The treatment efficacy of pharmacotherapies for rapid eye movement sleep behavior disorder with polysomnography evaluation: A systematic review and meta-analysis

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HIGHLIGHTS

- Treatment options for RBD are limited.
- Dopamine receptor agonists appears to be effective and well tolerated.
- Pramipexole is shown to be associated with an increase in TST and a reduction in the PLMS index.

ABSTRACT

Clonazepam and melatonin are commonly used as first-line medications for the treatment of rapid eye movement (REM) sleep behavior disorder (RBD), with other medications used in the clinic including pramipexole, ramelteon, and rotigotine. We performed a systematic review and meta-analysis of randomized and non-randomized controlled trials to assess the efficacy of these treatment options in RBD patients with polysomnography. We systematically retrieved results of randomized and non-randomized controlled trials using the PubMed, Embase, and Cochrane databases.

Of the 454 studies identified, 13 were considered eligible for inclusion in the study. In comparison to baseline, clonazepam was found to significantly decrease the percentage of stage 2 sleep (4.00 (95% CI = 0.90 to 7.10)) in RBD patients. Melatonin was found to significantly improve patients’ sleep efficiency (2.51 (95% CI = 0.75 to 4.28)), significantly reduce the time spent in bed (TIB) (–11.71 (95% CI = –23.05 to –0.37)), phasic activity (–25.79 (95% CI = –42.13 to –9.46)) and tonic activity (–10.44 (95% CI = –12.24 to –8.64)). RWA (–5.87 (95% CI = –8.25 to –3.50)) significantly improve with the use of ramelteon. Pramipexole was found to significantly increase the total sleep time (TST) (27.17 (95% CI = 0.06 to 54.29)), and significantly reduce the periodic limb movements of sleep (PLMS) index (–11.42 (95% CI = –21.38 to –1.47)). We also found that pramipexole had different effects on idiopathic RBD (iRBD) and secondary RBD (sRBD). These results will help to guide the clinical use of medication in patients with RBD.

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1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a type of parasomnia, with the clinical presentation in patients being the experience of abnormal and excessive motor activity during dreaming in REM sleep, known as dream enactment behavior (DEB) [1]. The results of large population studies indicate that the prevalence of RBD is between 0.38% [2] and 0.5% [3]. A recent study showed that in a population aged between 70 and 89, more than 6% of the population suffered from RBD, indicating that the prevalence of RBD may be much higher than previously believed [4].

Glutamatergic neurons located within the microcerebellar pontine nucleus on the ventral side of the laterodorsal tegmental nucleus [sub-laterodorsal tegmental nucleus (SLD) in rats and the locus subcoeruleus in humans] are responsible for inducing hypotonia during REM sleep [5]. These experiments [6] showed that GABA glycine neurons located on the ventral side of the medulla oblongata projected into motor neurons during REM sleep and hyperpolarized them, resulting in muscle weakness. Functional neuroimaging and brain postmortem studies [7, 8] reported that RBD might be due to specific neurodegeneration of glutamate SLD and/or GABA/glycine medullary neurons. The activation of the motor cortex might be one of the mechanisms of RBD [9].

Patients with RBD often experience abnormal muscle tone during REM sleep, which in turn can cause the patient to produce movements ranging from simple limb twitching to more complex, aggressive, and vigorous movements. These clinical symptoms may result in harm to the patient and/or their sleeping partner. In addition, longitudinal studies have shown that 80–90% of patients with RBD will develop Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy [10, 11, 12].

Pharmacological interventions such as pramipexole, clonazepam, melatonin, rotigotine, and ramelteon maybe effectively improve the clinical features of RBD. Both melatonin and clonazepam have been shown to reduce the incidence of injury and the frequency and severity of RBD behavior, but melatonin has been associated with less significant side effects and is typically better tolerated than clonazepam [4]. Melatonin has shown great promise in RBD patients with sleep apnea or memory problems [13]. However, clonazepam may exacerbate sleep apnea and cognitive impairment, so it should be used with caution in patients with such symptoms [1, 14].

There are, however, currently no studies showing which of these five drugs is more effective in improving the clinical symptoms of RBD. To address this, we conducted a comprehensive analysis of the treatment efficacy of these five pharmaceutical options for the treatment of clinical symptoms in patients with RBD, to compare the clinical efficacy of the five medicines, determining which option(s) provide the most clinically effective reduction in the symptoms of RBD, and providing a guide to the rational use of drug treatments.

2. Method

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15].

