Pharmacological Interventions for REM Sleep Behavior Disorder in Parkinson’s Disease: A Systematic Review

Junqiang Yan 1,2*, Anran Liu 2, Jiarui Huang 2, Jiannan Wu 1, Ruile Shen 2, Hongxia Ma 2 and Jianxue Yang 1,3*

1 Key Laboratory of Neuromolecular Biology, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China, 2 Department of Neurology, The First Affiliated Hospital, College of Clinical Medicine of Henan University of Science and Technology, Luoyang, China, 3 School of Nursing, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China

To review the therapeutic effects of drugs on REM sleep behavior disorder (RBD) in Parkinson’s disease (PD) by searching the MEDLINE/PubMed, Embase, Cochrane, and CBM databases. According to the inclusion and exclusion criteria, studies were included after excluding duplicate data. We evaluated the safety and efficacy of pharmacological intervention to improve RBD in patients with Parkinson’s disease (PD-RBD). This systematic review mainly describes the drugs that can be used to treat PD-RBD patients. The results have shown that melatonin can be used as the first-line drug for PD-RBD, and clonazepam provides significant improvement on PD-RBD, androtigotine can be used as an alternative drug. However, further large-scale clinical trial studies are still needed to provide the best guidelines for the pharmacological treatment of PD-RBD.

Keywords: Parkinson’s disease, rapid eye movement, drugs, systematic review, sleep

INTRODUCTION

Parkinson’s disease (PD) is the second most common progressive neurodegenerative disease in elderly individuals over the age of 65 (Sherer et al., 2012). In addition to the typical motor symptoms, there are also non-motor symptoms such as constipation, dysphagia, cognitive impairment, and sleep disorders (McDonald et al., 2018) which seriously affect patients’ quality of life (Chaudhuri and Schapira, 2009). Sleep disorders in PD mainly include insomnia, excessive daytime sleepiness (EDS), restless legs syndrome (RLS), and rapid eye movement (REM) sleep behavior disorder (RBD) (Chahine et al., 2017; Stefani and Hogl, 2021).

RBD is a sleep disorder characterized by dreams and physical activities during REM sleep. Most RBD patients have dream-related violent behavior, which often results to injure themself or others. RBD can be divided into idiopathic RBD (iRBD) and secondary RBD (sRBD) according to different causes. The iRBD appears as an independent symptom without other accompanying symptoms; sRBD includes drug-induced, symptomatic and neurodegenerative diseases related RBD. iRBD is the most reliable clinical marker for pro-synucleinopathy, such as Parkinson’s disease (PD) (Hogl et al., 2018). Patients may eventually develop neurodegenerative diseases after a few years or decades, and the risk of occurrence ranges from more than 30% at 5 years to more than 90% at 14 years. Idiopathic RBD can be used as a pre-exercise biomarker for PD and about 20% of RBD occurred before PD and about 20% of cases had both Parkinson’s disease and RBD and more than
50% of RBD occurred for several years after the clinically manifest of Parkinson’s disease (Diaconu et al., 2021).

The incidence of RBD in PD patients is ~20–50% (Sixel-Doring et al., 2011; Romenets et al., 2012; Bugalho and Viana-Baptista, 2013). The main symptoms can vary from simple muscle tension to complex behavioral disorders (Gagnon et al., 2002; Schenck and Mahowald, 2002). Patients often yell, laugh and even have violent behavior in their sleep, which is usually discovered by their bed partners. Patients can often remember their vivid dreams and dream enactment when they wake up (Sforza et al., 1997; Olson et al., 2000). PD-RBD is generally observed and diagnosed by polysomnography (PSG) (Duchna, 2006). PD patients with RBD not only suffer from a decline in sleep quality, but also easily cause injuries to the patients themselves and their bed partners, increasing the risk of intimacy interruption and bed partner injuries (Postuma et al., 2012; Schenck et al., 2013a).

