0	2	0
Oksenberg, 2002	44	CR	IRBD + PLMS and/or OSA	6	Clonazepam (0.5)	PSG	4	0	2
Kimura, 2000	45	CR	Pontine ischemic lesion	1	Clonazepam (0.25)	PSG	1	0	0
Ringman, 2000	46	CR	IRBD	1	Clonazepam (1.5)	PSG	0	0	1
Schuld, 1999	47	CR	RBD + NT1 +PLMS	1	Clonazepam (0.5-1)	PSG	0	0	1!
Chiu, 1997	48	CR	IRBD	2	Clonazepam (0.75-1.25)	PSG	1	1	0
Morfis, 1997	49	CR	IRBD	1	Clonazepam (0.5-1)	PSG	1	0	0
Uchiyama, 1995	50	CR	IRBD	1	Clonazepam (0.5)	PSG	1	0	0
Schenck, 1987	51	CR	Mixed	5	Clonazepam (0.5)	PSG	5	0	0
Schenck, 1986	52	CR	IRBD	2	Clonazepam (0.5-1.5)	PSG	2	0	0
Total clinical effectiveness for Clonazepam (N subjects)							**684**	**159**	**183**
Total clinical effectiveness for Clonazepam (% subjects)							**66.7%**	**15.5%**	**17.8%**

NOTE: Scoring of effectiveness: YES = Responders - authors reported clear sustained benefits with no troublesome side-effects; PARTIAL = Partial responders - authors reported partial improvement with some RBD symptoms remaining or some non-troublesome adverse events; NO = Non-responders - patients and/or bed-partners reported no improvement or the drug had to be withdrawn or dosage changed due to troublesome side-effects. Mixed = Sample of interest consisted of a mixture of patients with a variety diagnoses besides RBD. Clinical = diagnosis of probable RBD based on clinical history or questionnaire data only; PSG = Polysomnography confirmed diagnosis of RBD. Dosage of treatment is presented as the range or mean ± SD. =One or more subjects could be <50 years of age; %=Sample includes six subjects with RBD + parasomnia overlap disorder and 3 subjects with a familial form of RBD with sleep walking, sleep terror, narcolepsy and periodic/aperiodic limb movements; #=Both papers describe the treatment outcomes on the same sample of RBD cases and are therefore listed together; $=Includes 1 RBD case with major depression disorder, 1 with a history of alcohol abuse, 1 with amphetamine drug abuse, 1 with chronic anxiety disorder, and 1 with recurrent major depression disorder and alcohol abuse whose parasomnia became worse during periods of alcohol abstinence. ¥ = Although RBD was confirmed with PSG, the RBD could have been of toxin-metabolic nature due to cancer treatment; !=Induced OSA; (~)=authors reported treatment was (partially) successful despite adverse events noted by some patients. Abbreviations: AD=Alzheimer's disease; CR=Case report; CT=Until clinical resolution or tolerability; DLB=Dementia with lewy bodies; FTD=Frontotemporal dementia; IRBD=idiopathic REM sleep behavior disorder; MSA=Multiple system atrophy; NR=Not reported; NT1=Narcolepsy Type 1; OSA=Obstructive sleep apnea; PAPT=Palatal tremor with ataxia; PD= Parkinson's disease; PLMS=Periodic limb movements;

POD=Parasomnia overlap disorder; POS=Prospective open-label study; PSG=Polysomnography; RCT=Randomised Controlled Trial; Ref=Reference; RMH=Retrospective medical history.

Table S2: Reports on the clinical effectiveness of *Clonazepam + Melatonin* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Fernandez-Acros, 2016	7	RMH	Mixed	24	CZP (NR) + MLT (NR)	PSG	NR	NR	NR
Lee, 2020	5	RMH	Mixed	1	CZP (NR) + MLT (NR)	PSG	1	0	0
McCarter, 2013	8	RMH	Mixed*	2	CZP (NR) + MLT (NR)	PSG	0	2	0
Boeve, 2003	15	RMH	Mixed*	7	CZP (0.5-1) + MLT (6-12)	PSG	2	3	2
Moghadam, 2017	22	CR	IRBD	1	CZP (2) + MLT (5)	PSG	0	0	1
Pierre-Justin, 2017	53	CR	Familial IRBD	1	CZP (2) + MLT (12)	PSG	0	1	0
Liebenthal, 2016	24	CR	PD with DBS + mild OSA	1	CZP (1) + MLT (12)	PSG	0	0	1
Total clinical effectiveness for Clonazepam + Melatonin (N subjects)							**3**	**6**	**4**
Total clinical effectiveness for Clonazepam + Melatonin (% subjects)							**23.1%**	**46.1%**	**30.8%**

