Sleep disturbance in Movement Disorders – insights, treatments and challenges

Grace A Bailey[1], Emily K Hubbard[2], Alfonso Fasano[3,4], Marina AJ Tijssen[5], Tim Lynch[6], Kirstie N Anderson[7], Kathryn J Peall[1]

[1]Neuroscience and Mental Health Research Institute, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK

[2]School of Medicine, Cardiff University, Heath Park, Cardiff, UK

[3]Edmond J Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital – UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada.

[4]Krembil Brain Institute, Toronto, Ontario, Canada

[5]University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, The Netherlands.

[6]Dublin Neurological Institute, Mater Misericordiae University Hospital, Dublin, Ireland

[7]Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK

Corresponding Authors:

Grace Bailey, Neuroscience and Mental Health Research Institute, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ. Email: Baileyga@cardiff.ac.uk, Telephone: +442920 874000

Dr Kathryn Peall, Neuroscience and Mental Health Research Institute, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ. Email: PeallKJ@cardiff.ac.uk. Telephone: +442920 688338

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Abstract

Objectives

Sleep and circadian rhythm disturbances are central features of many movement disorders, exacerbating motor and non-motor symptoms and impairing quality of life. Understanding these disturbances to sleep is clinically important and may further our understanding of the underlying movement disorder.

Methods

This review evaluates the current anatomical and neurochemical understanding of normal sleep and the recognised primary sleep disorders. In addition, we undertook a systematic review of the evidence for disruption to sleep across multiple movement disorders.

Results

REM sleep behaviour disorder has emerged as the most reliable prodromal biomarker for the alpha synucleinopathies, including Parkinson's Disease and Multiple System Atrophy, often preceding motor symptom onset by several years. Abnormal sleep has also been described for many other movement disorders, but further evidence is needed to determine whether this is a primary or secondary phenotypic component of the underlying condition. Medication used in the treatment of motor symptoms also affects sleep and can aggravate or cause certain sleep disorders. Within the context of movement disorders, there is also some suggestion of a shared underlying mechanism for motor and sleep pathophysiology, with evidence implicating thalamic and brainstem structures and monoaminergic neurotransmission.

Conclusion

This review highlights the need for an understanding of normal and abnormal sleep within the movement disorder clinic, an ability to screen for specific causes of poor sleep and to treat sleep disturbance to improve quality of life. Key sleep disorders also act as important biomarkers and have implications in diagnosis, prognosis and the development of future therapies.

Introduction

Abnormal sleep and circadian rhythm disorders are seen in many patients with movement disorders, although they remain underdiagnosed and are a significant unmet need in clinical care. Sleep and circadian rhythms are generated from specific regulatory centres, including the forebrain, thalamus and midbrain dopaminergic neurons, regions also implicated in movement disorder pathogenesis.

The rate, nature and temporal pattern of these sleep disturbances vary across the different movement disorders. For example, in Parkinson's disease the rate of sleep disorders has been estimated to be as high as 98%, with REM sleep behaviour disorder well established as pre-dating motor symptom onset.[1] In contrast, those such as adult-onset primary, idiopathic dystonia, may have poor sleep with evidence suggesting a link to psychiatric symptom severity.[2]

This review provides an overview of the common sleep disorders and the evidence to date for the patterns and prevalence across a spectrum of movement disorders. We discuss the tools available for sleep assessment, the impact of medication used in motor symptom management upon sleep, and how disturbed sleep can affect daytime motor function. Finally, we highlight future challenges to the field, and general considerations in the assessment and treatment of sleep disorders in patients diagnosed with a movement disorder.

Sleep Structure, Anatomy and Physiology

Sleep cycles approximately every 90-120 minutes between an initial non-REM (NREM) stage (subdivided into N1-3 stages), followed by a rapid eye movement (REM/R) phase with a relative muscle atonia. Figure 1 summarises the typical hypnogram, although with normal ageing, night awakenings increase, N3 decreases and total sleep time shortens.

Maintenance of the sleep/wake circuit is regulated by the fast-acting neurotransmitters glutamate and GABA, while an array of excitatory neurotransmitters are thought to have a modulatory role, including hypocretin/orexin (lateral hypothalamus), histamine (tuberomammillary nucleus), acetylcholine (pedunculopontine and laterodorsal tegmentum), noradrenaline (locus coeruleus), dopamine (ventral periaqueductal grey matter) and serotonin (raphe nuclei) (Figures 2A-C). Sleep regulatory circuits are widespread throughout the brainstem and hypothalamus. GABAergic parvalbumin neurons in the basal forebrain arousal system and GABAergic neurons in the parafacial zone (PZ) of the medulla are essential for driving wakefulness, with the latter promoting sleep via inhibition of glutamatergic neurons in the parabrachial nucleus (PB). More recently, evidence

suggests that GABAergic neurons in the lateral hypothalamus (LH) contribute to promoting wakefulness by inhibiting the thalamus and preoptic area. The ventrolateral preoptic area (VPLO) also contains GABAergic neurons, essential for promoting sleep via inhibition of the arousal system.

Glutamatergic REM-promoting neurons in the sublaterodorsal nucleus (SLD) are inhibited by GABAergic NREM-promoting neurons in the ventral periaqueductal grey (vPAG), while activation of GABAergic neurons in the ventral medulla which innervate vPAG promotes transition to REM sleep by disinhibition of the SLD. NREM sleep is driven by GABAergic neurons in the ventral periaqueductal grey (vPAG) and glutamatergic neurons located ventromedial to the superior cerebellar peduncle (SCP). These neurons suppress both wakefulness and REM sleep by inhibiting the SLD, with additional inhibition of the medial parabrachial nucleus by GABAergic neurons also promoting NREM sleep. Newer models of the sleep/wake circuit recognise that these interactions are modulated by several brain regions including the pedunculopontine (PPT), laterodorsal tegmental nuclei (LDT), projections from the medulla and the melanin-concentrating neuron system (MCH) (Figure 2A and 2B).[3]

Types of sleep disorders

The different forms of sleep disorders, as defined by the International Classification of Sleep Disorders (ICSD-3), their clinical features, diagnostic criteria, proposed underlying pathophysiology and currently suggested treatments are summarised in Table 1.

Diagnosing sleep disorders

Supplementary Table 1 summarises the available sleep questionnaires. Sleep diaries and wrist actigraphy are often used for the diagnosis of insomnia and circadian rhythm disorders as well as population screening in research cohorts. The gold standard for objective sleep staging remains in-patient video polysomnography (PSG), involving video, electroencephalography, electromyography, and electrooculography. PSG is required for confirming the diagnosis of REM Sleep Behavioural Disorder (RBD), while PSG and multiple sleep latency test (MSLT) are used in the diagnoses of narcolepsy and other central hypersomnias.

Technology to aid diagnostic and therapeutic management

Development of consumer wearables is becoming recognised as a prospective clinical tool, aiding early diagnosis as well as the opportunity to monitor disease progression particularly, for example, in response to therapeutics. Actigraphy, an accelerometer validated to detect sleep/wake activity

patterns, is particularly useful for documenting sleep-wake patterns for periods of days or weeks in the patient's own environment, as well as measuring physical activity during periods of wakefulness. Use of these wearable devices extends far beyond disease alone, potentially providing avenues to better understand the association between sleep and health, as well as opportunities to optimise interventions and reduce the adverse health impacts of poor sleep.