RBD not only affects sleep quality but also cognitive function in PD patients (Nomura et al., 2013a; Yarnall et al., 2013). Research by Schenck et al. showed that RBD is related to cognitive decline, and more than 80% of elderly patients with RBD develop Parkinson’s disease or dementia (Schenck et al., 2013b). Compared with PD patients without RBD, the cognitive dysfunction (especially delayed memory function) of PD patients with RBD is more prominent (Zhang J. R. et al., 2016). A recent clinical study confirmed that there is a significant correlation between sleep efficiency and overall cognitive ability in patients with PD (Sobreira et al., 2019). Therefore, the clinical treatment of patients has become important and needed. This article mainly collects all relevant studies to analyse and evaluate the effectiveness and safety of drug interventions, and puts forward some suggestions and questions.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

This study used the search generators available in each database to search all relevant literature up to January 1, 2020 in the MEDLINE/PubMed, Embase, Cochrane, and CMB databases. The search method was based on the following terms: “Parkinson’s disease” and synonyms and “rapid eye movement sleep behavior disorder” and related terms; the search commonly used acronyms for these phrases, and duplicate studies were excluded.

Study Selection

The search results were independently evaluated by two reviewers, and differences were resolved through discussion. The inclusion criteria included the following: 1. Studies with crossover trials or open-label designs; 2. Studies that involved patients with Parkinson’s disease; 3. The study targeted RBD among sleep disorders; 4. The treatment involved a single drug; and 5. Experiments were performed in vivo. The exclusion criteria were as follows: 1. Duplicate studies; 2. Studies that involved patients with diagnosis other than Parkinson’s disease; 3. The studies sleep events related to PD other than RBD; 4. The treatment involved non-drug therapy or non-monotherapy; 5. Experiments were performed in vitro. In theory, we followed the PRISMA guidelines (Liberati et al., 2009) for a systematic review. However, due to the qualitative and non-quantitative research in this study, we did not further conduct bias risk assessment and data extraction synthesis.

RESULTS

Literature searches were conducted based on PRISMA’s preferred reporting project guidelines (Figure 1) (Liberati et al., 2009). After duplicate studies were excluded, resulting in 1,564 articles. Based on the study’s inclusion criteria, 55 related clinical drug studies were selected, of which seven clinical trials met the criteria.

Clonazepam

Clonazepam has long been considered the first-line treatment for PD-RBD (Sforza et al., 1997; Olson et al., 2000; Schenck and Mahowald, 2002; Aurora et al., 2010) and has been widely used clinically (Seppi and Ray Chaudhuri, 2019). However, evidence for its effectiveness is based only on case reports and follow-up studies (Aurora et al., 2010; Li et al., 2016), and evidence for treatment in randomized controlled clinical trials is lacking. In 2013, the International RBD Study Group (IRBD-SG) published a consensus statement on the design of controlled clinical studies for RBD (Schenck et al., 2013a). Shin compared the overall clinical improvement score at the fourth week of using 0.5 mg clonazepam and placebo, and the results showed no significant difference ($p = 0.253$) (Shin et al., 2019). However, this experiment was mainly evaluated by the Clinical Global Impressions-Improvement (CGI-I) score, without further clarification with PSG. At the same time, research shows side effects (morning sedation, confusion, dizziness, and falls) which may limit the effectiveness of clonazepam, especially in the elderly and/or RBD that coexists with obvious neurodegenerative diseases (Anderson and Shneerson, 2009). The result remains to be demonstrated by more experiments.