2.1. Search method

The screening process considered all available randomized and non-randomized clinical controlled trials conducted in patients with RBD and using clonazepam, melatonin, pramipexole, ramelteon, or rotigotine. The time range used was from the beginning of the database to August 2021. The search covered the databases of PubMed, Embase, the Cochrane BIOSIS, the World Health Organization’s International Clinical Trials Registry Platform, and ClinicalTrials.gov.

To reduce the effect of language bias, the relevant databases were searched in several languages with no restriction applied to language. The reference of each retrieved article was screened to identify the relevance of the study. The complete search terms used for PubMed were as follows:

- ((Pramipexole[MeSH Terms]) OR (Pramipexole[Title/Abstract]) OR (Pramipexole[All Fields])) OR ((Clonazepam[MeSH Terms]) OR (Clonazepam[Title/Abstract]) OR (Clonazepam[All Fields])) OR ((Rotigotine[MeSH Terms]) OR (Rotigotine[Title/Abstract]) OR (Rotigotine[All Fields])) OR ((Ramelteon[MeSH Terms]) OR (Ramelteon[Title/Abstract]) OR (Ramelteon[All Fields])) OR (melatonin[Title/Abstract]) OR (melatonin[All Fields])) AND (((((Rapid Eye Movement Sleep Behavior Disorder[MeSH Terms]) OR (Behavior Disorder, Rapid Eye Movement Sleep[MeSH Terms])) OR (REM Behavior Disorder[MeSH Terms])) OR (REM Behavior Disorders[MeSH Terms])) OR (Behavior Disorder, REM[MeSH Terms])) OR ((Behavior Disorder, REM[Title/Abstract])) OR (Behavior Disorder, REM[Title/Abstract])) OR (((((Rapid Eye Movement Sleep Behavior Disorder[Title/Abstract])) OR (Behavior Disorder, Rapid Eye Movement Sleep[Title/Abstract])) OR (REM Behavior Disorder[Title/Abstract]) OR (Behavior Disorders, REM[Title/Abstract])) OR (Behavior Disorder, REM[Title/Abstract])) OR (((((Rapid Eye Movement Sleep Behavior Disorder[All Fields]) OR (Behavior Disorder, Rapid Eye Movement Sleep[All Fields]) OR (Behavior Disorder, REM[Title/Abstract])) OR (Behavior Disorder, REM[Title/Abstract])) OR (Behavior Disorder, REM[Title/Abstract])) OR (Behavior Disorder, REM[Title/Abstract]))

2.2. Eligibility criteria

1. Clinical trials using melatonin, ramelteon, rotigotine, clonazepam, or pramipexole for the treatment of RBD.
2. Subjects: patients with a clinical diagnosis of RBD.
3. Outcomes: studies that used polysomnography (PSG) to measure the clinical efficacy of each intervention.
4. Studies that included one or more of the following five interventions: melatonin, ramelteon, rotigotine, clonazepam, and pramipexole.

2.3. Exclusion criteria

1. Trials that used melatonin, ramelteon, rotigotine, clonazepam, or pramipexole for other diseases, such as non-RBD.
2. Repeat articles publishing the same patient data.
3. Articles with missing data or data that could not be extracted.

2.4. Quality assessment and data extraction

Two independent researchers used the Cochrane collaboration’s risk-of-bias tool to jointly assess the eligibility of each manuscript. Differences were discussed between the two researchers until a consensus was reached. The following variables were extracted: name of the first author, publication date, the age range of participants, interventions, the sex ratio of participants, duration of participants’ RBD, dosages of interventions, the sample size, and the geographic location of the study site.

2.5. Recorded measures

The diagnosis of RBD requires documentation of RSWA, coupled with video evidence of dream enactment or a supportive clinical history [16]. Therefore video polysomnography (PSG) recorded using an extended electromyography (EMG) montage is the basic requirement for the diagnosis of RBD. PSG involves the simultaneous recordings of sleep stage, eye movements, electromyographic tone, respiratory parameters, and electrocardiogram (ECG) activity. It helps to characterize complex behaviors that occur during sleep, including sleep movement disorders and sleep abnormalities. PSG may be the only way to help distinguish certain complex behaviors during sleep, especially in the case of RBD [16]. Parameters measured during PSG include the total sleep time, sleep latency, REM density, the periodic limb movements of sleep (PLMS).
index, sleep efficiency, stages of sleep (1 or 2), REM-stage sleep, REM, time in bed (TIB), and the duration of each sleep period phasic activity(%), tonic activity and REM sleep without atonia (RWA). Sleep efficiency (SE), defined as the ratio of total sleep time (TST) to time in bed (TIB), plays a key role in insomnia research and practice [17]. It is reported that TIB includes non-sleep-related activity (e.g., reading, texting, conversing with a partner, watching television), both prior to initiating sleep and after the final awakening. According to the International Classification of Sleep Disorders (ICSD-3) [18], the demonstration of RWA is essential to the diagnosis of RBD. Some researchers [19, 20] found that tonic/phasic activity in muscles could lead to the diagnosis of RBD. Data extraction comprised extracting only the parameters that could be statistically analyzed, namely the total sleep time (min), sleep latency (min), REM density (%), PLMS index (n), sleep efficiency (%), Stage 1 (%), Stage 2 (%), REM-stage (%), REM (%), TIB (min), sleep period time duration (min), phasic activity(%), tonic activity (%) and RWA(%).