Review of the evidence for sleep disturbance across degenerative and non-degenerative movement disorders

The literature search included the key words "sleep disturbances", "sleep disorders"; "RLS"; "PLMS"; "sleep related breathing disorders"; "RBD"; "excessive daytime sleepiness"; "insomnia" in combination with degenerative movement disorders: PD, Dementia with Lewy bodies (DLB), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Corticobasal Syndrome (CBS), Huntington's Disease (HD), Dentatorubral-pallidoluysian Atrophy (DRPLA), Spinocerebellar Ataxia (SCA), Anti-IgLON5 disease, Wilson's Disease (WD), Niemann-Pick disease Type C (NPC), Neurodegeneration with Brain Iron Accumulation (NBIA) including: pantothenate kinase-associated neurodegeneration (PKAN), PLA2G6-associated neurodegeneration (PLAN), Beta-propeller protein-associated neurodegeneration (BPAN), mitochondrial membrane protein-associated neurodegeneration (MPAN) and fatty acid hydroxylase-associated neurodegeneration (FAHN), neuroacanthocytosis (NA) including: McLeod Syndrome (MLS) and Chorea-acanthocytosis (ChAc), and non-degenerative movement disorders: Dystonia, Essential Tremor (ET), Dystonic Tremor, Myoclonus (excluding myoclonus in relation to epilepsy), Tourette's syndrome (TS), Tic Disorders and Benign Hereditary Chorea (BHC). Studies identified were divided according to cohort size and methods of assessment (Supplementary Tables 2-6). Only those involving PSG studies undertaken in case-control cohorts are discussed below and summarised in Tables 2 and 3. Where there is evidence, we have also sought to discuss potential underlying pathophysiological mechanisms.

Parkinsonism

Sleep disorders in Parkinson's Disease

Sleep disturbance, which is typically multifactorial, is as high as 74-98% in individuals diagnosed with PD, with well documented evidence of parasomnias including RBD, PLMS and sleep related breathing disorders. Many sleep symptoms are related to disease duration, for example, there are increased disturbances to sleep architecture, insomnia and somnolence in later disease stages compared to earlier timepoints. Two recent review articles provide detailed oversight of the

polysomnographic findings and therapeutic management of sleep disturbance in PD, and therefore we have only provided a brief overview below.[4,5]

RBD is well characterised in PD populations with longitudinal case-control studies identifying 73.5% of patients with idiopathic RBD (iRBD) develop a neurodegenerative disorder after 12-years.[6] Those patients diagnosed with PD and RBD tend towards more severe clinical features, including increased motor symptom severity, higher rates of axial symptoms, psychiatric symptoms, hallucinations, autonomic dysfunction, cognitive impairment and impulse control disorders, as well as a generally longer motor disease duration, when compared to PD patients without RBD.[7–9] Recent imaging studies of those with co-morbid PD and RBD demonstrate prominent loss of volume in the pontomesencephalic tegmentum, PPN network dysfunction and reduced signalling in the locus coeruleus compared to those with PD alone.[10–12]

Although often reported, systematic studies of RLS and Periodic Limb Movements During Sleep (PLMS) have found conflicting results, but with close matching of control populations a general absence of RLS was observed, while use of actigraphy demonstrated high rates of PLMS. Evidence for the pathogenesis of PD and RLS is conflicting, some studies have reported reduced nigrostriatal dopaminergic activity in idiopathic RLS,[13] while one longitudinal imaging study demonstrated increased dopaminergic transporter availability in both the caudate and putamen to be associated with the presence of RLS.[14] It is also possible that RLS in PD is related to dopaminergic treatment rather than the disease itself. The prevalence of RLS in *de novo* PD patients is comparable to controls, with a longitudinal study showing significantly higher rates of RLS at 3 year follow-up than that at baseline in drug naïve patients.[15] Stimulation of the STN has also been shown to increase rates of RLS, with overstimulation of the dopaminergic system thought to resemble the clinical features of augmentation.[7]

Conflicting results have been found for rates of sleep apnea syndromes (SAS), with some studies identifying comparable AHI levels and a comparable risk of OSA and CSA, while elevated apnea-hypopnea indices (AHI) have also been reported at higher rates in those with PD compared to controls.[16–19] However, several of these studies have not identified the typical oxygen desaturation profiles observed with OSAS, as well as the body mass indices (BMI) of those with PD being significantly lower compared to that of controls. These findings suggest that the sleep disordered breathing identified may represent nocturnal motor involvement of respiratory muscles or a precursor to later stage dysautonomia, rather than the more typical OSA observed in the general

population.[20] Extensive loss of neurons, in particular within respiratory control structures such as the brainstem, may also contribute to respiratory disorders. PD patients show abnormal ventilatory response to hypoxia and hypercapnia suggesting involvement of the medulla, with neuronal and astrocyte reduction in the retrotrapezoid nucleus, nucleus of the solitary tract and pre-Bötzinger complex resulting in abnormal respiratory function in murine models of PD.[21]

Several studies have also reported reduced melatonin secretion in patients, with a case-control study showing a four-fold decrease in circulating melatonin levels in those with PD, and reduced melatonin rhythm amplitude in those with excessive daytime sleepiness.[22] These circadian disturbances are present in early disease stages and are often associated with cognitive decline and psychiatric disorders.[23] In addition, reduced expression of *Bmal1* (a clock gene) has been found to correlate positively with PD severity and PSQI scores, providing further evidence of a link between circadian rhythm and sleep disturbances.[24]

Sleep disorders related to motor symptoms in Parkinson's Disease
Studies involving PD cohorts (n=45) have shown a positive correlation between PLMS, daytime sleepiness and more severe motor rating scores and reduced mobility.[25] A number of studies have also established a strong link between iRBD and subsequent neurodegenerative disorders, with retrospective analysis of PSG data (n=59 PD patients) identifying faster motor progression in those with RBD (n=15) and RWA (n=22) compared to those with preserved REM sleep atonia (n=22, p=0.015). However, this could also be due to increased disease severity and degeneration associated with RBD in PD patients.[26] Several studies also implicate cognitive impairment in the exacerbation of sleep disorders and altered sleep structure.[27] PD patients with primary sleep disorders (RBD and insomnia) had significantly poorer global cognition, visuospatial and executive function in comparison to both unaffected controls and PD patients without sleep disorders.[28]

Impact of treatment used in the management of motor symptoms on sleep
Dopaminergic Therapy
Night-time akinesia can worsen underlying disturbances to sleep. A placebo-controlled study of controlled release levodopa/carbidopa in PD patients (n=40) found improved nocturnal akinesia and therefore increased total hours slept, however immediate release preparations result in reduced total sleep time and lower rates of RBD related symptoms.[17] In contrast, several studies have shown that the use of dopamine agonists results in increased levels of nocturnal activity and higher levels of daytime sleepiness compared to levodopa therapy.[29] Sudden-onset sleep is sometimes described in

PD and attributed to the sedative effects of dopamine agonists, with these 'sleep attacks' prompting safety concerns, particularly in relation to driving.[30] However, transdermal rotigotine patches have been shown to effectively aid sleep continuity, sleep stability and REM sleep, with comparable outcomes to pramipexole and superior to treatment with ropinirole.[31,32] Dopamine agonists are also licensed for use in the treatment of RLS and PLMS however, increasing recognition of impulse control disorder and augmentation as common side effects have limited their use, with pregabalin or gabapentin frequently used as alternatives.

Monoamine Oxidase Inhibitors

Rasagiline can be alerting, with fatigue-related questionnaires completed by those with PD showing significant improvements to baseline scores at 12-weeks (n=16, p=0.003). Dopamine-naïve PD patients (n=1176) demonstrated dose-related improvements at week-36 compared to placebo (1mg p=0.003; 2mg p<0.0001), while PSG studies show increased sleep maintenance and lower WASO compared to controls.[33] Safinamide also improves sleep disorders in PD, likely due to its dual dopaminergic and glutaminergic mechanisms, while amphetamine-like derivatives of selegiline can worsen sleep quality by promoting the onset of insomnia.