Melatonin

Clinical evidence has indicated that melatonin can be an effective adjuvant therapy for RBD in PD patients (Aurora et al., 2010). A study showed that after 4 weeks of treatment with 3–6 mg melatonin, RBD symptoms in 84% of PD patients significant improvement (Lyashenko et al., 2015). A randomized controlled study including 30 PD patients also showed that the extended release of 4 mg of melatonin did not significantly reduce PD-RBD symptoms ($P = 0.92$) (Gilat et al., 2020), but the study was mainly based on the Movement Disorder Society (MDS)-UPDRS questionnaire score, and the small sample couldn’t detect group differences on secondary outcomes, and there were differences in the primary data at baseline level ADDIN EN.CITE (Gilat et al., 2020). In a multi-site, double-blind, placebo-controlled, crossover trial, 50 mg of melatonin improved sleep quality better than 5 mg (Dowling et al., 2005). Ramelteon, a melatonin receptor agonist, can significantly improve the RBD symptoms of PD patients compared with control group in a Multicenter Open Trial ($P < 0.05$) (Kashihara et al., 2016).
But, the study mainly used the Japanese version of the RBD screening questionnaire to diagnose RBD, and did not use PSG, therefore, it had limitations. In another case report, PD-RBD patient was treated with ramelteon (8 mg/day before sleeping), PSG monitoring found that RBD symptoms were significantly improved (Nomura et al., 2013b). A meta-analysis in 2016 further demonstrated that melatonin showed significant improvements on sleep disorders in neurodegenerative diseases through nine randomized controlled trial (Zhang W. et al., 2016). The results of the latest 4-week randomized, double-blind, placebo-controlled pilot study showed that there was no difference between the iRBD patients receiving sustained-release melatonin and the placebo group. Although the study subjects were not PD-RBD, they didn’t effect on results (Jun et al., 2019).

**Rotigotine**
Wang et al. (2016) studied rotigotine transdermal patches for 7 months in PD-RBD patients through interviews with PD patients themselves and their families, the REM Sleep Behavior Disorder Questionnaire (RBDQ-HK) and video polysomnography (VPSG) measurements, and VPSG analysis showed that total sleep time (TST) and stage 1% were increased, and the PLMS index decreased (Wang et al., 2016). The results suggested that rotigotine can improve symptoms of RBD of PD patients. Pierantozzi et al. also designed a randomized, double-blind, placebo-controlled parallel experiment, and they found that rotigotine could significantly improve sleep efficiency of patients with PD through PSG, but the study lacked the definition of RBD (Pierantozzi et al., 2016).

**Rivastigmine**
A double-blind crossover trial study (Di Giacopo et al., 2012) using rivastigmine at 4.6 mg/d showed a significant reduction in the frequency of RBD episodes recorded by bed partners (P = 0.027). However, four patients underwent multiple PSG tests, and REM sleep without atonia (RSWA) showed no significant changes (Di Giacopo et al., 2012).

**Pramipexole**
In a prospective study, through bed partner recording and PSG monitoring, patients’ PD symptoms improved, but RBD was not significantly improved (P > 0.05) (Kumru et al., 2008). This study was more accurate because of the combined subjective and objective detection methods, but the sample size was insufficient.

In addition, we briefly summarize the 55 articles in the query that involved drugs for treating sleep disorders but did not conform to the inclusion criteria, such as individual case reports or non-PD-RBD patients. This study provides additional information regarding these drug treatments as follows.
Levodopa

Ozekmekçi et al. used levodopa at 460.3 and 320.3 mg/d in PD patients with RBD. Studies have shown that dopamine can improve the scores of UPDRS (Unified Parkinson’s Disease rate Scale; Ozekmekçi et al., 2005). However, Wailke et al. did not find any improvement in REM sleep among PD patients’ sleep status after taking 200 mg levodopa/carbidopa controlled-release tablet (CR) by PSG ($P = 0.615$) (Wailke et al., 2011). Tan et al.’s case report showed that RBD preceded PD in all three cases, and the three patients significantly improved their RBD after levodopa use, but without polygraph detection (Tan et al., 1996). There was a significant difference in subjective sleep symptoms ($P = 0.082$), six patients with PD-RBD received intestinal levodopa infusion after 6 months treatment (Zibetti et al., 2017).

Cannabinoids

Cannabinoids (CBD) can also improve sleep quality and reduce sleep disorders (Kuhathasan et al., 2019). Clinical studies have shown that cannabinoids were beneficial for sleep disorders of PD patients, and the mechanism may be related to the distribution of cannabinoid receptors in the structure of the basal ganglia (Buhmann et al., 2019). In an observational study of four PD patients receiving CBD treatment, it was found that the frequency of RBD in patients was rapidly and significantly reduced, and there were no side effects (Chagas et al., 2014).