2.6. Statistical analysis

Revman 5.3 from the Cochrane Library was used for statistical analysis. Results of the meta-analysis were expressed as mean differences and 95% confidence intervals (CIs). I² testing was used to assess the heterogeneity of studies. An I² of greater than 50% was regarded as moderate-to-highly heterogeneous.

2.7. Risk of bias evaluation

Two independent reviewers used the Cochrane Collaboration’s risk-of-bias tool to assess the quality of each included study. Six fields were assessed, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome measures, incomplete outcome data, and selective reporting. The evaluation results were assigned to one of three classifications; high risk, low risk, or unclear risk. If the reviewers’ assessments differed, any conflicts were resolved by discussion to reach a consensus.

3. Results

3.1. Description of studies

Articles were identified from PubMed, Embase, and the Cochrane database using subject words and free words. The initial search produced a total of 454 articles. By screening the title and abstract of each article to assess the relevance of the article, 421 articles were excluded (Figure 1). Eight further articles were excluded upon reviewing the full text. The reasons for exclusion were: 6 studies did not have the necessary parameters [4, 21, 22, 23, 24], one was a case report [25], and one article [26] provided data in a format that did not meet the requirements of the study. Eventually 13 articles [1, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38] were included in the meta-analysis. Included articles were published

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**Figure 1. The study flow diagram.**
**Table 1. The baseline characteristics of the studies included in the meta-analysis.**

| Nos. | Study          | Drug      | Dosage        | Sample size | Duration of follow-up | Age(years) | Duration of RBD (years) | Sex (% females) | Geographic location |
|------|----------------|-----------|---------------|-------------|-----------------------|------------|-------------------------|-----------------|---------------------|
| 1    | Raffaele Ferri 2013 [32] | Clonazepam | 0.5–1 mg/day | 15          | 2.6 ± 1.08 years      | 68.2 ± 6.22 | 7.2 ± 4.16              | 13.3            | Italy               |
| 2    | Shirley Xin Li 2016 [1] | Clonazepam | starting dose: 0.45–0.16 mg/day to follow-up 0.98–0.63 mg/day | 39          | 28.8 ± 13.3 months (age at diagnosis) | —          | —                      | 25.6%           | Hong Kong SAR       |
| 3    | N Takeuchi 2001 [27] | Melatonin | 3–9 mg/day     | 15          | —                     | 63.5       | —                      | 7.1%            | Japan               |
| 4    | DIETER KUNZ 2010 [30] | Melatonin | 3 mg/day       | 8           | 8 weeks               | 53.8 ± 53.8 | 8.1 ± 5.1              | 0%              | Germany             |
| 5    | Jin-Sun Jun 2019 [37] | Melatonin | 2/6 mg/day     | 9           | 4 weeks               | 64.7 ± 8.3 | 3.7 ± 2.9              | 44.0%           | Korea               |
| 6    | Moran Gilat 2019 [38] | Melatonin | 4 mg/day       | 15          | 8 weeks               | 65.3 ± 6.9 | 5.07 ± 3.9            | 20.0%           | Australia           |
| 7    | M L Fantini 2003 [28] | Pramipexole | 0.78 ± 0.25 mg/day (data analyzed for 6 mg/day) | 8           | 4.5 months            | 66 ± 6.8   | 8.3 ± 5.1              | 37.5%           | Canada              |
| 8    | Hatice Kumru 2008 [29] | Pramipexole | 0.54 mg/day | 11          | 3 months              | 62.1 ± 8.0 | 3.9 ± 2.8              | 27.3%           | Spain               |
| 9    | Taeko Sasai 2012 [31] | Pramipexole | 0.21 ± 0.09 mg/day | 15          | 9.1 ± 7.1 months      | 66.5 ± 5.2 | —                      | 46.7%           | Japan               |
| 10   | Takashi Nomura 2013 [33] | Ramelteon   | 8 mg/day       | 2           | —                     | 75, 58     | 1, 11                  | 50.0%           | Japan               |
| 11   | Kenichi Kashihara 2016 [35] | Ramelteon   | 8 mg/day       | 35          | 12 weeks              | 69.1 ± 11.1 | —                      | 51.4%           | Japan               |
| 12   | Yuichi Esaki 2016 [34] | Ramelteon   | 8 mg/day       | 12          | 4 weeks               | 70.9 ± 8.7 | 4.5 ± 2.3              | 33.3%           | Japan               |
| 13   | Yan Wang 2016 [36] | Rotigotine  | 12.36 ± 4.27 mg/day | 11          | 24.73 ± 2.41 weeks    | 66.27 ± 8.47 | 12.90 ± 8.32          | 27.3%           | China               |