***=One or more subjects could be <50 years of age. Abbreviations: CR=Case report; CZP=Clonazepam; DBS=Deep Brain Stimulation; IRBD=idiopathic REM sleep behavior disorder; MLT=Melatonin; NR=Not reported; OSA=Obstructive sleep apnea; PD= Parkinson's disease; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.**

Table S3: Reports on the clinical effectiveness of *Clonazepam + Other add-on therapies* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Lee, 2020	5	RMH	Mixed	14	CZP (NR) + Carbamezapine (NR)	PSG	6	0	8
Lee, 2020	5	RMH	Mixed	3	CZP (NR) + Zolpidem (NR)	PSG	2	0	1
Lee, 2020	5	RMH	Mixed	4	CZP (NR) + Carbamezapine (NR) + Zolpidem (NR)	PSG	0	0	4
Abenza Abildúa, 2019	6	RMH	IRBD+ Insomnia	1	CZP (NR) + Trazodone (NR)	PSG	1	0	0
Abenza Abildúa, 2019	6	RMH	IRBD+PLMS	2	CZP (NR) + Gabapentin (NR)	PSG	2	0	0
Sasai, 2013	9	RMH	IRBD	33	CZP (0.7 ± 0.3) + Pramipexole (0.3 ± 0.1)	PSG	25	0	8
Anderson, 2009	10	RMH	Mixed*	1	CZP (NR) + MLT (NR) + Gabapentin (NR)	PSG	1	0	0
Anderson, 2009	10	RMH	Mixed*	1	CZP (NR) + Zoplicone (NR)	PSG	1	0	0
Moghadam, 2017	22	CR	IRBD	1	CZP (2) + Carbamazepine (400)	PSG	0	0	1
Moghadam, 2017	22	CR	IRBD	1	CZP (2) + Lamotrigine (25)	PSG	0	0	1
Moghadam, 2017	22	CR	IRBD	1	CZP (2) + Pramipexole (0.36)	PSG	0	0	1
Moghadam, 2017	22	CR	IRBD	1	CZP (2) + Sodium Oxybate (3)	PSG	1	0	0
Liebenthal, 2016	24	CR	PD with DBS + mild OSA	1	CZP (1) + MLT (12) + Ramelteon (NR) + Prazosin (NR) +	PSG	0	0	1

					Cyproheptadine (NR)				
Yeh, 2010	54	CR	AD	1	CZP (0.5) + Rivastigmine (4.5)	PSG	1	0	0
Shinno, 2008	36	CR	IRBD	2	CZP (0.25-0.5) + Yi-Gan San (7.5)	PSG	1	1	0
Chung, 1994	55	CR	IRBD	1	CZP (0.75) + Clomipramine (75)	PSG	0	1	0
Clarke, 2000	56	CR	OSA + MD + MCI	1	CZP (0.75) + Setraline (150)	PSG	0	1	0
Total clinical effectiveness for Clonazepam + Add-on therapies (N subjects)							**41**	**3**	**25**
Total clinical effectiveness for Clonazepam + Add-on therapies (% subjects)							**59.4%**	**4.4%**	**36.2%**

***=One or more subjects could be <50 years of age. Abbreviations: AD=Alzheimer's Disease; CR=Case report; CZP=Clonazepam; DBS=Deep Brain Stimulation; IRBD=idiopathic REM sleep behavior disorder; MCI=Mild Cognitive Impairment; MLT=Melatonin; NR=Not reported; OSA=Obstructive sleep apnea; PD= Parkinson's disease; PLMS=Periodic limb movements; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.**

Table S4: Reports on the clinical effectiveness of *Temazepam* for reducing RBD

Study ***(First author, year)***	**Ref**	**Study design**	**Clinical population**	**Total N**	**Treatment (mg/day)**	**RBD screening**	**Clinical effectiveness (N subjects)**		
							YES	**PARTIAL**	**NO**
Anderson, 2009	10	RMH	Mixed*	1	Temazepam (NR)	PSG	0	0	1
Bonakis, 2009A	11	RMH	IRBD	1	Temazepam (NR)	PSG	1	0	0
Shneerson, 2009	33	CR	IRBD + MD	1	Temazepam (NR)	PSG	0	0	1
Total clinical effectiveness for Temazepam (N subjects)							**1**	**0**	**2**
Total clinical effectiveness for Temazepam (% subjects)							**33.3%**	**0%**	**66.7%**