Deep Brain Stimulation

PSG studies have noted improvements following subthalamic nuclei stimulation, with increased total sleep time, decreased WASO (p<0.05), and longer periods of continuous sleep (p<0.05), while PPN stimulation – although experimental and performed in few patients – resulted in increased percentage REM sleep in both PD and PSP populations.[34] The efficacy of DBS in the management of sleep disorders in PD is conflicting, the majority of studies suggest that DBS has no impact on RBD[35], although restoration of REM-sleep without atonia has been noted.[36] Several studies have shown improvement in RLS symptoms following DBS,[37,38] while one study found that STN-DBS resulted in the emergence of RLS in 19% of those with PD.[7]

Therapeutics used in the management of sleep disorders in Parkinson's Disease

Wake-promoting agents

These include stimulants such as modafinil and methylphenidate, used to promote wakefulness in hypersomnolence. A recent meta-analysis demonstrated improvement in subjective sleepiness with modafinil, although no subjective improvement in fatigue or objective measures of sleepiness (MSLT or MWT).[39] Studies of other agents have also shown promising results with sodium oxybate (GABA$_B$

receptor agonist) decreasing ESS scores and increasing mean sleep latency, while methylphenidate resulted in a significant reduction to fatigue compared to placebo in PD populations.[40]

Melatonin

Melatonin is produced by the pineal gland with levels rising in darkness and acting as a key regulator of the sleep wake cycle. It has a short half-life at 30-60 minutes and is licensed to treat sleep onset insomnia as well as being used off license to treat RBD with PSG studies showing restoration of REM atonia, with case-controlled studies suggesting fewer side effects compared to clonazepam.[41] However, a recent placebo-controlled RCT found prolonged-release melatonin to have no significant impact on the subjective reporting of RBD symptoms.[42] Agomelatine, a synthetic melatonin analogue, initially developed for treatment of depression, has also been shown to alleviate sleep disturbances (PLMS and awakenings) in PD.[43]

Anti-depressants and anti-psychotics

Trazodone, a serotonin antagonist and reuptake inhibitor, is licensed for use in the treatment of insomnia in some countries. While there are no studies which evaluate its therapeutic use for sleep disorders within the PD population, effective doses within animal models alleviate dyskinesia and psychosis, but appear to cause sedation.[44] Other atypical anti-depressants including mirtazapine can be effective for insomnia due to potent anti-histamine effects but have also been reported to induce or aggravate RBD symptoms in PD cohorts, while use of doxepin in those with PD demonstrated substantial improvements to insomnia, sleep quality and fatigue. Commonly used for the management of hallucinations and delusions, quetiapine, clozapine and pimavenserin are not typically associated with the worsening of motor symptoms in movement disorders. While quetiapine leads to improvements in PD-related psychosis, it has not been shown to impact disturbances to sleep architecture. In contrast, preliminary data relating to pimavanserin (a novel 5-HT2A agonist) suggests improvements to nocturnal symptoms without worsening daytime sedation.[45] Finally, while there are no RCTs, clonazepam remains widely used in the treatment of RBD, in doses from 0.5mg to 2mg, although side effects of sedation at higher doses can be problematic.

Sleep disorders in Dementia with Lewy Bodies (DLB) and the impact of motor disease treatment on sleep

Fluctuating levels of alertness and REM sleep behaviour disorder form core diagnostic criteria for DLB, while PSG evidence of loss of REM atonia also forms a supportive diagnostic biomarker. RBD in DLB, is often experienced several years before the onset of cognitive decline with PSG studies

indicating rates of RBD in DLB to be as high as 71%.[46] Case-control studies have also identified higher levels of PLMS, with sleep architecture abnormalities evident in 75%, predominantly in the form of REM sleep without atonia (44%).[46] Cholinesterase inhibitors (galantamine, donepezil and rivastigmine) used to treat cognitive decline in DLB have been shown to improve sleep quality, reduce fragmented sleep and reduce nocturnal activity.[47,48]

Sleep disorders in Multiple System Atrophy (MSA)

Sleep disorders are also well documented for multiple system atrophy (MSA). In brief, particularly high rates of RBD are reported (64-100%), with 76% (n=21) of one study reporting onset prior to their motor symptoms.[49] Respiratory stridor is also well-recognised, as well as being associated with more severe disease progression and sudden death. Case-control studies have identified increased rates of OSA and AHI levels >5, compared to controls with continuous positive airways pressure (CPAP) improving stridor and sleep apnea.[50] Disruption to subcortical serotonergic neurotransmission is considered to be a key pathophysiological contributor, with depletion of the serotonergic innervation of the raphe nuclei and neurodegeneration of regions involved in respiratory regulation – the brainstem ventral arcuate nucleus and pre-Bötzinger complex cells - considered central in pathogenesis.

REM sleep behaviour disorder in α-synuclein disorders

As outlined above, RBD is a recognised early clinical manifestation amongst the α-synucleinopathies; PD, MSA and DLB, often preceding disease onset by several years and representing a key prodromal marker.[51] Several imaging studies of those with iRBD have identified changes in multiple brainstem structures, namely the PPN, sublaterodorsal nucleus and laterodorsal tegmental region, with those without changes in these regions not observed to later develop PD.[52]

Sleep disorders in Progressive Supranuclear Palsy (PSP)

Studies to date suggest at least 60% of patients diagnosed with PSP report sleep disturbance, with insomnia being the dominant symptom. RBD and REM sleep without atonia also occur, but at lower rates (5-13%) than that seen in PD, with this not seeming to antedate motor disease onset.[53] Imaging studies show degeneration of REM-promoting structures, including the PPN and pontine tegmentum, as the likely cause.[54] A recent study also reported that patients diagnosed with PSP with Lewy type alpha-synucleinopathy were more frequently diagnosed with probable RBD compared to those with PSP without Lewy pathology.[55]

Sleep disorders in Corticobasal Syndrome (CBS)

Two small PSG studies reported sleep disorders in all of the patients involved, these included PLMS and/or RLS and sleep related breathing disorders including OSA and CSA. Alterations to sleep architecture were also observed, with patients showing decreases in sleep maintenance, total sleep time and REM sleep without atonia.[56,57]Although no studies have reported narcolepsy in CBS, there is evidence of reduced hypocretin in cerebral spinal fluid (CSF) compared to those with PD.[58]

Neurodegenerative Trinucleotide Repeat Disorders

Sleep disorders in Huntington's Disease (HD)

While sleep disturbance is a frequent complaint, with at least 90% of carers describing poor sleep, it remains less well characterised due to motor and psychiatric symptoms often dominating, as well as a lack of patient insight. Approximately two-thirds of patient cohorts report insomnia, describing difficulty falling asleep and maintaining sleep, with PSG showing increased sleep fragmentation, decreased N3 and REM compared to controls. Insomnia is often present early in disease, as well as being reported in pre-motor manifesting *HTT* carriers, and increasing with disease progression.[59] Reduced REM sleep (n=30) has also been shown to be inversely correlated with motor symptom severity ($p<0.05$), with cognitive impairment also implicated in the exacerbation of sleep disorders and altered sleep structure.[27]