**Figure 2.** Meta-analysis risk of bias summary and graph.
| parameters | Drug        | Study                      | After treatment | Baseline | Weight(%) | Mean difference IV, Fixed, 95% CI |
|------------|-------------|----------------------------|-----------------|----------|-----------|----------------------------------|
| TST        | Pramipexole | Hatice Kumru 2008          | 418.2 32.3 11   | 367.6 55.7 11 | 8.7 | 50.60 [12.55,88.65] |
|            |             | M L Fantini 2003          | 390.4 65 8      | 390.5 43.5 8  | 4.3 | 0.10 [−54.30,54.10] |
|            |             | Taeko Sasai 2012          | 409 88.6 15     | 402.6 63.4 15 | 4.1 | 6.20 [−48.93,61.33] |
|            |             | **Subtotal (95% CI)**     | **34**          | **17.1**    |           |                                  |
| PLMS index | Clonazepam  | Raffaele Ferri 2013       | 378.4 29.93 13  | 349.3 62.68 13 | 8.8 | 29.10 [−8.66,66.86] |
|            |             | **Subtotal (95% CI)**     | **13**          | **8.8**     |           |                                  |
| Sleep efficacy | Pramipexole | Hatice Kumru 2008          | 85 6.5 11       | 76 10.3 11  | 4.7 | 9.00 [1.80,16.20] |
|            |             | Taeko Sasai 2012          | 79.4 14.1 15    | 82.5 10.3 15 | 3.1 | −3.10 [−11.94,5.74] |
|            |             | **Subtotal (95% CI)**     | **26**          | **7.8**     |           | 4.17 [−1.41,9.75] |
|            | Clonazepam  | Raffaele Ferri 2013       | 85.4 6.4 13     | 78.3 14.61 13 | 3.2 | 7.10 [−1.57,15.77] |
|            |             | Shirley Xin Li 2016       | 75.9 11.1 39    | 73.3 11.9 39 | 9.3 | 2.60 [−2.51,7.71] |
|            |             | **Subtotal (95% CI)**     | **52**          | **12.5**    |           | 3.76 [−0.64,8.16] |
|            | Rotigotine  | Yan Wang 2016             | 73.98 12.7 11   | 65.27 12.31 11 | 2.2 | 8.71 [−1.74,19.16] |
|            |             | **Subtotal (95% CI)**     | **11**          | **2.2**     |           | 8.71 [−1.74,19.16] |
| Stage 2%   | Melatonin   | Dieter Kunz 2010          | 86.4 11.8 8     | 76.4 16.1 8  | 1.3 | 10.00 [−3.83,23.83] |
|            |             | N Takeuchi 2001           | 85.26 2.5 15    | 82.87 2.48 15 | 76.2 | 2.39 [0.61,4.17] |
|            |             | **Subtotal (95% CI)**     | **23**          | **77.5**    |           | 2.51 [0.75,4.28] |
|            | Rotigotine  | Yan Wang 2016             | 46.12 15.6 11   | 45.79 13.44 11 | 5.0 | 0.33 [−11.84,12.50] |
|            |             | **Subtotal (95% CI)**     | **11**          | **5.0**     |           | 0.33 [−11.84,12.50] |