Memantine

In a randomized controlled study (Larsson et al., 2010), sleep scale evaluation scores showed that 20 mg/d memantine reduced

---

**TABLE 1 | Main characteristics of the eligible studies.**

| References | Design | Experimental intervention | Dosage | Duration of treatment | Measures | Findings |
|------------|--------|---------------------------|--------|-----------------------|----------|----------|
| Gilat et al. (2020) | Randomized, double-blind, placebo-controlled, parallel-group trial ($n = 30$) | Melatonin | 4 mg | 8 weeks | Video polysomnography (PSG); weekly CIRUS-RBD Questionnaire (wCIRUS-RBDQ); RBD Screening Questionnaire; Innsbruck RBD Inventory; RBD Questionnaire-Hong Kong; CGI; and International Parkinson and Movement Disorder Society (MDS)-UPDRS | 4 mg of melatonin is well-tolerated, but not efficacious in ameliorating self-reported RBD in PD patients. |
| Lyashenko et al. (2015) | Open trial ($n = 30$) | Melatonin | 3–6 mg | 4 weeks | Polysomnography; RBD Screening Questionnaire (RBDSQ); Parkinson Disease Sleep Scale (PDSS) | 84% of patients reported reduction in RBD symptoms. |
| Shin et al. (2019) | Randomized, double-blind, placebo-controlled trial ($n = 40$) | Clonazepam | 0.5 mg | 4 weeks | Clinical Global Impressions-Improvement (CGI-I) scores | Both clonazepam and placebo tended toward improvements on RBD symptoms in patients with PD. |
| Kashihara et al. (2016) | A multi-center open trial ($n = 24$) | Ramelteon | 8 mg/d | 12 weeks | Japanese version of the RBD Questionnaire (RBDQ-JP); PD Sleep Scale Version-2 (PDSS-2); Unified PD Rating Scale (UPDRS) | The RBDQ-JP score was markedly reduced after the initiation of ramelteon treatment, ramelteon markedly improved RBDQ-JP scores, as well as UPDRS part III and PDSS-2 scores in patients with PD with RBD. |
| Di Giacopo et al. (2012) | Double-blind, crossover pilot trial ($n = 12$) | Rivastigmine | 4.6 mg/d | 3 weeks (T1), 3 weeks (T2) | RBD episode frequency reduction according to the bed partner’s diary | Mean frequency of RBD episodes was significantly lower with rivastigmine treatment than with placebo ($Z = 2.207; P = 0.027$). |
| Kumru et al. (2008) | Prospective study ($n = 11$) | Pramipexole | 0.54 mg/d | 3 months | Video polysomnography (VPSG) | In PD patients, pramipexole improved parkinsonism but did not modify RBD-related symptoms and objective video-polysomnographic abnormalities. |
| Wang et al. (2016) | Prospective open-label study ($n = 11$) | Rotigotine patches | 2–16 mg/d | 7 months | Patient and bed partner interviews; a validated evaluation scale (REM sleep behavior disorder questionnaire-Hong Kong, RBDQ-HK) video polysomnography (VPSG) | Rotigotine improved parkinsonism and subjective sleep quality in PD patients with RBD. |
REM sleep behavior disorder that may occur in PD patients, but the specificity of PD-RBD was unclear.

**DISCUSSION AND CONCLUSIONS**

We hereby conducted a systematic review of all relevant drug clinical trials to evaluate the safety and efficacy of drug treatment for PD-RBD. The latest consensus guidelines for the clinical management of PD non-motor symptoms published in 2020 mentioned that there is currently a lack of RCT (Randomized Controlled Trial) studies for PD-RBD treatment, and that clonazepam or/and melatonin can be used to treat PD-RBD (Askenasy and Yahr, 1985). Clonazepam can improve RBD by Poewe et al., 2003; Boeve et al., 2007). Videnovic et al. concluded that donepezil and quetiapine/clozapine can improve the symptoms of RBD, but these are individual case studies, and a large number of clinical studies are needed (During and Miglis, 2019).

