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Review

Sleep Disorders and Circadian Disruption in Huntington's Disease

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Abstract. Sleep and circadian alterations are common in patients with Huntington's disease (HD). Understanding the pathophysiology of these alterations and their association with disease progression and morbidity can guide HD management. We provide a narrative review of the clinical and basic-science studies centered on sleep and circadian function on HD. Sleep/wake disturbances among HD patients share many similarities with other neurodegenerative diseases. Overall, HD patients and animal models of the disease present with sleep changes early in the clinical course of the disease, including difficulties with sleep initiation and maintenance leading to decreased sleep efficiency, and progressive deterioration of normal sleep architecture. Despite this, sleep alterations remain frequently under-reported by patients and under-recognized by health professionals. The degree of sleep and circadian alterations has not consistently shown to be CAG dose-dependent. Evidence based treatment recommendations are insufficient due to lack of well-designed intervention trials. Approaches aimed at improving circadian entrainment, such as including light therapy, and time-restricted feeding have demonstrated a potential to delay symptom progression in some basic HD investigations. Larger study cohorts, comprehensive assessment of sleep and circadian function, and reproducibility of findings are needed in future in order to better understand sleep and circadian function in HD and to develop effective treatments.

Keywords: Huntington's disease, sleep, sleepiness, circadian rhythm

INTRODUCTION

Huntington's disease (HD) is the first genetic disease mapped using DNA polymorphisms [1]. HD is a monogenic autosomal-dominant neurodegenerative disease caused by an abnormal expansion of a trinucleotide-cytosine-adenosine-guanosine (CAG) repeat in exon 1 of the huntingtin gene on chromosome 4, resulting in mutant huntingtin [1,2]. The number of CAG expansions is inversely correlated with the age of clinical onset. Most patients with HD are heterozygous, have an average of 42 CAG repeats, and have midlife onset of the disease. Investigations preceding the genetic characterization of HD were only able to include overtly symptomatic patients, whereas nowadays it is possible to study alterations at the prodromal stage.

HD is characterized by abnormal movements and progressive cognitive and psychiatric disturbances. This triad has expanded to include sleep abnormalities [3]. Sleep and circadian disturbances can precede motor manifestations of HD by years and can have an impact on disease severity and rate of progression [3–6]. There is an interesting bidirectional relationship between sleep and HD symptoms, reviewed in detail in Videnovic et al. [7] as neuroanatomical degeneration results in sleep abnormalities, which in turn worsen the cognitive and psychiatric symptoms of HD [7–9].

Animal models have played a fundamental role in the study of the molecular pathophysiology of

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HD. In fact, the pathognomonic nuclear aggregates of mutant huntingtin were first identified in mice and subsequently in the human cortex and striatum, first identified by Roizin et al. [10–12]. Mutant huntingtin disrupts many cellular processes, including neuroepithelial junctional complexes, neurogenesis, and cellular polarity [13–15]. Mutant huntingtin may influence human cortex formation as early as during fetal neurodevelopment [13].

Currently, there is no cure for HD. Available treatments are centered on symptomatic management. Considering the impact of sleep and circadian homeostasis on overall well-being and its common disruption in neurodegeneration, improved understanding of sleep and circadian abnormalities in HD can not only inform potential treatment strategies but also shed light on the underlying pathophysiology of HD. In this review we summarize investigations centered on sleep and circadian rhythms in animal models of the disease and affected individuals.

METHODS

We performed a literature search of human and animal studies and review articles published up to January 2023 in the PubMed and Science Direct databases with the following MeSH terms: "sleep disorder, intrinsic", "dyssomnias", "sleep disorders, circadian rhythm", "cycle disorders, sleep wake", "parasomnias", "parasomnias, REM sleep"; and non-MeSH terms "sleep disorders" and "circadian rhythm", in combination with "Huntington's disease".