***=One or more subjects could be <50 years of age. Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MD=Major Depression; NR=Not reported; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.**

Table S5: Reports on the clinical effectiveness of *Zopiclone* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Anderson, 2009	10	RMH	Mixed*	9	Zopiclone (3.75-7.5)	PSG	6	0	3
Bonakis, 2009A	11	RMH	IRBD	1	Zopiclone (NR)	PSG	1	0	0
Shneerson, 2009	33	CR	IRBD+MD	1	Zopiclone (NR)	PSG	0	0	1
Nash, 2003	42	CR	IRBD	1	Zopiclone (NR)	PSG	0	0	1
Total clinical effectiveness for Zopiclone (N subjects)							**7**	**0**	**5**
Total clinical effectiveness for Zopiclone (% subjects)							**58.3%**	**0%**	**41.7%**

NOTE: Zopiclone is a drug of the cyclopyrrolone class, which has similar GABAergic effects as benzodiazepines; *=One or more subjects could be <50 years of age. Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MD=Major Depression; NR=Not reported; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Table S6: Reports on the clinical effectiveness of *Other benzodiazepines* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Escriba, 2016	57	RMH	Mixed	1	'Benzodiazepines' (0.5-2)#	PSG	1	0	0
Anderson, 2009	10	RMH	Mixed*	1	Temazepam + Zopiclone (NR)	PSG	1	0	0
Olson, 2000	16	RMH	Mixed*	2	Triazolam (NR)	PSG	1	0	1
Fernandez-Acros, 2016	7	RMH	Mixed	14	'Benzodiazepines' (NR)	PSG	0	0	14
Shinno, 2008	36	CR	IRBD	1	Nitrazepam (5)	PSG	0	0	1
Shinno, 2008	36	CR	IRBD	1	Bromazepam (5)	PSG	0	0	1
Schenck, 1986	52	CR	IRBD	2	Alprazolam (0.5)	PSG	0	0	2
Total clinical effectiveness for Other benzodiazepines (N subjects)							**3**	**0**	**19**
Total clinical effectiveness for Other benzodiazepines (% subjects)							**13.6%**	**0%**	**86.4%**

 # - Authors do not report which benzodiazepines were administered; *=One or more subjects could be <50 years of age. Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; NR=Not reported; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Melatonin + agonist

Table S7: Reports on the clinical effectiveness of *Melatonin* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Gilat, 2020	58	RCT	PD	15	PR-Melatonin (4)	PSG	2	3	10
Jun, 2019	59	RCT	IRBD	16	PR-Melatonin (2-6)	PSG	4	3	9
Kunz, 2010	60	RCT	Mixed*	8	Melatonin (3)	PSG	7	1	0
Takeuchi, 2001	61	POS	NR	15	Melatonin (3-9)	PSG	3	10	2
Kunz, 1999	62	POS	Mixed*	6	Melatonin (3)	PSG	5	1	0
Abenza Abildúa, 2019	6	RMH	Mixed*	7	Melatonin (NR)	PSG	3	0	4
Escriba, 2016	57	RMH	Mixed	5	PR-Melatonin (2)	PSG	4	0	1
Fernandez-Acros, 2016	7	RMH	Mixed	5	Melatonin (1.9-9)	PSG	0	1	4
McCarter, 2013	8	RMH	Mixed*	25	Melatonin (<6-25)	PSG	3	15	7
Anderson, 2009	10	RMH	Mixed*	2	Melatonin (10)	PSG	2	0	0
Bonakis, 2009A	11	RMH	IRBD	2	Melatonin (NR)	PSG	2	0	0
Bonakis, 2009A	11	RMH	MSA	1	Melatonin (NR)	PSG	1	0	0
Boeve, 2003	15	RMH	Mixed*	9	Melatonin (3-12)	PSG	5	0	4
Feemster, 2019	63	CR	PTSD+OSA	1	Melatonin (3-6)	PSG	0	0	1
Xu, 2019	64	CR	PD with childhood onset POD	1	Melatonin (3)	PSG	1	0	0
Kunz, 2018	65	CR	PD	1	PR-Melatonin (2)	PSG	1	0	0
Pierre-Justin, 2017	53	CR	Familial IRBD	1	Melatonin (6)	PSG	1	0	0
Wierzbicka, 2017	66	CR	IRBD	1	Melatonin (5)	PSG	0	1	0
Felix, 2016	67	CR	OSA + Pons cavernoma	1	Melatonin (NR)	PSG	0	1	0
Di Giacopo, 2012	29	CR	PD	12	Melatonin (≤5)	PSG	0	0	12
Shneerson, 2009	33	CR	IRBD + MD	1	Melatonin (NR)	PSG	0	0	1