In this study, according to the seven included literature studies, the results of a single trial show that (1) clonazepam and melatonin can currently be used as first-line drugs for the treatment of PD-RBD; (2) rotigotine can become a substitute for the above two drugs; and (3) rivastigmine, memantine, and cannabinoids may be effective for RBD in PD patients. According to the results of this systematic review, these drugs can improve the symptoms of PD-RBD and have been used clinically (Table 1). However, due to the insufficient sample size of these trials and the defects in evaluation methods, large-scale clinical trials are still needed for further confirmation.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

AL and JW were involved in the execution. RS and JYang were involved in the statistical analysis and manuscript preparation. HM and JH were involved in analyzing the data. JYan was involved in the research project (conception, design, writing, and organization). All authors contributed to the article and approved the submitted version.

**FUNDING**

This work was supported by the Project of Henan Province Science and Technology (202102310216) and the Key projects of medical science and technology in Henan Province (SBG202002099).

**REFERENCES**

Anderson, K. N., and Shneerson, J. M. (2009). Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. J. Clin. Sleep Med. 5, 235–239. doi: 10.5664/jcsm.27492
Askenasy, J. J. (1993). Sleep in Parkinson’s disease. Acta Neurol. Scand. 87, 167–170. doi: 10.1111/j.1600-0404.1993.tb04095.x
Askenasy, J. J., and Yahr, M. D. (1985). Reversal of sleep disturbance in Parkinson’s disease by antiparkinsonian therapy: a preliminary study. Neurology 35, 527–532. doi: 10.1212/WNL.35.5.527
Aurora, R. N., Zak, R. S., Maganti, R. K., Auerbach, S. H., Casey, K. R., Chowdhuri, S., et al. (2010). Best practice guide for the treatment of REM sleep behavior disorder (RBD). J. Clin. Sleep Med. 6, 85–95. doi: 10.5664/jcsm.27717
Dowling, G. A., Mastick, J., Colling, E., Carter, J. H., Singer, C. M., and Aminoff, M.

Diaconu, S., Falup-Pecurariu, O., Tint, D., and Falup-Pecurariu, C. (2021). REM

Duchna, H. W. (2006). Sleep-related breathing disorders—a second e dition

Di Giacopo, R., Fasano, A., Quaranta, D., Marca, G. D., Bove, F.,

Chaudhuri, K. R., and Schapira, A. H. (2009). Non-motor symptoms of Parkinson's

Frontiers in Aging Neuroscience | www.frontiersin.org
6 August 2021 | Volume 13 | Article 709878
Yan et al. RBD in Parkinson's Disease

clonazepam in rapid eye movement sleep behavior disorder. Sleep Med. 21, 114–120. doi: 10.1016/j.sleep.2015.12.020

Liberiati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., et al. (2009). The PRISMA statement for reporting

systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. 151, W65–W94.
doi: 10.7326/0003-4819-151-4-200908180-00136

Lyashenko, C. A. C., Levin, O. S., and Poluektov, M. G. (2015). Melatonin in correction of REM-sleep behavior disorders in Parkinson's disease. Zh Nevr

Psikhiatr Im S S Korsakova 115, 40–43. doi: 10.7326/0003-4819-151-4-200908180-00136

200 years of Parkinson's disease: what have we learnt from James Parkinson? Age

Aging 47, 209–214. doi: 10.1003/ageing/afx196

Nomura, T., Inoue, Y., Kagimura, T., and Nakashima, K. (2013a). Clinical

significance of REM sleep behavior disorder in Parkinson's disease. Sleep Med. 14, 131–135. doi: 10.1016/j.sleep.2012.10.011

Nomura, T., Kawase, S., Watanabe, Y., and Nakashima, K. (2013b). Use of

ramelteon for the treatment of secondary REM sleep behavior disorder. Intern.