(continued on next page)
| Parameters       | Drug          | Study                    | After treatment | Baseline | Weight(%) | Mean difference IV, Fixed, 95% CI |
|------------------|---------------|--------------------------|-----------------|----------|-----------|----------------------------------|
|                  |               |                          | Mean    | SD       | Total     | Mean    | SD       | Total     |                          |
| TIB              | clonazepam    | Raffaele Ferri 2013      | 443.5   | 25.23    | 13        | 447.3   | 17.6     | 13        | 31.5                  | –3.80 [–20.52,12.92] |
|                  |               | Subtotal (95% CI)        | 13      |          |           | 13      |          |           | 31.5                  | –3.80 [–20.52,12.92] |
| melatonin        |               | Moran Gilat 2019         | 422.2   | 74.5     | 15        | 426.7   | 48.4     | 15        | 4.4                   | –4.50 [–49.46,40.46] |
|                  |               | N Takeuchi 2001          | 512.33  | 18.44    | 15        | 524.53  | 14.01    | 15        | 12.20                 | –12.20 [–25.92,–0.48] |
|                  |               | Subtotal (95% CI)        | 30      |          |           | 30      |          |           | 68.5                  | –11.71 [–23.05,–0.37] |
| tonic activity   | melatonin     | N Takeuchi 2001          | 5.99    | 1.41     | 15        | 16.43   | 3.27     | 15        | 91.3                  | –10.44 [–12.24,–8.64] |
|                  |               | Subtotal (95% CI)        | 15      |          |           | 15      |          |           | 91.3                  | –10.44 [–12.24,–8.64] |
| pramipexole      |               | Hatrice Kumru 2008       | 28      | 37.4     | 11        | 31.2    | 35.8     | 11        | 0.3                   | –3.20 [–33.80,27.40] |
|                  |               | Taeko Sasai 2012         | 9.8     | 11.1     | 15        | 11.2    | 8.7      | 15        | 5.8                   | –1.40 [–8.54,5.74]   |
|                  |               | Subtotal (95% CI)        | 26      |          |           | 26      |          |           | 6.1                   | –1.49 [–8.44,5.46]   |
| pramipexole      |               | RWA                      | 8       |           |           | 4.1     |          |           | –0.30                 | [–25.59,24.99]       |
| phasic activity  | melatonin     | DIETER KUNZ 2010         | 48.3    | 25.4     | 8         | 48.6    | 26.2     | 8         | 4.1                   | –0.30 [–25.59,24.99] |
|                  |               | rotigotine               | 7.64    | 1.2      | 15        | 51.69   | 42.27    | 15        | 5.7                   | –44.05 [–65.45,–22.65] |
|                  |               | Subtotal (95% CI)        | 23      |          |           | 23      |          |           | 9.8                   | –25.79 [–42.13,–9.46] |
| pramipexole      |               | RWA                      | 11.9    | 9.4      | 11        | 16.8    | 14.6     | 11        | 24.7                  | –4.90 [–15.16,5.36]  |
|                  |               | Taeko Sasai 2012         | 24.5    | 21.4     | 15        | 28.1    | 18.9     | 15        | 12.5                  | –3.60 [–18.08,10.85] |
|                  |               | Subtotal (95% CI)        | 26      |          |           | 26      |          |           | 37.2                  | –4.46 [–12.83,3.90]  |
| ramelteon        |               | RWA                      | 13.7    | 11       | 12        | 18.3    | 13       | 12        | 28.1                  | 4.60 [–5.04,14.24]   |
|                  |               | Taeko Sasai 2012         | 13.7    | 11.94    | 11        | 15.72   | 12.5     | 11        | 25.0                  | –1.99 [–12.21,8.23]  |
|                  |               | Subtotal (95% CI)        | 13      |          |           | 13      |          |           | 25.0                  | –1.99 [–12.21,8.23]  |
| rotigotine       |               | RWA                      | 34.5    | 38.6     | 8         | 44.1    | 41.7     | 8         | 0.4                   | –9.60 [–48.98,29.78] |
|                  |               | Taeko Sasai 2012         | 34.7    | 21.6     | 15        | 39.2    | 19.3     | 15        | 2.5                   | –4.50 [–19.16,10.16] |
|                  |               | Subtotal (95% CI)        | 23      |          |           | 23      |          |           | 2.9                   | –5.12 [–18.86,6.92]  |
| RWA              | melatone      | Takashi Nomura 2013      | 3.7     | 0.28     | 2         | 9.7     | 1.7      | 2         | 96.0                  | –6.00 [–8.39,3.61]   |
|                  |               | Yuichi Esaki 2016        | 41      | 24.4     | 12        | 35.5    | 31.8     | 12        | 1.1                   | –5.50 [–17.18,28.18] |
|                  |               | Subtotal (95% CI)        | 14      |          |           | 14      |          |           | 97.1                  | –5.87 [–8.25,–3.50]  |
between 2003 and October 2019. The following data were extracted for meta-analysis: the 6 mg group in Jin-Sun Jun’s study [37], the iRBD + Clo group in Raffaele Ferri’s study [32], and the melatonin group in Moran Gilat’s study [38]. Table 1 shows the basic characteristics of participants in studies included in the meta-analysis (Table 1). A bias-risk summary and chart were used to evaluate the studies included in the analysis (Figure 2) (see Table 2).

3.2. Effect of intervention on TST

The TST meta-analysis comprised 10 studies, representing a total of 110 participants, as shown in Figure 3. TST significantly increased with the use of pramipexole (27.17 (95% CI = 0.06 to 54.29)), with an I² (statistical inconsistency) of 33%. However, neither clonazepam, rotigotine, ramelteon, or melatonin were found to significantly improve TST.