We selected articles that presented information regarding sleep disorders and/or circadian rhythm disorders in HD patients and/or HD animal models, with the full manuscript available in English. We also searched the list of references from the selected manuscripts to identify additional articles not included in the initial search.

CLINICAL INVESTIGATIONS OF SLEEP IN HD PATIENTS

There has been a slow increase in the number of clinical investigations of sleep in the HD population. The methodologies are various, and studies range from case reports [16,17], retrospective chart reviews [18,19], sleep diaries and locomotor activity assessments [20], self-reported patient questionnaires [21–24], to the more objective and reproducible polysomnography-based investigations [3,25–30]. After the identification of the causative mutation of HD in 1993, the inclusion of premanifest mutation carriers in clinical investigations has advanced our understanding of early-stage HD. These premanifest HD patients have sleep abnormalities, which precede cardinal clinical features of chorea, psychiatric, and cognitive symptoms. Sleep issues have a prevalence of 58–77% in HD patients [22,24]. Excessive daytime somnolence is also common, affecting 12–50% with variably significant differences when compared to controls [22,24].

Self-reports assessments of sleep in HD

Patient questionnaires are easily accessible. Most reported clinical studies included standardized assessments of sleep, such as the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Daytime Sleepiness Scale (ESS). Nonetheless, patients may be unaware of sleep abnormalities, which makes self-reporting unreliable, leading to an underestimation of the prevalence of sleep abnormalities in HD.

Aziz et al. evaluated sleep with a series of questionnaires (ESS, PSQI, SCales for Outcomes in Parkinson's disease (SCOPA)-Sleep, and Beck's Depression Inventory (BDI)) in 21 premanifest mutation carriers, 63 HD patients, and 84 controls. Delayed sleep onset latency and later wake-up time were significantly more prevalent in HD patients, 58.1% compared to controls 34.9% [22].

Goodman et al. evaluated 66 HD patients at different stages of disease, using a 45-question questionnaire designed specifically for this study, including questions about sleep quality and quality of life [23]. Results were compared with two groups of controls, one comprised of patient's relatives (30 participants), and another group of 60 non-relatives. HD patients reported more sleep initiation difficulties, taking 60 minutes or more to fall asleep, longer periods of nocturnal awakenings, and frequent early awakenings. There was no difference in the total hours of nocturnal sleep reported. The study did not assess depression, which is common in HD and can negatively impact sleep quality.

Videnovic et al. included an assessment of depression using the BDI, along with the PSQI and ESS. 77% of the 30 HD patients included had poor sleep, with a significant association between poor sleep and co-existent depression [24]. No associations were found between poor sleep and disease severity, irritability, or daytime sleepiness.

Excessive daytime sleepiness has been found to correlate with disease duration [26]. The reported prevalence of sleepiness in HD patients is variable. Videnovic et al. reported a prevalence of up to 50% in HD, as opposed to a few studies where no difference in daytime sleepiness was found when comparing HD patients to controls [22–24]. Aziz et al. report a prevalence of 12.7% and of 7.9% in controls based on the ESS and SCOPA scales, without a statistically significant difference between groups [22]. Others also failed to find a difference in daytime sleepiness when comparing HD and control groups as measured by ESS and the objective measure of sleepiness, the Multiple Sleep Latency Tests (MSLT) [23].

Objective assessments of sleep in HD

Several investigations employed polysomnography (PSG) in HD patients [3,4,19,25–32]. The major sleep abnormalities identified are poor sleep quality (reduced sleep efficiency, fragmented sleep) and altered REM sleep.

Goodman et al. evaluated 9 HD patients and 10 controls, excluding patients with concomitant major psychiatric illness and/or history of sleep disorders. Patients underwent PSG for two consecutive nights, followed by the MSLT [4]. HD patients had reduced sleep efficiency due to fragmented sleep, and significantly more time awake during the night.