	68	CR	probable AD + OSA	1	Melatonin (10)	PSG	0	1	0
Kunz, 1997	69	CR	IRBD	1	Melatonin (3)	PSG	1	0	0
Total clinical effectiveness for Melatonin (N subjects)							**45**	**37**	**55**
Total clinical effectiveness for Melatonin (% subjects)							**32.9%**	**27.0%**	**40.1%**

***=One or more subjects could be <50 years of age. Abbreviations: AD=Alzheimer's Disease; CR=Case report; CZP=Clonazepam; DBS=Deep Brain Stimulation; IRBD=idiopathic REM sleep behavior disorder; MCI=Mild Cognitive Impairment; MLT=Melatonin; NR=Not reported; OSA=Obstructive sleep apnea; PD= Parkinson's disease; PLMS=Periodic limb movements; POD=Parasomnia Overlap Disoder; POS=Prospective open-label study; PR=Prolonged Release; PSG=Polysomnography; PTSD=Posttraumatic Stress Disorder; RCT=Randomised Controlled Trial; Ref=Reference; RMH=Retrospective medical history.**

Table S8: Reports on the clinical effectiveness of *Melatonin + Add-on therapies* for reducing RBD

Study ***(First author, year)***	**Ref**	**Study design**	**Clinical population**	**Total N**	**Treatment (mg/day)**	**RBD screening**	**Clinical effectiveness (N subjects)**		
							YES	**PARTIAL**	**NO**
Abenza Abildúa, 2019	6	RMH	IRBD	1	Melatonin + Gabapentin (NR)	PSG	NR	NR	NR
Bonakis, 2009B	32	CR	IRBD+PAPT	1	Melatonin (3) + Ropinorole (4)	PSG	0	1	0
Moghadam, 2017	22	CR	IRBD	1	Melatonin (5) + Pramipexole (0.45)	PSG	0	0	1
Moghadam, 2017	22	CR	IRBD	1	Melatonin (5) + Pramipexole (0.45) + Sodium Oxybate (4.5)	PSG	0	1	0
Total clinical effectiveness for Melatonin + Add-on therapies (N subjects)							**0**	**2**	**1**
Total clinical effectiveness for Melatonin + Add-on therapies (% subjects)							**0%**	**66.7%**	**33.3%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; NR=Not reported; PAPT=Palatal tremor with ataxia; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Table S9: Reports on the clinical effectiveness of *Ramelteon* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Esaki, 2016	70	POS	IRBD	12	Ramelteon (8)	PSG	1	1	10
Kashihara, 2016	71	POS	PD	24	Ramelteon (8)	Clinical	NR	NR	NR
Kasanuki, 2013	72	CR	DLB	2	Ramelteon (8)	Clinical	2	0	0
Nomura, 2013	28	CR	MSA	1	Ramelteon (8)	PSG	1	0	0
Nomura, 2013	28	CR	PD	1	Ramelteon (8)	PSG	1	0	0
Total clinical effectiveness for Ramelteon (N subjects)							**5**	**1**	**10**
Total clinical effectiveness for Ramelteon (% subjects)							**31.3%**	**6.2%**	**62.5%**

Abbreviations: CR=Case report; DLB=Dementia with lewy bodies; IRBD=idiopathic REM sleep behavior disorder; MSA=Multiple system atrophy; PD= Parkinson's disease; POS=Prospective open-label study; PSG=Polysomnography; Ref=Reference.

Table S10: Reports on the clinical effectiveness of *Agomelatine* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Bonakis, 2012	73	CR	IRBD	3	Agomelatine (25-50)	PSG	3	0	0
Total clinical effectiveness for Agomelatine (N subjects)							**3**	**0**	**0**
Total clinical effectiveness for Agomelatine (% subjects)							**100%**	**0%**	**0%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; PSG=Polysomnography; Ref=Reference.