Figure 3. Forest plot of the meta-analysis showing the effect of different drugs on total sleep time (TST).

Figure 4. Forest plot of the meta-analysis showing the effect of different drugs on the periodic limb movements of sleep (PLMS) index.
3.3. Effect of intervention on PLMS index

The PLMS index meta-analysis included data from 5 studies, representing 58 participants (Figure 4). Pramipexole significantly improved the PLMS index compared to baseline \( [11.42 (95\% \text{ CI} = 21.38 \text{ to } 1.47)] \), with an \( I^2 \) of 60%.

3.4. Effect of intervention on sleep efficiency

The sleep efficiency meta-analysis included 3 studies, representing 112 participants (Figure 5). Melatonin was found to significantly improve sleep efficiency \( [2.51 (95\% \text{ CI} = 0.75 \text{ to } 4.28)] \), with a heterogeneity of \( I^2 = 13\% \).

3.5. Effect of intervention on percentage of stage 2 sleep

The stage 2 sleep meta-analysis included two studies representing 52 participants (Figure 6). Clonazepam significantly improved the percentage of stage 2 sleep compared to baseline \( [4.00 (95\% \text{ CI} = 0.90 \text{ to } 7.10)] \), with 0% heterogeneity.

3.6. Effect of intervention on TIB

The TIB meta-analysis included 3 articles, representing 43 participants (Figure 7). Melatonin was found to significantly improve the TIB...
compared to baseline [-11.71(95% CI = -23.05 to -0.37)], again with 0% heterogeneity.

3.7. Effect of intervention on tonic activity

The tonic activity meta-analysis included 5 studies, representing 64 participants (Figure 8). Melatonin was found to significantly improve tonic activity [-10.44 (95% CI = -12.24 to -8.64)].

3.8. Effect of intervention on phasic activity

The phasic activity meta-analysis included 6 articles, representing 72 participants (Figure 9). Melatonin was found to significantly improve the phasic activity compared to baseline [-25.79 (95% CI = -42.13 to -9.46)], with 85% heterogeneity.

3.9. Effect of intervention on RWA

The TST meta-analysis comprised 4 studies, representing a total of 37 participants (Figure 10). The use of ramelteon significantly improved RWA [-5.87 (95% CI = -8.25 to -3.50)], with an I² of 0%.

3.10. Subgroup analysis of interventions on RBD

In this meta-analysis, we sub-divided RBD into idiopathic RBD and secondary RBD, where idiopathic RBD is defined as RBD that is not accompanied by complications or inducements. We performed a subgroup analysis of interventions with sufficient data. Pramipexole did not have an obvious effect on either TST [3.00(95% CI = -35.65 to 41.65)] or sleep efficiency [-3.10(95% CI = -11.94 to 5.74)] in iRBD patients. However, pramipexole did show an effect on TST in sRBD patients [50.60(95% CI = 12.55 to 88.65)] and also on sleep efficiency in sRBD patients [9.00(95% CI = 1.80 to 16.20)] (Figures 11 and 12). Melatonin had a greater effect on TIB in iRBD patients [-23.92 to -9.48] compared to that in sRBD patients [-49.46 to 40.46] (Figure 13). Differences between subtypes of RBD may be one of the reasons for the observed heterogeneity in treatment efficacy.

3.11. Sensitivity analysis, meta regression, and publication bias analysis

A sensitivity analysis was conducted, but after removing four high-risk studies, the remaining data were not sufficient for sensitivity...
**Figure 9.** Forest plot of the meta-analysis showing the effect of different drugs on phasic activity.

| Study or Subgroup | Baseline Mean (SD) | After treatment Mean (SD) | Mean Difference (IV, Fixed, 95% CI) |
|-------------------|--------------------|---------------------------|-------------------------------------|
| Melatonin         | 8 25.4 (8 48.6)    | 27.4 (22.5 26.2)          | -0.30 [-0.25, 0.04]                 |
| Takeshita 2001    | 7.64 1.2 (15 51.69) | 42.77 (15.7 28.9)        | -4.45 [-6.45, -2.46]               |
| Subtotal (95% CI) | 23                 | 23                        | 9.8% [-25.79, -9.46]               |

**Figure 10.** Forest plot of the meta-analysis showing the effect of different drugs on REM sleep without atonia (RWA).

| Study or Subgroup | Baseline Mean (SD) | After treatment Mean (SD) | Mean Difference (IV, Fixed, 95% CI) |
|-------------------|--------------------|---------------------------|-------------------------------------|
| 3.1.1 Melatonin   | 13.7 11.9 (11 15.7) | 12.5 (11 25.0)            | -1.99 [-12.21, 8.23]                |
| Subtotal (95% CI) | 12                 | 12                        | 9.4% [-8.49, 1.72]                  |