Zhang et al. performed a meta-analysis of seven case-control PSG investigations in HD patients 33]. PSG was interpreted using the American Academy of Sleep Medicine criteria in two studies [19,26], while four studies used the Rechtschaffen and Kales (R&K) criteria [3,4,31,32]. Four studies included one night of PSG, while two studies included two consecutive nights of polysomnography allowing for one night of adaptation [3,4]. Overall, these seven investigations including a total of 152 HD patients and 144 controls, revealed reduced sleep efficiency, slow wave sleep, and REM sleep in HD patients when compared to controls. Light sleep, specifically N1, was longer as well as wake time after sleep onset, and REM latency [33].

A recently published study evaluating video-PSG in 23 HD patients and 13 controls revealed reduced REM sleep and increased wakefulness after sleep onset [25]. Reduced REM sleep was associated with disease severity as assessed by the Unified Huntington's Disease Rating Scale (UHDRS). Preceding studies also documented reduced REM sleep duration [32]. Piano et al. characterized REM sleep in 23 HD patients, showing significantly decreased theta and alpha power when compared to controls [30]. Decreased theta power in REM sleep was also documented in another study including two nights of laboratory-based PSG and the MSLT in the sleep laboratory among 38 premanifest HD patients compared to 36 healthy controls [26]. A preceding study that included 25 HD patients had documented significantly reduced sleep duration [32].

REM-sleep behavior disorder is not a common feature of HD, with one study reporting three HD patients with REM sleep behavior disorder on video-PSG polysomnography and a case report of REM sleep without atonia in HD [32,34]. One case report described restless leg syndrome in HD [17].

In summary, disturbed sleep/wake cycle is common in the HD population, emerging in early stages of the disease. The nature of sleep disturbances is variable, and most commonly reported are long latency to sleep, sleep fragmentation, and excessive daytime sleepiness. This occurs on the background on altered sleep architecture, specifically reduced slow wave and REM sleep.

CIRCADIAN RHYTHM INVESTIGATIONS IN HD

Studies centered on circadian rhythms in the HD population are scarce. Table 1 provides a summary of human investigations of sleep and/or circadian biomarkers in HD patients to date. Circadian rhythm of melatonin, a well-accepted marker of endogenous circadian rhythmicity has been explored in HD patients. While some studies demonstrated no change in melatonin levels with phase delay of the rhythm [35,36], others reported reduced concentration and flattened circadian rhythm of melatonin [37]. Several studies have documented increased levels of cortisol, another well-established makers of circadian rhythms [38,39].

Unlike multifactorial neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease, HD's monogenic nature facilitates the development and exploration of varied animal models to study HD pathophysiology and therapeutics [40]. No single HD model replicates the full range of human disease. A good understanding of HD animal models is much needed for the proper interpretation of studies centered on sleep and circadian function in HD. We briefly outline major findings in these HD models as its detailed description is beyond the scope of this review [41].

Table 1
Chronological summary of sleep and/or circadian investigations in HD patients