Patients with HD also demonstrate strikingly abnormal circadian rhythms with both a delayed and irregular phase to sleep, with evidence from actigraphy monitoring, as well as abnormal melatonin and cortisol profiles. These changes are also consistently observed in animal models of disease, and are attributed to degeneration of the suprachiasmatic nucleus, hypothalamus and striatum.[60,61] They can also occur early in the condition and are associated with higher levels of cognitive impairment and anxiety.[62] Human post-mortem studies have shown a loss of orexin-releasing neurons in individuals diagnosed with HD, while transgenic HD mouse models suggest that changes to SCN circuitry are central in driving circadian disruption.[60]

Sleep in relation to the treatment of Huntington's Disease

Tetrabenazine, a monoamine reuptake inhibitor, is often used in the management of chorea associated with HD although daytime sleepiness is a commonly reported side effect. A study examining the effect of quetiapine (a partial D2 receptor antagonist) in those with HD found amelioration of their symptoms of insomnia, without any worsening of motor function.[63]

Sleep disorders in the Spinocerebellar Ataxias (SCAs)

A broad spectrum of sleep disorders is described amongst the spinocerebellar ataxias (SCAs), potentially representing widespread brain degeneration beyond the cerebellum. However, technical difficulties exist in measuring rapid eye movements in those who have developed impaired eye movements and saccades, with this likely accounting for some of the previous reports of abnormal or absent REM sleep. Individuals with SCA2 mutations often report good sleep quality but have abnormal PSG, including reduced N3 sleep and REM sleep.[64] NREM sleep appears to be the stage most severely affected in those with SCA3 and SCA6 mutations, with increased arousals from slow wave sleep and increased wake after sleep onset.[65,66] In contrast, a study of SCA10 patients found changes predominantly in REM sleep, including an increased number of REM sleep arousals.[67]

Overall, low rates (0-10%) of PLMS have been noted in those with SCA1 and SCA6 mutations, while higher rates and symptomatic RLS are more often seen in SCA3 cohorts (77%).[66] RLS is thought to reflect the basal ganglia involvement, with functional imaging supporting reduced striatal dopamine transporter activity in this region. Further investigation of the postsynaptic dopaminergic system has shown progressive loss of D2 receptors in the caudate, dorsal putamen and ventral striatum.[68]

Sleep-related breathing disorders have been identified in those with SCA2 and SCA6 mutations, including an increased central sleep apnea (CSA) index (events/h = 0.97) and AHI (p=0.022) in those with SCA2 mutations, and increased CSA events during sleep (p=0.024) and oxygen desaturations (p=0.03) in those with SCA6 mutations.[66] The underlying causative mechanisms remain unknown, although vocal paralysis and dysphonia in combination with neurodegeneration of the supramedullary pathway and brainstem neurons have been proposed.[69]

Sleep disorders in Wilson's Disease and the impact of motor symptom treatment on sleep

Two video-PSG case-control studies have reported abnormal sleep architecture, with REM stages predominantly affected and a third demonstrating objective daytime sleepiness on MSLT and cataplexy-like epsiodes.[70,71] There is some limited evidence for higher rates of RLS amongst those with Wilson's disease compared to the general population, with 31% of a single cohort (n=42) meeting diagnostic criteria, and subsequent PSG demonstrating increased PLMS compared to controls (p=0.009).[72] Albeit in a single case-report, D-penicillamine resolved complaints of hypersomnia, while a case-control study identified higher rates of probable RBD found in those treated with D-penicillamine.[71,73]

Sleep disorders in Niemann Pick Type C

The heterogeneous and nonspecific clinical presentation of Niemann Pick Type C challenges its diagnostic process, although secondary cataplexy is an important and discriminatory clinical feature. A single, small (n=5) PSG study has been performed to date, with evidence of reduced total sleep time (p<0.01), sleep efficiency (p<0.001), shorter sleep latency (p<0.01), increased wake after sleep onset (WASO, p<0.05) and decreased REM sleep (p<0.05).[74] Reduced CSF hypocretin levels were also observed compared to controls, a feature also seen in narcolepsy and cataplexy, and consistent with hypothalamic dysfunction (Figure 2C).[74]

Sleep disorders in Anti-IgLON5 and the impact of disease treatment on sleep

Immunoglobulin-like cell adhesion molecule 5 (IgLON5) is a recently described disorder in which sleep disturbance is pronounced, as well as gait instability and movement disorders. The underlying aetiology of this disorder is thought to be a combination of neuroinflammation and neurodegeneration, with post-mortem evidence of hyperphosphorylated tau deposition.[75] The sleep disorders described include REM and NREM sleep parasomnias, sleep disordered breathing, namely stridor and obstructive apnea, insomnia and hypersomnolence. Three PSG studies have identified altered sleep architecture, with evidence of undifferentiated NREM sleep and poorly structured N2 associated with abnormal behavioural manifestations.[76–78] Treatment of IgLON5 with intravenous steroids show normalised sleep onset and N1 and N2 stages, although marked abnormal sleep re-remerged three months later in spite of additional immunotherapy.[78]

Sleep Disorders in Dystonia

Disturbances to sleep have been reported in 40-70% of dystonia cohorts, with insomnia and abnormal movements during sleep (e.g. RLS) most commonly described, although several studies have also reported few or no disturbances to sleep.[79,80] A probable contributory role of the common psychiatric comorbidities (depression and anxiety in particular) to these sleep-related symptoms, is also likely and important to bear in mind. As such, varying changes in sleep architecture have been observed in distinct types of isolated idiopathic dystonia with PSG recordings of individuals with cervical dystonia (CD) (n=22), blepharospasm (BSP) (n=3), Meige Syndrome (n=7), and in combined genetic forms, such as *GCH1* mutation positive dopa-responsive dystonia (n=6), showing increased N1 phase (NREM) duration and reduced REM periods, compared to controls.[79,81]

Sleep in relation to the treatment of Dystonia

Levodopa has been shown to benefit sleep in those with *GCH1* mutation positive dopa-responsive dystonia, reducing rates of excessive daytime sleepiness, although also reducing total REM sleep.[82]

Trihexyphenidyl has been reported to increase wakefulness and decrease REM sleep however, the drowsiness experienced at lower doses has limited its clinical use. Benzodiazepines are also often used in the management of dystonia, and as traditional hypnotics they decrease sleep latency but also suppress slow-wave sleep, lengthen REM sleep latency and can cause habituation with rebound insomnia. Also sometimes used, is gabapentin, an alpha 2 delta ligand that increases slow wave sleep, although when used during the day can be associated with drowsiness, fatigue and sedation. However, in children diagnosed with dystonia, gabapentin has been shown to reduce motor symptoms severity (n=69), as well as improve sleep quality and duration (p<0.01).[83]

Sleep Disorders in Essential Tremor

Sleep disturbances in ET are milder than those seen in PD, with a single PSG based study showing few objective changes compared to controls, in contrast to those with PD, although examination of the phenotypic heterogeneity amongst the ET cohort found that those PSG changes observed were most prominent in those with mild cognitive impairment.[84] A recent review, albeit using questionnaire only data, describes excessive daytime somnolence, RLS, insomnia and nocturia to be frequently reported by patients diagnosed with ET.[85] Once again, psychiatric comorbidities (anxiety in particular) likely play some role in contributing to the symptoms described.

Sleep in relation to the treatment of Essential Tremor

Commonly used in the treatment of essential tremor, beta-blockers often cause or worsen nightmares and restless legs, with 12 studies to date reporting rates of sleep disturbance between 12% and 60%.[86] Primidone has also been reported to have sedative side effects, including daytime sleepiness and tiredness (50%), often resulting in discontinuation of treatment (27%). As described above, Gabapentin, also sometimes used in the management of tremor, carries with it side effects that include drowsiness, fatigue and sedation.