Med. 52, 2123–2126. doi: 10.2169/internalmedicine.52.9179

Olson, E. J., Boeve, B. F., and Silber, M. H. (2000). Rapid eye movement sleep

behaviour disorder: demographic, clinical and laboratory findings in 93 cases.

Brain 123, 331–339. doi: 10.1093/brain/123.2.331

Ozekmekci, S., Apaydin, H., and Kilic, E. (2005). Clinical features of 35 patients

with Parkinson's disease displaying REM sleep behavior disorder. Clin. Neurol.

Neurosurg. 107, 306–309. doi: 10.1016/j.clineuro.2004.09.021

Perez-Llort, S., and Cardinali, D. P. (2021). Melatonin as a chronobiotic and
cytoprotective agent in Parkinson's disease. Front. Pharmacol. 12, 650597.
doi: 10.3389/fphar.2021.650597

Pierantozzi, M., Placidi, F., Liguori, C., Albanese, M., Imbriani, P., Marciani, M. G.,
et al. (2016). Rotigotine may improve sleep architecture in Parkinson's disease: a

double-blind, randomized, placebo-controlled polysomnographic study. Sleep

Med. 21, 140–144. doi: 10.1016/j.sleep.2016.01.016

Poewe, W. H., Rascol, O., Quinn, N., Tolosa, E., Oertel, W. H., Martignoni, E.,
et al. (2007). Efficacy of pramipexole and transdermal rotigotine in advanced

Parkinson's disease: a double-blind, double-dummy, randomised controlled

trial. Lancet Neurol. 6, 513–520. doi: 10.1016/S1474-4227(07)70108-4

Postuma, R. B., Bertrand, J. A., Montplaisir, J., Desjardins, C., Vendette, M., Rios

Romenets, S., et al. (2012). Rapid eye movement sleep behavior disorder and

risk of dementia in Parkinson's disease: a prospective study. Mov. Disord. 27, 720–726. doi: 10.1002/mds.24939

Romenets, S. R., Gagnon, J. F., Latreille, V., Panniset, M., Chouinard, S.,
Montplaisir, J., et al. (2012). Rapid eye movement sleep behavior disorder and subtypes of Parkinson's disease. Mov. Disord. 27, 996–1003.
doi: 10.1002/mds.25086

Schenck, C. H., Boeve, B. F., and Mahowald, M. W. (2013b). Delayed emergence

of a parkinsonian disorder or dementia in 81% of older men initially
diagnosed with idiopathic rapid eye movement sleep behavior disorder: a

16-year update on a previously reported series. Sleep Med. 14, 744–748.
doi: 10.1016/j.sleep.2012.10.009

Schenck, C. H., and Mahowald, M. W. (2002). REM sleep behavior disorder:
clinical, developmental, and neuroscience perspectives 16 years after its formal

identification in SLEEP. Sleep 25, 120–138. doi: 10.1093/sleep/25.2.120

Schenck, C. H., Montplaisir, J. Y., Frauscher, B., Hogl, B., Gagnon, J. F.,
Postuma, R., et al. (2013a). Rapid eye movement sleep behavior disorder: deising controlled active treatment studies for symptomatic and

neuroprotective therapy—a consensus statement from the International Rapid

Eye Movement Sleep Behavior Disorder Study Group. Sleep Med. 14, 795–806.
doi: 10.1016/j.sleep.2013.02.016

Seppi, K., and Ray Chaudhuri, K. (2019). Update on treatments for nonmotor

symptoms of Parkinson's disease—an evidence-based medicine review. Mov.