Study	Country	Population	Methods	Notable findings in HD patients
Annapureddy et al. (2022) [25]	India	–23 HD patients –13 controls	PSG	• Higher wakefulness after sleep onset • Reduced REM sleep percentage • Low REM sleep was associated with disease severity
Gavrielov-Yusim et al. (2021) [18]	Israel	109 HD patients	Retrospective chart review (20-year HD patient database)	• 21% of HD pts had sleep disorders
Bartlett et al. (2019) [77]	Australia	–18 HD patients with intervention –11 HD patients without intervention –29 controls	–Brain MRI –Biomarkers: serum cortisol and melatonin levels –Multidisciplinary rehabilitation (exercise, cognitive training, social events) for 9 months	• Reduced hypothalamic grey matter volume on brain MRI, attenuated in intervention group • Increased awakenings • Reduced sleep efficiency • No difference in circadian markers (morning cortisol, evening melatonin)
Tanigaki et al. (2020) [21]	USA	29 HD patients	Questionnaire: Pittsburgh Sleep Quality Index (PSQI)	• Awakenings in the middle of the night or early morning • Increased sleep latency • Worse quality of sleep was associated with anxiety and depression
Bartlett et al. (2018) [78]	Australia	–32 premanifest HD pts –29 healthy controls	–Brain MRI –Biomarkers: cortisol and melatonin levels –Wrist-worn actigraphy –Consensus Sleep Diary –Questionnaire: PSQI	• Significantly reduced grey matter volume in the hypothalamus • Decreased habitual sleep efficiency • Increased awakenings • No alterations in morning cortisol or evening melatonin release
Diago et al. (2018) [79]	Spain	38 HD mutation carriers (23 premanifest and 15 early-stage patients) –38 controls	Questionnaires: PSQI, ESS	• Impaired sleep quality (PSQI > 5) • Excessive daytime sleepiness (ESS > 9) • Increased sleep onset latency • Later wake-up time • Sleep abnormalities were associated with worse cognitive performance, depression, and anxiety
Adamczak-Ratajczak et al. (2017) [80]	Poland	–11 HD patients –8 acute ischemic stroke patients	Biomarkers: serum melatonin and cortisol levels (obtained at twelve timepoints in 12-hour light/dark cycle and controlled room conditions)	• Melatonin phase delay • Cortisol phase advancement
Piano et al. (2017) [30]	Italy	–23 HD patients –23 controls	Continuous EEG recording during sleep	• NREM sleep: increased alpha power and decreased theta power • REM sleep: decreased theta and alpha power

Piano et al. (2015) [26]	Italy	–30 HD patients –30 healthy controls	–PSG –Questionnaires: ESS, Berlin's Questionnaire	• Shorter sleep • Reduced sleep efficiency index • Increased number of awakenings • No REM-sleep behavior disorder observed • Disease severity inversely correlated with percentage of REM sleep • Disease duration correlated with ESS score
Neutel et al. (2015) [19]	France	–29 HD patients –29 healthy controls	Retrospective chart and PSG review	• Longer REM sleep onset latency • No correlation between CAG repeat length and sleep measures • Nocturnal agitation: clumsy and opisthotonos-like movements during arousals
Kalliolia et al. (2014) [37]	UK	–14 premanifest HD patients –13 Stage II/III HD patients –15 controls	Biomarkers: serum melatonin levels	Significantly reduced melatonin concentrations
Van Wamelen et al. (2013) [67]	The Netherlands	–8 HD patients –8 controls	Expression of vasoactive intestinal polypeptide, arginine/vasopressin, and melatonin receptors in post-mortem paraffin-embedded tissue (suprachiasmatic nucleus)	• 85% fewer neurons immunoreactive for vasoactive intestinal polypeptide and 33% fewer neurons for arginine vasopressin • No change in the number of melatonin receptor immunoreactive neurons
Goodman et al. (2010) [23]	UK	–6 patients –98 controls (38 carers and 60 non-carers)	45-question original questionnaire	• Sleep initiation difficulties • Longer periods of nocturnal awakenings • Early awakenings • No difference in the total hours of nocturnal sleep reported
Van Duijn et al. (2010) [81]	The Netherlands	–26 presymptomatic HD patients –58 symptomatic HD patients –28 controls	Biomarkers: salivary cortisol (HPA axis functioning: cortisol day curve, cortisol awakening response, dexamethasone suppression test)	No differences found between HD and controls
Aziz et al. (2010) [22]	The Netherlands	–63 HD patients –21 premanifest mutation carriers –84 controls	Questionnaires: ESS, PSQI, SCOPA-Sleep, Beck's Depression Inventory (BDI)	• Higher prevalence of sleep issues (58.1% in patients vs 34.9% controls) • Delayed sleep onset latency • Delayed wake-up time • Significant association of sleep abnormalities with cognitive score and depression
Aziz et al. (2009) [35]	The Netherlands	–9 early-stage HD patients –9 healthy controls	Biomarkers: 24-h melatonin secretion	• Delayed melatonin evening rise • No difference in diurnal melatonin levels