Sleep in Tourette Syndrome

Many with Tourette's Syndrome (TS) have both insomnia and increased movements at night, during both REM and NREM stages, with studies of those with co-morbid attention deficit hyperactivity disorder (ADHD) reporting rates of sleep disorders to be as high as 80%.[87] Comparison with healthy controls has shown significant reductions in sleep efficiency (p<0.05) and total sleep time (p<0.01), while sleep latency (p<0.05) and WASO (p<0.001) were increased. In contrast, changes to the REM portion of sleep has varied between studies, with some reporting reduced periods (n=18/34), while others show increased or comparable levels to controls.[88] Other studies have sought to separate TS

patients with and without symptoms of ADHD, with reduced REM sleep latency and increased REM sleep observed in both groups, while those with ADHD symptoms also had evidence of insomnia, RLS/PLMS and NREM parasomnias.[89] Interestingly, variants in the orexin-2/hypocretin-2 (OX2R) receptor gene, mutated in canine narcolepsy, have also been found to be present in those diagnosed with TS.[90]

Sleep in relation to the treatment of Tourette Syndrome

Albeit in only a small cohort of patients with tics (n=3), abnormal NREM sleep and sleep apnea resolved in two when treated with tetrabenazine.[91] A recent review article also noted that those treated with anti-psychotics (risperidone, aripiprazole and tiapride) were more likely to experience somnolence, sedation and sleep disturbance.[92]

Challenges in the field

As outlined above, increasing data suggests sleep disorders to be prevalent across the spectrum of movement disorders, although much of this work is limited by small, heterogenous cohorts. Larger studies often involve questionnaire-based assessments alone, while those that do involve PSG measurements vary in their approach with differences in single night versus multi-night assessments. The night-to-night variability typical of all sleep patterns questions the validity of single-night studies, particularly those undertaken in unfamiliar environments. To counter this, portable devices are now widely used in the home setting, allowing longer periods of monitoring. Further work with these non-laboratory-based techniques is needed in order to establish more robust normative values on an individual and disorder-specific level.

While motor symptoms are usually considered as the first cause of sleep disturbance (e.g. dystonia in PD), it is important to recognise that comorbidities such as mood disorders and pain also have the potential to impact sleep. The relationship between depression and disturbed sleep is complex and bidirectional, for example, insomnia may be a direct result of depression or secondary to the movement disorder. Although few studies have addressed this issue, some have reported more impaired sleep (sleep maintenance insomnia) in patients with PD and depression than those without depression. Treatment of anxiety and depression should be managed as effectively as possible and may help consolidate the sleep/wake cycle.

Another important area for future understanding, and a potential avenue for therapeutic intervention is the glial-lymphatic (glymphatic) pathway, a highly organised fluid transport system moving cerebrospinal fluid (CSF) from the subarachnoid space to the peri-parenchymal interstitial

fluid (ISF).[93] Murine studies have shown that glymphatic function increases during sleep, allowing for clearance of metabolic by products. Several studies have demonstrated that during disrupted or impaired sleep, these processes do not have sufficient time for normal clearance, leading to the accumulation of metabolites with subsequent impact on cognition and behaviour. Protein aggregates found in the glymphatic system include alpha-synuclein, as well as amyloid β (Aβ) observed in Alzheimer's disease. Dopamine and noradrenaline also appear to contribute to regulating ISF flow within the glymphatic system, resulting in feed-forward enhanced neurotransmission increasing dopamine and noradrenaline neurotransmission during wake states.[94]

Assessment and treatment considerations

A detailed discussion of the management of different sleep disorders is beyond the scope of this review, and only general guidelines are provided. An initial clinical history from both patient and bed partner wherever possible, alongside simple questionnaires, often allows good differentiation of many sleep disorders. Consideration of the impact of motor symptom onset, severity and prescribed medication is also important. Co-morbid medical conditions that may cause or contribute to sleep disorders should be considered, for example primary treatment of psychiatric disorders may improve sleep-related symptoms. Sleep hygiene should be reviewed (e.g. caffeine use) and simple behavioural interventions considered in the first instance. CBT is recommended as standard therapy for the long-term management of insomnia, with digital forms of this treatment becoming increasingly available to broaden access and availability. Pharmacotherapy is effective in the treatment of moderate or severe RLS, with several clear treatment algorithms available, while extensive evidence supports the use of CPAP in the management of OSA, again aided by standardised therapy guidelines.

Conclusion

This review demonstrates that many patients with movement disorders also experience symptoms related to sleep disorders. Dysfunction of the medulla, raphe nuclei, pons and basal ganglia potentially form a shared underlying mechanism for both motor and sleep pathophysiology. For some, there are specific patterns to the sleep problems but for many, changes to sleep are multifactorial, involving medication side effects, motor and non-motor symptoms, suggesting the need for a systematic approach to assessment. Further work is needed to better understand the aetiology of sleep disturbances across distinct movement disorders in order to facilitate more targeted and effective therapeutic strategies, and to understand whether targeting poor sleep leads to clear improvements in motor outcomes. Future studies should be directed towards combining

limited PSG assessment with far wider application of wearable or mobile home devices in order to

identify robust digital biomarkers of utility in diagnosis and symptomatic monitoring.

Contributorship Statement
Grace Bailey: Conception, acquisition, analysis and interpretation of the data, drafting and revising critically for important intellectual content.
Emily Hubbard: acquisition, analysis and interpretation of the data, drafting and revising critically for important intellectual content.
Alfonso Fasano: drafting and revising critically for important intellectual content
Marina Tijssen: drafting and revising critically for important intellectual content
Timothy Lynch: drafting and revising critically for important intellectual content
Kirstie Anderson: acquisition, analysis and interpretation of the data, drafting and revising critically for important intellectual content.
Kathryn Peall: Conception, acquisition, analysis and interpretation of the data, drafting and revising critically for important intellectual content.

Competing Interests
The authors report no competing interests.

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Figure Legends

Figure 1. Sleep hypnogram illustrating a normal sleep cycle and physiological changes. Abbreviations: NREM1/2/3: Non-Rapid eye movement sleep stages 1, 2 and 3, REM sleep: Rapid eye movement.

