Sleep Medicine Reviews 35 (2017) 33–50

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015☆

Lama M. Chahine [a, *, 1], Amy W. Amara [b, 1], Aleksandar Videnovic [c]

[a] Parkinson's Disease and Movement Disorders Center, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, 330 S. 9th st, Philadelphia, PA 19107, USA
[b] Division of Movement Disorders, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
[c] Neurobiological Clinical Research Institute, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 4 February 2016
Received in revised form
10 August 2016
Accepted 12 August 2016
Available online 31 August 2016

Keywords:
Parkinson's disease
Sleep and neurodegeneration
REM sleep behavior disorder
Insomnia
Restless legs syndrome
Periodic limb movements
Sleep disordered breathing
Excessive daytime sleepiness
Circadian rhythm disorders

SUMMARY

Sleep disorders are among the most common non-motor manifestations in Parkinson's disease (PD) and have a significant negative impact on quality of life. While sleep disorders in PD share most characteristics with those that occur in the general population, there are several considerations specific to this patient population regarding diagnosis, management, and implications. The available research on these disorders is expanding rapidly, but many questions remain unanswered. We thus conducted a systematic review of the literature published from 2005 to 2015 on the following disorders of sleep and wakefulness in PD: REM sleep behavior disorder, insomnia, nocturia, restless legs syndrome and periodic limb movements, sleep disordered breathing, excessive daytime sleepiness, and circadian rhythm disorders. We discuss the epidemiology, etiology, clinical implications, associated features, evaluation measures, and management of these disorders. The influence on sleep of medications used in the treatment of motor and non-motor symptoms of PD is detailed. Additionally, we suggest areas in need of further research.

Introduction

While the non-motor manifestations of Parkinson's disease (PD) were noted when it was first described in 1817, early research focused on motor symptoms. Decades of research have improved management of motor manifestations in PD, while also shedding light on the protean non-motor manifestations. Among these, sleep disorders stand out given their high prevalence and their severe impact on quality of life (QOL) [1–3]. Additionally, sleep dysfunction can be associated with and influence other motor and non-motor symptoms in this patient population. While the past decade has seen major advances in our understanding of sleep disorders in PD, much remains to be learned. Applying rigorous and comprehensive literature search/identification criteria, we review the state of our knowledge from the past decade on some of the most common disorders of sleep and wakefulness in PD, namely, rapid eye movement (REM) sleep behavior disorder (RBD), insomnia, nocturia, restless legs syndrome (RLS)/periodic limb movement disorder (PLMD), sleep disordered breathing (SDB), excessive daytime sleepiness (EDS), and circadian rhythm disorders. We provide an overview of findings from the past decade of research, and propose key priorities for research in this area for the coming decade.

Methods

This was a qualitative systematic review conducted according to PRISMA guidelines [4]. This methodology was chosen as it allows for systematic vetting of all references on a given topic that meet pre-specified inclusion and exclusion criteria, and provides a comprehensive account of all references meeting those criteria (in contrast to narrative reviews) [4]. Two electronic databases, PubMed and Embase, were searched for articles published between January 1, 2005 and January 1, 2015. The supplement to this manuscript details the search terms and methodology used for queries pertaining to each sleep disorder, including article inclusion and exclusion criteria.

☆ Refs [101] – [355] were present in the Supplementary material.

* Corresponding author. Fax: +1 215 829 6606.
E-mail address: lamachahine@hotmail.com (L.M. Chahine).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.smrv.2016.08.001
1087-0792/

Abbreviation

AHI	apnea hypopnea index
BP	blood pressure
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
DBS	deep brain stimulation
DLB	dementia with lewy bodies
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
HRQoL	health related quality of life
HR	heart rate
LED	levodopa equivalent dose
LED-DA	levodopa equivalent dose contributed by dopamine agonists
MSA	multiple system atrophy
OSA	obstructive sleep apnea
PD	Parkinson's disease
PDD	parkinsons disease dementia
PLMD	periodic limb movement disorder
PLMS	periodic limb movements of sleep
pRBD	probable REM sleep behavior disorder (not polysomnographically confirmed)
PSP	progressive supranuclear palsy
QOL	quality of life
RBD	REM sleep behavior disorder
RLS	restless legs syndrome
RSWA	REM sleep without atonia
SIT	suggested immobility test
SOS	suddent onset sleep
SPECT	single-photon emission computed tomography
STN	subthalamic nucleus
SWEDD	scans without evidence of dopamine deficiency
TST	total sleep time
WASO	wake time after sleep onset