(*Continued*)

Table 1
(*Continued*)

Study	Country	Population	Methods	Notable findings in HD patients
Videnovic et al. (2009) [24]	USA	30 HD patients	Standardized questionnaires: PSQI, ESS, BDI	• 77% prevalence of abnormal sleep • Median global PSQI score: 6 (range 2–19) • Median sleep latency: 20 min (range 1–90) • Poor nocturnal sleep (higher PSI scores) significantly associated with co-existent depression
Aziz et al. (2009) [39]	The Netherlands	–8 early-stage HD patients –8 controls	Biomarker: 24-hour cortisol secretion	• Higher total cortisol secretion rate • Higher diurnal cortisol
Savva et al. (2009) [17]	Switzerland	One patient	Case report	RLS preceded HD symptoms in patient with genetically demonstrated HD
Arnulf et al. (2008) [32]	France	–25 HD patients (including 2 premanifest carriers) –Controls and narcolepsy patients	Clinical interview PSG Daytime multiple sleep latency tests	• Frequent insomnia • Earlier sleep onset • Lower sleep efficiency • Increased light sleep • Delayed and shortened REM-sleep • Increased periodic leg movements • REM-sleep behavior disorder in 3 patients (12%) • No sleep abnormality correlated with CAG repeat length
Morton et al. (2005) [20]	UK	–8 HD patients –3 controls	–Wrist actigraphy over 24 – 48 hours –Sleep diary	• Higher nocturnal activity • Increased ratio of nighttime to daytime activity
Banno et al. (2005) [16]	Canada	One patient	Case report	Coexistent HD and sleep apnea
Wiegand et al. (1991) [27]	Germany	–16 HD patients –16 controls	PSG	• Increased sleep onset latency • Reduced sleep efficiency • Frequent nocturnal awakenings • More time spent awake • Less slow wave sleep
Emser et al. (1988) [28]	Germany	–10 HD patients –22 controls	PSG	• Significant increase in sleep spindle density • Normal slow-wave sleep
Hamsotia et al. (1985) [29]	USA	–7 HD patients –6 controls	PSG	• Mild disease: Normal sleep • Moderate disease: prolonged sleep-onset latency, increased interspersed wakefulness, and reduced sleep efficiency

HD, Huntington's disease; PSG, polysomnography; REM, rapid-eye-movement; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Daytime Sleepiness Scale; SCOPA, SCales for Outcomes in Parkinson's disease.

Circadian rhythm studied in HD flies revealed decreased nocturnal sleep and increased sleep latency [40,41]. A sheep model of HD with full-length huntingtin protein and CAG repeats comparable to HD patients, exhibits sleep-wake disturbances and progressive behavior abnormalities around evening time, like the sundowning of patients with cognitive disorders, and more abrupt sleep-to-wake transitions when compared to normal sheep. Of great interest, these alterations tend to resolve upon housing HD animals with unaffected sheep [42–44]. Studies employing several rodents models of HD demonstrated progressive circadian disorganization [20,45–51]. Unlike human studies where there has not been a correlation between sleep abnormalities and CAG repeat length, this association has been reported in the Q175 HD model, with increased wakefulness and reduced NREM sleep duration [52].

MECHANISMS OF CIRCADIAN DISRUPTION IN HD

Circadian rhythms are determined by clock genes expressed in all nucleated cells, including "core" clock genes PER, CLOCK, ARNTL, and CRY genes [53]. Several studies have demonstrated changes in the circadian expression of these genes. Morton et al. demonstrated marked disruption of the mPer2 and mBmal1 circadian clock genes in the suprachiasmatic nucleus of R6/2 mice [20].