Figure 2A. Neurotransmitters and brain regions involved in the sleep-wake cycle **(B) REM sleep circuitry:** Hypothesized pathways include synucleinopathic degeneration in the SLD in DLB, in addition to vM in PD, causing loss of REM sleep atonia. Pathological changes to the LDT/PPN and LC in MSA may contribute to RBD **(C) Schematic of neurotransmitters involved in movement disorders and sleep. (I) Hypocretin/orexin and acetylcholine:** 1: Reduced hrct-1 in the CSF of NPC, PSP and PD, 2: Reduced immunostaining of hcrt-1 neurons in MSA and HD, 3: Decreased hcrt-1 in mouse models of HD, 4: Deletion of torsinA protein associated with cholinergic neuronal loss in dystonia, 5: Cholinergic neuronal loss in the striatum of PD and PSP patients. (**II) Monoamines:** 6: Reduced NA concentrations in dystonia patients, 7: Loss of NA neurons in PD, 8: Reduced DAT in WD, NPC and TS, and RBD patients who developed PD, 9: Reduced D3 receptors in PD associated with EDS, reduced D2 receptors in DYT1, DYT6, DYT11, *NKX2.1,* increased D2 receptors in TS, 10: Elevated DA uptake in TS, 11: Reduced SERT in PD, MSA, CD, 12: Reduced 5-HT levels in CD, 13: Increased 5-HT binding in TS, 14: Up-regulation of 5-HT$_{2A}$ receptors in TS, 15: Reduced 5-HIAA in MD, 16: Depleted 5-HT in raphe nuclei of MSA. **(III) Glutamate and GABA:** 17: Reduced glutamatergic neurotransmission in mouse models of NPC, 18: Reduced NMDA receptors in HD, 19: Increase in GABA$_A$ receptors in *HTT* gene carriers, 20: Reduced GABAergic neurons in TS brains, 21: Reduced GABA$_A$ receptors in dystonia. **Abbreviations:** 5-HIAA: 5-hydroxyindoleacetic acid, 5-HT: Serotonin, ACh: Acetylcholine, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, BF: Basal forebrain, DA: Dopamine, DAT: Dopamine transporter, D2/3: Dopamine receptors, DRN: Dorsal raphe nuclei, GABA: Gamma aminobutyric acid, Glu: Glutamate, Hcrt/Orx: Hypocretin/orexin, Hcrt-1: Hypocretin-1 receptor, HIST: Histamine, LC: Locus Coeruleus, LDT: Lateral Dorsal Tegmentum, LPT: Lateral Pontine Tegmentum, LH: Lateral Hypothalamus, MCH: Melanin-concentrating Hormone, mACh: Muscarinic acetylcholine receptors, NA: Noradrenaline, nACH: Nicotinic acetylcholine receptors, NMDA: N-methyl-D-aspartate, PB: Parabrachial Nucleus, PPN: Pedunculopontine nucleus, PPT: pedunculopontine, PZ: Parafacial zone, SCP: Superior Cerebellar Peduncle, SERT: Serotonin transporter, SLD: Sublaterodorsal Nucleus, SN: Substania Nigra, TMN: Tuberomammillary nucleus, VLPO: Ventrolateral preoptic nucleus, vM: Ventromedial Medulla, vPAG: Ventral Periaqueductal gray matter, VTA: Ventral tegmental area, α: Alpha-adrenergic receptor, β: Beta-adrenergic receptor.

Table 1: Characteristic features of sleep disorders defined by the International Classification of Sleep Disorders (ICSD-3)

Sleep Disorder	Clinical Features	Diagnostic Criteria	Treatment	Proposed Pathophysiology
Chronic Insomnia	Difficulty falling asleep and/or maintaining sleep, with symptoms impacting daytime activity. Symptoms present on most nights for at least 3 months and occur at least three times per week.	Problems initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance going to bed on appropriate schedule or difficulty sleeping without parent/caregiver intervention. Sleep/wake complaints cannot be explained by inadequate opportunity or circumstances. In addition, fatigue, impaired performance, prone to errors/accidents	1st Line: CBT where available. Other treatments: Antihistamines, melatonin, benzodiazepines	1. Disinhibition of the VPLO 2. Impaired disengagement of cortical regions involved in executive control and attention 3. REM instability 4. Melatonin deficiency
Sleep Related Breathing Disorders				
Obstructive Sleep Apnoea	Chronic disorder characterised by snoring with episodes of upper airway collapse during sleep, waking with choking or breath holding. Associated fragmented, unrefreshing night sleep, insomnia and excessive daytime sleepiness. Risk factors: hypertension, type 2 diabetes mellitus and congestive cardiac failure.	PSG detecting ≥ 5/hour obstructive respiratory events alongside other criteria (e.g. partners reports of habitual snoring or breath interruptions) *or* ≥15/hour obstructive respiratory events during PSG.	CPAP: recommended first line therapy	1. Altered arousal threshold 2. Instability of ventilatory control 3. Increased glutamate and decreased GABA neurotransmission 4. Small pharyngeal airway
Central Sleep Apnoea	Abnormal brainstem ventilatory responses leading to reduced or absent respiratory effort, with no evidence of snoring. Results in insufficient/absent ventilation, frequent night-time awakenings and excessive daytime sleepiness. Common causes: opiate use and cardiac failure	PSG demonstrating ≥5/hour central apnoeas, number of central apnoeas is >50% of the total number of apnoeic and hypopneic episodes	CPAP treatment is less effective than in OSA.	1. Absence of ventilatory drive
Hypersomnolence				
Narcolepsy	Orexin/Hypocretin deficiency resulting in daytime sleepiness, sleep paralysis, hypnagogic hallucinations +/- cataplexy cause by instability in transitions between wake, NREM and REM sleep.	Narcolepsy Type 1: Diagnosed by the presence of one or both of i) cataplexy and a mean sleep latency of ≤8 minutes and ii) two or more sleep-onset REM periods (SOREMPs) on an MSLT. Narcolepsy Type 2: Daily periods of irrepressible need to sleep or daytime lapses into sleep confirmed with MSLT. Absence of cataplexy confirmed with CSF hypocretin-1 concentrations (>110 pg mL^{-1} or >1/3 of mean values obtained in normal subjects).	Amphetamine-like, Modafinil, Sodium oxybate	1. Unstable transitions between wake, REM and NREM sleep caused by loss of hypocretin neurons 2. Abnormal circadian regulation 3. Insufficient NREM sleep 4. Hypothalamic lesions

Idiopathic Hypersomnia	Excessive daytime sleep and/or sleepiness, prolonged unrefreshing overnight sleep and difficulty waking occurring for at least 3 months.	MSLT shows fewer than two sleep onset REM periods or none if REM latency is ≤15 minutes. In addition to the presence of either an MSLT of ≤8 minutes, elevated total sleep time (12-14 hours) on PSG/wrist actigraphy or at least three daytime lapses into sleep associated with a sleep log (over seven nights).	Changes to routine, behavioural therapy, modafinil.	1. Abnormal neurotransmitter signalling of histamine, serotonin, dopamine and GABA
Parasomnias				
NREM Parasomnias	Confusional arousal, somnambulism and sleep terrors with incomplete/no recall. Predominantly arise during the first third of the night, during slow wave sleep.	<u>Confusional arousal:</u> Recurrent mental confusion on arousal/awakening, absence of fear, walking behaviour or hallucinations in association with episode. <u>Sleep walking:</u> Ambulation during sleep, difficulty arousing the patient during an episode, amnesia. <u>Sleep terrors:</u> PSG demonstrates tachycardia in associated with the episode and other sleep disorders e.g. nightmares, can be present.	Medical therapy used when episodes are frequent or violent. Melatonin and benzodiazepines, notably clonazepam, most commonly used.	1. Reduced regional perfusion in the frontal and parietal areas during N3 sleep 2. Activity in the thalamus and cingulate cortex during N3 sleep
REM Sleep Behaviour Disorder (RBD)	RBD occurs with loss of normal REM muscle atonia, resulting in dream enactment, often with injury to the patient/bed partner. Events tend to be memorable and associated with dreams.	Repeated episodes of sleep vocalisation and/or motor behaviours documented in video PSG during REM sleep or based on clinical history. PSG demonstrates REM sleep without atonia.	Melatonin and clonazepam, although no RCTs to date.	1. Dysfunction of the subcoeruleus nucleus, the medullary magnocellularis and the sublaterodorsal nucleus 2. Glutamatergic, GABAergic and cholinergic abnormalities
Sleep Related Movement Disorders				
Restless Leg Syndrome and Periodic Limb Movements During Sleep	Unpleasant sensation in the LL, affecting onset and maintenance of sleep. PLMS are periodic, repetitive LL movements typically co-occurring with RLS	<u>RLS:</u> Sensation begins or worsens during periods of rest (e.g. lying down), predominantly at night, which are relieved by movements. Symptoms should cause concern, sleep disturbance or impairment in important areas of functioning (e.g. physical, social). <u>PLMS:</u> PSG demonstrates PLMS with a frequency of >15h and causes significant sleep disturbance or impairs other important areas of functioning.	Dopamine agonists (rotigotine, pramipexole, ropinirole), gabapentin and pregabalin	1. Altered spinal circuits in sensory and motor processing areas 2. Dopaminergic and glutamatergic dysfunction 3. Iron deficiency