Dopamine + agonist

Table S11: Reports on the clinical effectiveness of *Levodopa* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Fernandez-Acros, 2016	7	RMH	Mixed	1	Levodopa (NR)	PSG	0	0	1
Bonakis, 2009A	11	RMH	IRBD	3	Levodopa (NR)	PSG	3	0	0
Bonakis, 2009A	11	RMH	PD	3	Levodopa (NR)	PSG	3	0	0
Özekmekçi, 2005	14	RMH	PD	10	Levodopa (NR)	Clinical	0	0	10
Özekmekçi, 2005	14	RMH	PD	25	Levodopa (NR) + Dopamine agonist (NR)	Clinical	0	0	25
Tan, 1996	74	CR	PD	3	Levodopa (NR)	Clinical	2	1	0
Total clinical effectiveness for Levodopa (N subjects)							**8**	**1**	**36**
Total clinical effectiveness for Levodopa (% subjects)							**17.8%**	**2.2%**	**80%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; NR= Not Reported; PD= Parkinson's disease; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Table S12: Reports on the clinical effectiveness of *Pramipexole* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Sasai, 2012	75	POS	IRBD+PLMS	15	Pramipexole (0.21 ± 0.09, 0.125-1.5)	PSG	12	0	3
Kumru, 2008	76	POS	PD	11	Pramipexole (0.54 - CT)	PSG	0	0	11
Fantini, 2003	77	POS	IRBD	8	Pramipexole (0.5-1)	PSG	5	0	3
Fernandez-Acros, 2016	7	RMH	Mixed	1	Pramipexole (NR)	PSG	0	0	1
Sasai, 2013	9	RMH	IRBD	81	Pramipexole (0.2 ± 0.1, 0.125-1.5)	PSG	50	0	31
Schmidt, 2006	78	CR	Mixed	10	Pramipexole (0.89 ± 0.31, 0.25-1.5) evening	PSG	4	4	2

					dose				
Total clinical effectiveness for Pramipexole (N subjects)							**71**	**4**	**51**
Total clinical effectiveness for Pramipexole (% subjects)							**56.3%**	**3.2%**	**40.5%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; PD= Parkinson's disease; PLMS=Periodic limb movements; POS=Prospective open-label study; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Table S13: Reports on the clinical effectiveness of *Ropinirole* for reducing RBD

Study ***(First author, year)***	**Ref**	**Study design**	**Clinical population**	**Total N**	**Treatment (mg/day)**	**RBD screening**	**Clinical effectiveness (N subjects)**		
							YES	**PARTIAL**	**NO**
Dušek, 2010	79	POS	PD	5	PR-Ropinirole (17.2±6)	PSG	0	0	5
Fernandez-Acros, 2016	7	RMH	Mixed	1	Ropinirole (NR)	PSG	0	0	1
Bonakis, 2009B#	32	CR	IRBD+PAPT	1	Ropinirole (4)	PSG	0	1	0
Total clinical effectiveness for Ropinirole (N subjects)							**0**	**1**	**6**
Total clinical effectiveness for Ropinirole (% subjects)							**0%**	**14.3%**	**85.7%**

 # = Presumably the same IRBD+PAPT patient is also reported by Bonakis 2009A. Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; PAPT=Palatal tremor with ataxia; PD= Parkinson's disease; POS=Prospective open-label study; PSG=Polysomnography; Ref=Reference.

Table S14: Reports on the clinical effectiveness of *Rotigotine* for reducing RBD

Study ***(First author, year)***	**Ref**	**Study design**	**Clinical population**	**Total N**	**Treatment (mg/day)**	**RBD screening**	**Clinical effectiveness (N subjects)**		
							YES	**PARTIAL**	**NO**
Wang, 2016	80	POS	PD	11	Rotigotine (12.4 ± 4.3)	PSG	7	0	4
Total clinical effectiveness for Rotigotine (N subjects)							**0**	**1**	**5**
Total clinical effectiveness for Rotigotine (% subjects)							**63.6%**	**16.7%**	**36.4%**

Abbreviations: PD= Parkinson's disease; POS=Prospective open-label study; PSG=Polysomnography; Ref=Reference.