**Figure 11.** Forest plot of the meta-analysis showing the effect of pramipexole on TST in different types of RBD.

| Study or Subgroup | Baseline Mean (SD) | After treatment Mean (SD) | Mean Difference (IV, Fixed, 95% CI) |
|-------------------|--------------------|---------------------------|-------------------------------------|
| 1.1.1 RBD         | 390.4 55 (390.5 43.5) | 25.0 (28 25.0)           | -0.10 [-0.55, 0.34]                |
| Takeshita 2012    | 11 42.8 (15 402.8)  | 63.4 (15 24.2)          | 6.20 [-4.93, 9.93]                 |
| Subtotal (95% CI) | 23                 | 23                       | 9.2% [-3.98, 1.60]                 |

**Figure 10.** Forest plot of the meta-analysis showing the effect of different drugs on REM sleep without atonia (RWA).
analysis. Furthermore, a meta-regression analysis of the included studies was performed. The meta-regression analyses did not identify any factors that were significantly associated with intervention improvement (P > 0.05). Finally, according to the publication bias analysis, it was found that Shirley Xin Li 2016 [1], Moran Gilat 2019 [38], N Takeuchi 2001 [27], M L Fantini 2003 [28], Taeko Sasai 2012 [31], Yuichi Esaki 2016 [34] and Yan Wang 2016 [36] were published in sources commonly regarded as “grey literature”.

4. Discussion

These results show that pramipexole can improve TST and the PLMS index in patients with RBD, melatonin can improve sleep efficiency, TIB, phasic activity and tonic activity, clonazepam can improve the percentage of stage 2 sleep, and ramelteon can improve RWA. These five interventions were not associated with significant changes in other PSG parameters (such as REM density, sleep latency, percentages of stage 1 sleep, or REM).

Pramipexole was shown to have a significant effect on TST and PLMS index in patients with RBD, but the other four interventions were not associated with any significant changes in TST or PLMS. A previous meta-analysis published by Ye Zhang et al [39] found the TST of the RBD patient group to be reduced in comparison to the control group, which may suggest that a general improvement in symptoms with treatment would be associated with an increase in TST. It has also previously been shown that TST increased after treatment with rotigotine [36], but this was not a statistically significant finding in the present study.

Pramipexole and rotigotine are dopamine receptor agonists. Dopa-mimetic dysfunction may also play a role in the pathophysiology of RBD [40]. Albin et al. [41] proposed that the mechanism for this may be through the influence of the basal ganglia on the pedunculopontine nucleus (PPN) or that degeneration in the basal ganglia occurs concurrently with damage to the PPN. The therapeutic effect of pramipexole on RBD has been shown to vary widely. It was reported by Youngsin Jung et al [42] that 0.5–1.5 mg of pramipexole reduced the frequency and severity of symptoms in 62–89% of RBD patients. Such an improvement in RBD symptoms may be caused by changes in dream content or by decreases in REM density [31]. The present study found no difference in the mean REM density, which is consistent with the results of Hatice Kumru [29] and M.L. Fantini [28]. We found a significant improvement in PLMS index associated with pramipexole treatment, consistent with a previous study by Taeko Sasai [31], who found a significant decrease in PLMS index in non-rapid eye movement (NREM) sleep, but not in REM. There may be other factors affecting the pathophysiology of PLMS during REM sleep in patients with RBD [31]. Consequently, these medications cannot be recommended for the first-line treatment of RBD due to an absence of strong evidence for their efficacy [43].

Sleep disorders may be caused by an underlying imbalance between synaptic excitation and inhibition [44]. Clinically, clonazepam is typically used as a first-line treatment of RBD symptoms. The results of this meta-analysis were consistent with a significant increase in the percentage of stage 2 sleep following treatment with clonazepam, in agreement with the findings of Shirley Xin Li et al [1].