Legend: AHI: Apnoea-Hypopnea index, CSF: Cerebral Spinal Fluid, GABA: Gamma aminobutyric acid, LL: Lower Limb, N3: Non-rapid Eye Movement stage 3, NREM: Non-rapid Eye Movement sleep, OSA: Obstructive Sleep Apnoea, PLMS: Periodic Limb Movements During Sleep, PSG: Polysomnography, QoL: Quality of Life, REM: Rapid Eye Movement sleep, RBD: REM Sleep Behaviour Disorder, RLS: Restless Leg Syndrome, VLPO: Ventrolateral Preoptic Nucleus

Table 2: Case-Control Polysomnography studies involving patients diagnosed with degenerative movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Huntington's Disease	Wiegand et al.	1991	HD (12) HC (12);	Two nights of PSG	Patients had an increased sleep onset latency, reduced sleep efficiency, increased number of awakenings and reduced slow wave sleep compared to controls
Huntington's Disease	Wiegand et al.	1991	HD (16) HC (16)	Two nights of PSG	HD patients had reduced sleep efficiency, increased sleep onset latency, reduced slow wave sleep and more time spent awake
Huntington's Disease	Emser et al.	1988	HD (10) HC (12); 7 volunteers,	Two nights of PSG	HD and HC had no differences except for two patients who had a reduction in slow wave sleep. Sleep spindle was also increased during N2 which correlated to duration of disease
Huntington's Disease	Arnulf et al.	2008	HD (25), HC (25) Narcolepsy (25)	Overnight PSG, MSLT, ESS, clinical interview	HD patients had insomnia, earlier sleep onset, lower sleep efficiency, increased PLMS and shortened REM sleep, ESS was normal. 12% exhibited RBD
Huntington's Disease	Cuturic et al.	2009	HD (12) HC (12)	One night of PSG, ESS	ESS score had no significant difference between groups. Sleep latency was significantly longer in patients. Nocturnal SRBD were absent
Huntington's Disease	Goodman et al.	2011	HD (9) HC (10);	3 nights v-PSG, MSLT, ESS, Actigraphy, FOSQ, MOS, BDI-2	FOSQ, ESS and MOS scores didn't differ from controls. Sleep architecture (lower percentage of REM sleep) and sleep efficiency differed compared to controls
Huntington's Disease	Neutel et al.	2015	HD (29) HC (29)	v-PSG	Patients had longer total sleep and REM sleep onset latency. 2 patients had RWA. 7 patients had giant sleep spindles and one control
Huntington's Disease	Lazar et al.	2015	HD (38): premanifest gene carriers HC (36)	Two nights PSG and MSLT, two weeks of Actigraphy	Gene carriers had more disrupted sleep, characterised by fragmented sleep profile: a decrease in REM sleep
Huntington's Disease	Piano et al.	2015	HD (30) HC (30);	1night v-PSG, ESS, IRLSSG, BQ, RBDSQ	Two patients reported RLS, 8 had scores ≥ 9.8 patients had high risk of OSA. 2 had pathological RBD. PSG showed no RWA and RBD. Disease duration correlated with ESS
SCA	Seshagiri et al.	2018	SCA1 (6), SCA2 (5) SCA3 (7), HC (6)	Overnight PSG	Sleep spindle density significantly decreased in SCA
SCA	Rodríguez-Labrada et al.	2019	SCA2 (20) SCA2 preclinical carriers (20), HC (20)	One whole night of PSG	Compared to controls sleep spindle density was significantly reduced in SCA2 and preclinical patients. Reduced spindle activity correlated with reduced N3 sleep in SCA2 patients
SCA	Rueda et al.	2016	SCA 6 (12) HC (12);	Overnight PSG	SCA6 had higher frequency of snoring, respiratory disorders and slow wave sleep compared to controls
SCA	Zanatta et al.	2019	SCA 2 (17) HC (17)	One night of v-PSG	Increased REM sleep in 70%, increased REM latency in 52%, increased OSA in 82% and absent REM density in 76%. Compared to controls SCA2 had reduced total sleep time, sleep efficiency, sleep latency, sleep N3 latency, REM quantity, N2 and N3 quantity. Disease progression correlated with a reduction in REM density and sleep efficiency
SCA	Iranzo et al.	2003	SCA3 (9) HC (9);	Overnight PSG, sleep questionnaire	55% of patients has RBD compared to no controls. SCA3 patients had reduced total sleep time, sleep efficiency, REM sleep percentage, increased WASO and PLMI
SCA	Pedroso et al.	2013	SCA3 (22) from 15 families	Overnight PSG, RBDSQ, IRLSSG	SCA3 patients; 54% had RLS, 77% had PLMS, 73% had RWA and 59% had RBD

			HC (20)		
SCA	Velázquez-Pérez et al.	2011	SCA2 (32) HC (32); age- and gender-matched	Two nights of v-PSG, ESS, sleep interviews	Reduced REM sleep percentage and REM density, an increase in RWA, PLMS in 37.5% of patients. 21.8% complained of insomnia vs 3% in HC and RLS diagnosed in 25% of patients compared to 3% in HC. No difference in ESS scores
SCA	Silva et al.	2016	SCA3 (47) HC (47);	Overnight PSG, IRLSSG, RBDSQ,	SCA3 had higher frequency of arousals from slow wave sleep, parasomnia complaints, RWA, PLMI, percentage of N1 and N3 sleep
SCA	Chi et al.	2013	SCA 3 (15) HC (16)	Overnight PSG, ESS	SCA3 patients had reduced sleep efficiency and percentage of REM sleep which negatively correlated with severity of ataxia. ESS was normal to controls
SCA	Reimold et al.	2006	SCA1 (10), SCA2 (4) SCA3 (2), HC (9);	Overnight PSG, ESS	RLS present in 25% of SCA1 and SCA2 patients, 100% of SCA3 patients. All RLS patients had abnormal PLMS score. One RLS had OSA. 1 SCA2 and SCA3 patient had EDS
SCA	London et al.	2018	SCA 10 (23) HC (23)	One night of PSG, ESS	SCA10 patients had longer REM sleep and more REM arousal than controls. REM sleep onset correlated with disease duration
Wilson's Disease	Netto et al.	2010	WD (25) HC (25)	PSG	Patients had reduced total sleep time, sleep efficiency, percentage of N3 sleep, and REM sleep, prolonged sleep-onset latency and latency to N2
Wilson's Disease	Trindade et al.	2017	WD (42) HC (42)	v-PSG, IRLSSG, ESS, PSQI, BDI	Sleep quality was worse compared to HC. WD patients showed lower sleep efficiency, less N2 sleep and more WASO and arousal compared to HC. WD with RLS showed significantly more PLM, more N1 sleep and a longer REM sleep latency
Wilson's Disease	Tribl et al.	2015	WD (41) HC (41)	v-PSG, RBDSQ, PSQI, ESS, MSQ, clinical and sleep interviews	5 WD patients fulfilled the RBD criteria and had significantly higher values in RWA. RWA in WD patients without RBD was still significantly increased compared to controls
Wilson's Disease	Nevsimalova et al.	2011	WD (55) HC (55);	PSG (24 WD and HC), ESS, RBDSQ,	13 WD patients fulfilled RLS criteria. WD patients were more prone to daytime napping, EDS and poor nocturnal sleep. Mean ESS and RBDSQ were higher than controls. TST was lower, with decreased sleep efficiency and increased wakefulness. WD had lower latency of N1 and N2 sleep. 14% had MSLT <8 minutes
Niemann-Pick Type C	Vankova et al.	2003	Juvenile NPC (5) HC (12)	At least one night of PSG, MSLT	In all patients, sleep was fragmented and disorganised. Total sleep time and sleep efficiency was lower, shorter sleep latency and increased WASO