Anticholinergic

Table 15: Reports on the clinical effectiveness of *Donepezil* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Boeve, 2003	15	RMH	DLB	50	Donepezil (NR)	NR	0	0	50
Ozaki, 2012	81	CR	DLB	1	Donepezil (5)	PSG	0	1	0
Massironi, 2003	41	CR	DLB	3	Donepezil (10)	Clinical	1	0	2
Ringman, 2000	46	CR	IRBD	1	Donepezil (15)	PSG	0	1	0
Ringman, 2000	46	CR	AD	1	Donepezil (10)	Clinical	0	1	0
Total clinical effectiveness for Donepezil (N subjects)							**1**	**3**	**52**
Total clinical effectiveness for Donepezil (% subjects)							**1.8%**	**5.4%**	**92.8%**

Abbreviations: AD=Alzheimer's Disease; CR=Case report; DLB=Dementia with lewy bodies; IRBD=idiopathic REM sleep behavior disorder; NR=Not Reported; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Table S16: Reports on the clinical effectiveness of *Rivastigmine* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Brunetti, 2014	82	RCT	IRBD+MCI	25	Rivastigmine (4.6)	PSG	18	0	7
Di Giacopo, 2012	29	RCT	PD	10	Rivastigmine (4.6)	PSG	7	1	2
Yeh, 2010	54	CR	AD	1	Rivastigmine (4.5)	PSG	0	0	1*
Total clinical effectiveness for Rivastigmine (N subjects)							**25**	**1**	**10**
Total clinical effectiveness for Rivastigmine (% subjects)							**69.4%**	**2.8%**	**27.8%**

***=Induced RBD. Abbreviations: AD=Alzheimer's Disease; CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MCI=Mild Cognitive Impairment; PD=Parkinson's Disease; PSG=Polysomnography; RCT=Randomised Controlled Trial; Ref=Reference; RMH=Retrospective medical history.**

Gabapentinoid

Table S17: Reports on the clinical effectiveness of *Gabapentin* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Escriba, 2016	57	RMH	Mixed	14	Gabapentin (300-800)	PSG	12	0	2
Anderson, 2009	10	RMH	Mixed*	1	Gabapentin (NR)	PSG	0	0	1
Shneerson, 2009	33	CR	IRBD+MD	1	Gabapentin (NR)	PSG	0	0	1
Total clinical effectiveness for Gabapentin (N subjects)							**12**	**0**	**4**
Total clinical effectiveness for Gabapentin (% subjects)							**75%**	**0%**	**25%**

***=One or more subjects could be <50 years of age. Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MD=Major Depression; NR=Not Reported; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.**

Table S18: Reports on the clinical effectiveness of *Pregabalin* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Escriba, 2016	57	RMH	Mixed	3	Pregabalin (75-150)	PSG	2	0	1
Total clinical effectiveness for Pregabalin (N subjects)							**2**	**0**	**1**
Total clinical effectiveness for Pragabalin (% subjects)							**66.7%**	**0%**	**33.3%**

Abbreviations: PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Noradrenergic agonist

Table S19: Reports on the clinical effectiveness of *Clonidine* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Shneerson, 2009	33	CR	IRBD + MD	1	Clonidine (NR)	PSG	0	0	1
Nash, 2003	42	CR	IRBD	1	Clonidine (100-200µg)	PSG	1	0	0
Total clinical effectiveness for Clondine (N subjects)							**1**	**0**	**1**
Total clinical effectiveness for Clondine (% subjects)							**50%**	**0%**	**50%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MD=Major Depression; NR=Not Reported; PSG=Polysomnography; Ref=Reference.

Antidepressants (per class)

Table S20: Reports on the clinical effectiveness of *Selective Serotonin Reuptake Inhibitors* (*SSRI)* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Yamamoto, 2006	83	POS	IRBD	19	Paroxetine (10-40)	PSG	0	16	3
Shinno, 2008	36	CR	IRBD	1	Paroxetine (20)	PSG	0	0	1
Takahashi, 2008	84	CR	IRBD	1	Paroxetine (10)	PSG	0	1	0
Takahashi, 2008	84	CR	IRBD	1	Fluvoxamine (50)	PSG	0	0	1
Nash, 2003	42	CR	IRBD	1	Trazodone (NR)	PSG	0	0	1
Clarke, 2000	56	CR	OSA + MD + MCI	1	Setraline (100-150)	PSG	0	0	1
Total clinical effectiveness for SSRI (N subjects)							**0**	**17**	**7**
Total clinical effectiveness for SSRI (% subjects)							**0%**	**70.8%**	**29.2%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MCI=Mild Cognitive Impairment; NR=Not reported; OSA=Obstructive sleep apnea; POS=Prospective open-label study; PSG=Polysomnography; Ref=Reference.