Ramelteon acts as a melatonin receptor agonist [35]. Melatonin is associated with control of the circadian rhythm and promotes sleep. According to the report of Kunz D et al [25], melatonin reduced the number of movements by 50%, and the authors proposed that melatonin might be able to reinforce REM sleep in RBD patients by enhancing its active inhibition of motor activity. The results of the present meta-analysis show that melatonin is associated with statistically significant improvements in sleep efficiency, TIB, phasic activity and tonic activity. And RWA significantly improve with the use of ramelteon. While statistically significant improvements were found in these PSG parameters, other commonly used markers of healthy sleep did not show significant changes associated with the administration of melatonin. Therefore, these findings support Moran Gilat’s view that the
effectiveness of these two currently accepted first-line interventions for RBD (melatonin and clonazepam) may be greatly overestimated. Subgroup analyses showed that pramipexole had different effects on iRBD and sRBD, and in sRBD was only effective in improving TST and sleep efficiency. This may be explained by differences in the clinical manifestations of these two RBD subtypes. There are changes in sleep structure in sRBD, but not in iRBD [45], potentially limiting the effect of pramipexole on either TST or sleep efficiency in iRBD. Melatonin was associated with shorter TIB in patients with iRBD, but had no significant effect in sRBD, for which a reasonable explanation has not yet been found. In addition to the above PSG parameters, other parameters, namely the number of simple motor behaviors occurring in REM sleep, the sleep quality, the PLMS arousal index (events/hour), and the PLMS index during NREM sleep (events/hour), can also provide clinical value. In practice, symptoms improve with the use of these medications, but the PSG parameters measured do not change significantly. Therefore, we propose two hypotheses. The first is that the features of sleep that are modulated by these interventions may not be characterized by conventional sleep monitoring methods. There is little existing literature reporting the use of these indicators, and as such a statistical meta-analysis is not yet possible. Secondly, for any given parameter, the effectiveness of different interventions will vary, as will the effectiveness of the same intervention between subjects. This suggests the existence of multiple RBD subtypes, potentially with different underlying causes and mechanisms.

In addition to the five medications included in the present study, acetylcholinesterase inhibitors (donepezil and rivastigmine) may improve nocturnal symptoms in RBD patients. However, only two studies report the effect of donepezil [46, 47] (including 6 patients), and only two small case series on rivastigmine. Other benzodiazepines (temazepam, triazolam, and alprazolam) have been shown to improve the symptoms of RBD. Two studies have reported the use of temazepam [48, 49], one for triazolam [50] and three for alprazolam [14, 51, 52]. Finally, clozapine [50, 53], sodium oxybate, and other interventions may also improve the symptoms of RBD. However, this field is limited by the small number of studies and the small sample sizes, with limited evidence for improving the symptoms of RBD.

Some scattered papers 19, 20 are available that use mathematical approaches or artificial intelligence analysis for classifying tonic/phasic activity in muscles and helping in the diagnosis of RBD. Brink-Kjaer A et al. [54] used end-to-end deep neural networks to analyze PSG and presented an automatic and interpretable diagnostic tool for RBD. Rechichi I et al. [55] used machine learning models to perform automatic identification of patients with RWA. Lo C et al. [56] showed that their 3-Sniff-Tick model had potential practicability and could be used to screen patients with RBD. Besides aforementioned studies, these studies [57, 58, 59, 60] also showed that mathematical approaches or artificial intelligence analysis had a great prospect in RBD diagnosis.

5. Limitations

The main limitation of this meta-analysis is that the diagnoses of the patients in the included studies are variable and complex. Studies included patients with both iRBD and sRBD, with different pathophysiology, creating heterogeneity in the patient population studied. Secondly, due to the relatively small number of studies available for inclusion in the meta-analysis, it was decided to include non-randomized controlled trials, introducing heterogeneity into the quality of the data and publication bias. Thirdly, this article provides no information on the subjective and objective effect of the various treatments used off label for REM sleep behavior disorder. Fourth, the sample sizes reported in most studies was small, limiting the inference possible from the meta-analysis. Fifth, this systematic review and meta-analysis was not registered on PROSPERO. Finally, the dosage, administration frequency, and patient inclusion criteria (e.g., duration of RBD prior to inclusion in the study) varied across the studies included in the meta-analysis, adding to the heterogeneity, and thus the noise present, in the data.

6. Conclusion

The results of this systematic review and meta-analysis support the argument that clonazepam can be administered to increase the percentage of stage 2 sleep in patients with RBD. The use of melatonin was associated with significant improvements in sleep efficiency and a reduction in TIB, phasic activity and tonic activity. RWA significantly improve with the use of ramelteon. Pramipexole was shown to be associated with an increase in TST and a reduction in the PLMS index, but had different effects on iRBD and sRBD.

Declarations

Author contribution statement

Zhiqiang Que, Cuifeng Zheng, Zhenhua Zhao: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Yanhong Weng, Zhibao Zhu, Yuqi Zeng: Contributed reagents, materials, Analysis tools or data.
Qinyong Ye, Fabin Lin, Guoen Cai: Conceived and designed the experiments; Analyzed and interpreted the data.

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Data availability statement

Data included in article/supp. material/referenced in article.
Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

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