Key: BDI/-2: Beck's Depression Inventory, BQ: Berlin Questionnaire, EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Scale, FOSQ: Functional Outcomes of Sleep Questionnaire, HC: Healthy control, HD: Huntington's Disease, HDSS: Hungtinton's Disease Sleepiness Scale, IRLSSG: International Restless Leg Syndrome Study Group, MSLT: Multiple Sleep Latency Test, MSQ: Mayo Sleep Questionnaire, OSA: Obstructive Sleep Apnea, PLMI: Periodic Limb Movement Index, PLMS: Periodic Limb Movement during Sleep, PSG: Polysomnography, PSQI: Pittsburgh Sleep Quality Index, RBD: Rapid Eye Movement sleep Behaviour Disorder, RBDSQ: Rapid Eye Movement sleep Behaviour Disorder Screening Questionnaire, REM: Rapid Eye Movement sleep, RLS: Restless Leg Syndrome, RWA: Rapid Eye Movement sleep Without Atonia, SCA: Spinocerebellar Ataxia, SRBD: Sleep-related Breathing Disorder, v-PSG: Video Polysomnography, WASO: Wake After Sleep Onset, WD: Wilson's Disease.

Table 3: Case-Control Polysomnography studies involving patients with non-degenerative movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Dystonia	Gadoth et al.	1989	HPD (3) HC (11)	PSG over two nights (two patients, and one night in one patient and HC)	Sleep structure appeared to be normal in all subjects
Dystonia	Jankel et al.,	1983	DMD (4) HC (4): age- and gender- matched	PSG over three nights	PSG showed increased sleep latency, reduced sleep efficiency, and unusually high voltage of sleep spindles (>100μV) sleep spindles during N2
Dystonia	Jankel et al.	1984	DMD (9) HC (9): age- and gender- matched	PSG over three nights	All patients slept poorly, patients with advance stages of dystonia all displayed high-amplitude (>150μV) spindles during N2 and N3, increased sleep latency, less REM sleep, increased number of awakenings and poor sleep efficiency
Dystonia	Fish et al.	1990	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10)	PSG over two nights	Four patients (taking benzodiazepines) with TD had increased sleep spindles more than both control groups. All patients with severe disease had abnormal sleep spindles
Dystonia	Fish et al.	1991	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10) Same sample as Fish et al., 1990	PSG over two nights	All patients and controls showed reduced EMG activity during REM sleep compared to wakefulness. Patients with secondary TD had fewer bursts of activity than normal subjects. RBD was absent in all groups
Dystonia	Fish et al.	1991	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10) Same sample as Fish et al., 1990	PSG over two nights	Movements were most frequent during awakening, proceeded by N1, with very few movements during N2 and REM sleep. Sleep-related movements in primary and secondary TD emerged after brief awakenings
Dystonia	Lobbezoo et al.	1996	CD (9) HC (9) age- and gender-matched	PSG over two nights	PSG in CD patient were normal. Sleep was associated with an improvement of symptoms in CD, with abnormal cervical muscle activity decreasing immediately when lying down and then being abolished when transitioning to light NREM sleep
Dystonia	Brüggemann et al.	2014	DRD (23) HC (26): age-matched	PSG over one night, PSQI, ESS, SSS, FEPS-2, BDI, self-administered comorbidity questionnaire	Sleep quality, SSS and ESS was similar across groups. 6 patients underwent PSG, 2 had reduced sleep efficiency, 2 increased sleep latency, 5 increased REM latency, 4 had initiation problems and 4 had increased in numbers of arousal

Dystonia	Antelmi et al.	2017	CD (20) HC (22): age- and gender-matched	One full night of PSG, RLS, PSQI, ESS, BDI	PSQI showed significant reduction in sleep quality, and correlation with higher scores of BDI. ESS scores were normal. Difficulties in sleep efficiency and increased sleep latency and increased REM sleep latency. Patients had lower muscle amplitude contraction over the dystonic muscles compared to HC in slow wave sleep and REM sleep
Tic Disorders	Hashimoto et al.	1981	TS (9) HC (9)	PSG	At all stages of sleep, body movements during sleep were more frequent in cases of TS. Twitch movements in REM sleep were significantly increased in TS. TS patients had increased total sleep time, REM sleep and NREM sleep
Tic Disorders	Voderholzer et al.	1997	TS (7) HC (7); age- and gender-matched	Two nights of PSG	5/7 showed frequent PLMS in NREM and total sleep time significantly lower in TS group (p<0.05)
Tic Disorders	Cohrs et al.	2001	TS (25); adults HC (11)	v-PSG over two consecutive nights	Patients with TS showed reduced sleep efficiency, total sleep time/time in bed, and percentage of slow wave sleep, as well as significantly prolonged sleep latency, significantly increased percentage of N1, percentage of time awake, and increased number of awakenings and sleep stage changes/hour sleep period time
Tic Disorders	Kostanecka-Endress et al.	2003	TS (17); children HC (16); age-, gender-, IQ-matched	Two nights of PSG, CBCL sleep items (parent), semi structured interview with parents and patients	Children with TS demonstrated longer sleep period time, longer sleep latency, reduced sleep efficiency, and prolonged wakefulness after sleep onset. Short arousal-related movements were increased in TS.
Tic Disorders	Kirov et al.	2007	TS (18) TS+ADHD (18) ADHD (18) HC (18)	Two nights of PSG	TS patients had lower sleep efficiency and elevated arousal index in sleep. TS+ADHD patients had reduced sleep efficiency, elevated arousal index and increase in REM sleep
Tic Disorders	Kirov et al.	2007	TS+ADHD (19) HC (19)	Two nights of PSG	Shorter REM sleep latency and increased REM sleep duration in patients with TS+ADHD
Tic Disorders	Stephens et al.	2013	TS (20) TS+ADHD (21) HC (16) ADHD (33)	Two nights of PSG, respiration belt	Total number of leg movements higher in TS+ADHD group compared to TS only. Children with TS and ADHD had a significant higher number of arousals from slow wave sleep and total arousals
Tic Disorders	Kirov et al.	2017	TS (21) ADHD/TS (21) ADHD (24) HC (22); age- and gender-matched	Two nights of PSG	Increased REM sleep and shorted REM latency in children with psychiatric disorders than controls

Key: ADHD: Attention Deficit Hyperactive Disorder, BDI: Beck's Depression Inventory, CD: Cervical Dystonia, DRD: Dopamine-responsive dystonia, EMG: Electromyography, ESS: Epworth Sleepiness Scale, FEPS-2: Sleep-related Personality Traits Questionnaire, HC: Healthy control, HPD: Hereditary Progressive Dystonia, NREM1/2/3: Non-Rapid Eye Movement Sleep stages, PLMS: Periodic Limb Movement during Sleep, PSG: Polysomnography, PSQI: Pittsburgh Sleep Quality Index, RBD: Rapid Eye Movement sleep Behaviour Disorder, REM: Rapid Eye Movement sleep, RLS: Restless Leg Syndrome, TD: Torsion Dystonia, TS: Tourette's Syndrome, v-PSG: Video Polysomnography.