Table S21: Reports on the clinical effectiveness of *Tryciclic antidepressants* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Fernandez-Acros, 2016	7	RMH	Mixed	1	Imipramine (NR)	PSG	0	0	1
Fernandez-Acros, 2016	7	RMH	Mixed	1	Carbamazepine (NR)	PSG	0	0	1
Nash, 2003	42	CR	IRBD	1	Amytriptyline (NR)	PSG	0	0	1
Clarke, 2000	56	CR	OSA + MD + MCI	1	Dothiepin (150)	PSG	0	0	1
Chung, 1994	55	CR	IRBD	1	Clomipramine (100)	PSG	0	0	1
Bamford, 1993	85	CR	IRBD	1	Carbamazepine (100)	PSG	1	0	0
Schenck, 1986	52	CR	IRBD	1	Amitriptyline (50)	PSG	0	0	1
Schenck, 1986	52	CR	IRBD	2	Desipramine (50-250)	PSG	0	0	2
Total clinical effectiveness for Tricyclic antipsychotics (N subjects)							**1**	**0**	**8**
Total clinical effectiveness for Tricyclic antipsychotics (% subjects)							**11.1%**	**0%**	**88.9%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; MCI=Mild Cognitive Impairment; NR=Not reported; OSA=Obstructive sleep apnea; PSG=Polysomnography; Ref=Reference.

Table S22: Reports on the clinical effectiveness of *Other antidepressants* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day) -*Type of antidepressant*	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Takahashi, 2008	84	CR	IRBD	1	Mianserin (10) -*Tetracyclic*	PSG	0	0	1
Takahashi, 2008	84	CR	IRBD	1	Tandospirone (NR) -*Azapirone*	PSG	0	0	1*
Nash, 2003	42	CR	IRBD	1	Nefazodone (NR) -SARI	PSG	0	0	1
Nash, 2003	42	CR	IRBD	1	Venlafaxine (NR) -*SNDRI*	PSG	0	0	1
Onofrj, 2003	86	CR	PD	4	Mirtazapine (15-30) -*NaSSA*	PSG	0	0	4**
Total clinical effectiveness for Other types of antipsychotics (N subjects)							**0**	**0**	**8**
Total clinical effectiveness for Other types of antipsychotics (% subjects)							**0%**	**0%**	**100%**

 # = Although RBD was confirmed with PSG, it could have been of toxin-metabolic nature due to cancer treatment. Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; NaSSA=Noradrenergic and specific serotonergic antipsychotic; NR=Not reported; PD=Parkinson's Disease; PSG=Polysomnography; Ref=Reference; SARI=Serotonin antagonist and reuptake inhibitor; SNDRI=Serotonin-norepinephrine-dopamine reuptake inhibitor. *=Worsened RBD; ** =Induced RBD.

Table S23: Reports on the clinical effectiveness of A*ntipsychotics* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Lin, 2009	12	RMH	NR	1	Quetiapine (25)	PSG	1	0	0
Olson, 2000	16	RMH	RBD + dementia	2	Clozapine (NR)	PSG	1	1	0
Boeve 1998	17	RMH	DLB	1	Clozapine (NR)	PSG	1	0	0
Fernandez-Acros, 2016	7	RMH	Mixed	1	Haloperidol (NR)	PSG	0	0	1
Shinno, 2010	31	CR	Cancer patients#	1	Haloperidol (5) -*Buryrophenone*	PSG	0	0	1
Shinno, 2010	31	CR	Cancer patients#	2	Quetiapine (25)	PSG	0	0	2
Schenck, 1987	51	CR	RBD + dementia	1	Haloperidol (NR) -*Buryrophenone*	PSG	0	0	1
Total clinical effectiveness for Atypical antipsychotics (N subjects)							**3**	**1**	**5**
Total clinical effectiveness for Atypical antipsychotics (% subjects)							**33.3%**	**11.1%**	**55.6%**

 # = Although RBD was confirmed with PSG, it could have been of toxin-metabolic nature due to cancer treatment. Abbreviations: CR=Case report; DLB=Dementia with Lewy Bodies; NR=Not reported; PSG=Polysomnography; RBD= REM sleep behavior disorder; Ref=Reference; RMH=Retrospective medical history.