REM sleep behavior disorder

RBD is a parasomnia characterized by loss of the atonia that normally occurs during REM sleep, associated with dream enactment behavior. RBD has been an intensive area of investigation over the past decade, both as a characteristic of the "premotor" PD state [5], and as a potential marker of more severe disease manifestations in PD.

Epidemiology

The prevalence of RBD among individuals without PD or other neurodegenerative parkinsonian syndromes has not been well studied. Studies on the prevalence of RBD among community-dwelling older adults have not been conducted in over a decade.

Among patients with established PD seen at tertiary care centers, the prevalence of polysomnographically-defined RBD is 39–46% [6,7]. In early and de novo PD, the prevalence may be lower, at 30% [8]. There are no apparent sex differences in prevalence in this population [7,8]. REM sleep behavioral events, i.e., purposeful motor behaviors and/or vocalizations in REM sleep (irrespective of REM sleep without atonia (RSWA)), were identified in half of early PD patients [9].

RBD accounts for the majority of complex motor behaviors during sleep in PD, though apnea-related arousals are on the differential diagnosis [10], as are periodic limb movements of sleep (PLMS). In studies of probable RBD (pRBD) in PD, violent dream content is often reported, especially in males [11], and there is a significantly increased risk of injury [12]. Normal language and non-violent, culturally-specific movements also occur [13]. Of note, seemingly normal motor function and vocalizations occur during dream enactment in PD patients with RBD [14], often in stark contrast to the bradykinesia and hypophonia seen during wakefulness.

As mentioned, RBD may precede PD motor manifestations or develop after PD onset [15]. In studies of pRBD in PD, RBD preceding PD was associated with younger age of PD onset and more severe disease manifestations [16]. Shorter duration between RBD symptom onset and development of motor manifestations has also been associated with greater risk of cognitive impairment [17], possibly indicating greater neurodegeneration in these cases [17]. RBD persists in some patients throughout the course of their disease but resolves in others; in one study, approximately 30% of PD patients had resolution of pRBD within 4 y [18].

Etiology

Progress to determine the etiology of RBD has been slow, but several theories have been put forth, based largely on animal data and supported by imaging and pathological data in humans. It has been proposed that RBD results from dysfunction in brainstem nuclei including the glutamatergic peri-locus coeruleus, combined with abnormalities in brainstem locomotor centers [19–21].

Evaluation

RBD diagnosis requires polysomnographic demonstration of RSWA combined with either a history of dream enactment or demonstration of dream enactment during polysomnography [22]. The definition of what constitutes RSWA is an area of active ongoing research [23–26]. Several screening questionnaires have been applied for the diagnosis of RBD in PD [27–31] (Table 1), but demonstrate low specificity [27,32]. Questionnaires also poorly predict RSWA [32]. On the other hand, actigraphy may have high specificity but low sensitivity for the diagnosis of RBD in PD [67]. Four main conclusions that may be drawn from the literature over the past decade on diagnosis of RBD in PD include i) both patient and bed-partner input is essential in optimizing sensitivity of any questionnaire used to diagnose RBD ii) questionnaire-based diagnosis has low specificity iii) RSWA is necessary for definitive diagnosis vi) polysomnography is required to detect RSWA.

Clinical implications

There are three broad implications of RBD. First, it is one of the strongest clinical predictors of future PD risk, and is thus seen as a prodromal state to PD [68] (as discussed further below, excessive daytime sleepiness [69] may be a manifestation prodromal to PD as well). As will be discussed, significant advancements have been made in identifying characteristics in RBD that are strongly associated with this risk of conversion to PD [70]. The second important implication is that among PD patients, several reports in recent years have suggested that RBD is associated with more severe motor and non-motor manifestations (Table 2). Finally, dream enactment behavior imposes significant risk of injury to the patient and bed-partner.