Disord. 34, 180–198. doi: 10.1002/mds.27602

Sforza, E., Krieger, J., and Pettau, C. (1997). REM sleep behavior disorder:
clinical and physiopathological findings. Sleep Med. Rev. 1, 57–69.
doi: 10.1016/S1299-933X(96)00056-X

Sherer, T. B., Chowdhury, S., Peabody, K., and Brooks, D. W. (2012). Overcoming obstacles in Parkinson's disease. Mov. Disord. 27, 1606–1611.
doi: 10.1002/mds.25260
Shin, C., Park, H., Lee, W. W., Kim, H. J., Kim, H. J., and Jeon, B. (2019). Clonazepam for probable REM sleep behavior disorder in Parkinson’s disease: a randomized placebo-controlled trial. *J. Neurol. Sci.* 401, 81–86. doi: 10.1016/j.jns.2019.04.029

Sixel-Doring, F., Trautmann, E., Mollenhauer, B., and Trenkwalder, C. (2011). Associated factors for REM sleep behavior disorder in Parkinson disease. *Neurology* 77, 1048–1054. doi: 10.1212/WNL.0b013e31822e56e

Sobreira, E., S. T., Sobreira-Neto, M. A., Pena-Pereira, M. A., Chagas, M., H. N., Fernandes, R. M. F., Eckeli, A. L., et al. (2019). Global cognitive performance is associated with sleep efficiency measured by polysomnography in patients with Parkinson’s disease. *Psychiatry Clin. Neurosci.* 73, 248–253. doi: 10.1111/jpcn.12819

Stampanoni Bassi, M., Sancesario, A., Morace, R., Centonze, D., and Iezzi, E. (2017). Cannabinoids in Parkinson’s disease. *Cannabis. Cannabinoid. Res.* 2, 21–29. doi: 10.1089/can.2017.0002

Stefani, A., and Fogl, B. (2021). Sleep disorders in Parkinson disease. *Sleep Med. Clin.* 16, 323–334. doi: 10.1016/j.smjc.2021.03.001

Tan, A., Salgado, M., and Fahn, S. (1996). Rapid eye movement sleep behavior disorder preceding Parkinson’s disease with therapeutic response to levodopa. *Mov. Disord.* 11, 214–216. doi: 10.1002/mds.870110216

Wailke, S., Herzog, J., Witt, K., Deuschl, G., and Volkman, J. (2011). Effect of controlled-release levodopa on the microstructure of sleep in Parkinson’s disease. *Eur. J. Neurol.* 18, 590–596. doi: 10.1111/j.1468-1331.2010.03213.x

Wang, Y., Yang, Y., Wu, H., Lan, D., Chen, Y., and Zhao, Z. (2016). Effects of rotigotine on REM sleep behavior disorder in Parkinson disease. *J. Clin. Sleep Med.* 12, 1403–1409. doi: 10.5664/jcsm.6200

Watts, R. L., Jankovic, J., Waters, C., Raiput, A., Boroojerdi, B., and Rao, J. (2007). Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 68, 272–276. doi: 10.1212/01.wnl.0000252355.79284.22

Yarnall, A. J., Rochester, L., and Burn, D. J. (2013). Mild cognitive impairment in Parkinson’s disease. *Age Ageing* 42, 567–576. doi: 10.1093/ageing/aft085

Zhang, J. R., Chen, J., Yang, Z. J., Zhang, H. J., Fu, Y. T., Shen, Y., et al. (2016). Rapid eye movement sleep behavior disorder symptoms correlate with domains of cognitive impairment in Parkinson’s disease. *Chin. Med. J.* 129, 379–385. doi: 10.4103/0366-6999.176077

Zhang, W., Chen, X. Y., Su, S. W., Jia, Q. Z., Ding, T., Zhu, Z. N., et al. (2016). Exogenous melatonin for sleep disorders in neurodegenerative diseases: a meta-analysis of randomized clinical trials. *Neurol. Sci.* 37, 57–65. doi: 10.1007/s10072-015-2357-0

Zibetti, M., Romagnolo, A., Merola, A., Priano, L., Montanaro, E., Angrisano, S., et al. (2017). A polysomnographic study in parkinsonian patients treated with intestinal levodopa infusion. *J. Neurol.* 264, 1085–1090. doi: 10.1007/s00415-017-8491-2

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Yan, Liu, Huang, Wu, Shen, Ma and Yang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.