Table S24: Reports on the clinical effectiveness of *Anticonvulants* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Fernandez-Acros, 2016	7	RMH	Mixed	1	Phenobarbital (NR)	PSG	0	0	1
Fernandez-Acros, 2016	7	RMH	Mixed	1	Lamotrigine (NR)	PSG	0	0	1
Fernandez-Acros, 2016	7	RMH	Mixed	1	Oxcarbazepine (NR)	PSG	0	0	1
Total clinical effectiveness for Gabapentin (N subjects)							**0**	**0**	**3**
Total clinical effectiveness for Gabapentin (% subjects)							**0%**	**0%**	**100%**

Abbreviations: NR=Not Reported; PSG=Polysomnography; Ref=Reference; RMH=Retrospective medical history.

Gamma-hydroxybutyric acid (GHB)

Table S25: Reports on the clinical effectiveness of *Sodium Oxybate* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Anderson, 2009	10	RMH	Mixed*	1	Sodium Oxybate (NR)	PSG	1	0	0
Moghadam, 2017	22	CR	IRBD	1	Sodium oxybate (4.5) + Pramipexole (0.45)	PSG	1	0	0
Liebenthal, 2016	24	CR	PD with DBS + mild OSA	1	Sodium Oxybate (5.5)	PSG	1	0	0
Mayer, 2016	87	CR	NT1	1	Sodium Oxybate (6)	PSG	1	0	0
Shneerson, 2009	33	CR	IRBD + MD	1	Sodium Oxybate (4.5)	PSG	1	0	0
Total clinical effectiveness for Sodium Oxybate (N subjects)							**5**	**0**	**0**
Total clinical effectiveness for Sodium Oxybate (% subjects)							**100%**	**0%**	**0%**

***=One or more subjects could be <50 years of age. Abbreviations: CR=Case report; DBS=Deep Brain Stimulation; IRBD=idiopathic REM sleep behavior disorder; MD=Major Depression; NR=Not reported; NT1=Narcolepsy Type 1; OSA=Obstructive sleep apnea; PSG=Polysomnography; Ref=Reference.**

Other drugs or combination of drugs trialled for reducing RBD

Table S26: Reports on the clinical effectiveness of *Yi-Gan San (Yokukansan)* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Matsui, 2019	88	RMH	IRBD	17	Yi-Gan San (2.5-5)	PSG	12	0	5
Matsui, 2019	88	RMH	IRBD	19	Yi-Gan San (2.5-5) + Add-on clonazepam (NR) and/or pramipexole (NR)	PSG	4	0	15
Shinno, 2008	36	CR	IRBD	1	Yi-Gan San (2.5)	PSG	1	0	0
Total clinical effectiveness for Yi-Gan San (N subjects)							**17**	**0**	**20**
Total clinical effectiveness for Yi-Gan San (% subjects)							**45.9%**	**0%**	**54.1%**

Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; NR=Not reported; POS=Prospective open-label study; PSG=Polysomnography; Ref=Reference.

Table S27: Reports on the clinical effectiveness of *Cannabidiol* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Chagas, 2014	89	CR	PD	4	Cannabidiol (75-300)	2 PSG, 2 Clinical	4	0	0
Total clinical effectiveness for Cannabidiol (N subjects)							**4**	**0**	**0**
Total clinical effectiveness for Cannabidiol (% subjects)							**100%**	**0%**	**0%**

Abbreviations: CR=Case report; PD=Parkinson's disease; PSG=Polysomnography; Ref=Reference.

Table S28: Reports on the clinical effectiveness of *cardiac medications* for reducing RBD

Study *(First author, year)*	Ref	Study design	Clinical population	Total N	Treatment (mg/day)	RBD screening	Clinical effectiveness (N subjects)		
							YES	PARTIAL	NO
Schenck, 1987	51	CR	IRBD	1	Metoprolol (NR) + Aspirin (NR)	PSG	0	0	1
Schenck, 1987	51	CR	IRBD	1	Aspirin (NR)	PSG	0	0	1
Total clinical effectiveness for Metropolol (N subjects)							**0**	**0**	**2**
Total clinical effectiveness for Metropolol (% subjects)							**0%**	**0%**	**100%**

NOTE: Authors of this study reported that a physician other than the authors themselves unsuccessfully tried to treat RBD with metoprolol and aspirin.
Abbreviations: CR=Case report; IRBD=idiopathic REM sleep behavior disorder; NR=Not reported; PSG=Polysomnography; Ref=Reference.

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