Circadian rhythms are entrained by "Zeitgebers" or environmental cues, including light, as well as food intake, physical activity, and socialization [42]. Light is the most potent Zeitgeber of the mammalian circadian system [54,55]. Several HD models exhibit progressive morphologic changes in the retina, including a reduced number of photosensitive ganglion retinal cells, downregulation of retinal melanopsin and cone opsin, retinal dystrophy, and mutant huntingtin inclusions in the retina [56–60]. Investigations of retinal structure and physiology in individuals affected with HD are scarce. Optical coherence tomography showed decreased color vision and reduced macular volume with HD progression [61]. These findings point to abnormal retinal response to light, and subsequent impaired light signaling to the hypothalamic suprachiasmatic nucleus, as a major mechanism underlying circadian dysregulation in HD.

Another proposed mechanism underlying circadian disruption in HD includes deficits in brain-derived neurotrophic factor expression and signaling [62,63]. A reduced diurnal rhythmic spontaneous firing rates in the dorsal suprachiasmatic nucleus were reported in BACHD mice [64]. Reduced number of orexigenic neurons in the lateral hypothalamus has been found in R6/2 mice [65]. Reduced levels of VIP and AVP have been found in postmortem examinations of the SCN [66,67]. These findings point to an intrinsically dysfunctional suprachiasmatic nucleus, as one of the neuroanatomical sites of circadian dysregulation in HD.

THERAPEUTIC APPROACHES TO SLEEP CIRCADIAN DYSFUNCTION IN HD

Given the lack of well-designed intervention studies aimed at treating sleep disturbance in the HD population, evidence-based treatment recommendations are insufficient. The management of disturbed sleep in HD is further complicated by psychiatric symptoms and involuntary movement that contribute to poor sleep and impaired alertness. Commonly used medications such as antidepressants, antipsychotics, tetrabenazine, and benzodiazepines should be used with caution as they may cause side effects in some patients. Melatonin has been beneficial for improving insomnia, and also has a potential to improve circadian phase changes reported in HD patients. It is certain that sleep and circadian dysregulation in HD represent a foundation for the development of sleep and circadian-based interventions aimed at improving HD symptoms and possibly altering the progression of the disease.

Behavioral therapies aimed at treating circadian dysfunction are centered on known synchronizers of the circadian system, such as time-restricted feeding, timed exercise, and light therapy [48,57,68–71]. Cuesta et al. treated R6/2 mice with bright-light therapy and scheduled exercise [48]. R6/2 mice without treatment showed disruption of rhythm activity starting around 11–12 weeks of age with complete disintegration by 15–16 weeks. The disintegration of activity rhythms was significantly delayed in treatment groups, with preservation of circadian rhythms until at least week 18 of age. Skillings et al. also demonstrated the delayed onset of circadian disorganization in R6/2 mice treated with food entrainment [72]. Similarly, Wang et al. showed delayed symptom progression in Q175 mice exposed to blue-wavelength enhanced light and time-restricted feeding [68,69]. Overall, circadian

entrainment seems to have a positive impact on HD progression and severity. Not all studies, however, documented these beneficial effects of food entrainment [72].

Investigations centered on the pharmacologic management of circadian dysfunction in HD rodent models explored timed administration of a histamine receptor 3 blocker [68], chronic ghrelin administration [73], orexin receptor antagonism [74], and intranasal administration of mesenchymal stem cells [75]. Rudenko et al. found that chronic ghrelin administration to R6/2 mice normalized the disrupted activity/rest cycle and partially normalized diurnal rhythms of water intake, both of which were markedly disturbed in untreated R6/2 mice [73]. Cabanas et al. found that the administration of Suvorexant, an orexin 1, 2 receptor antagonist, improved sleep and cognitive deficits in R6/1 mice [74]. Pallier et al demonstrated that inducing sleep with alprazolam slowed cognitive decline and reversed circadian rhythm dysregulation in R6/2 HD mice regardless of the anxiolytic effect [45,76]. There are no clinical studies assessing the impact of circadian entrainment or the effect of pharmacological sleep management on outcomes, such as cognitive performance, in HD patients to date.

RECOMMENDATIONS FOR FUTURE SLEEP AND CIRCADIAN RESEARCH IN THE HD POPULATION

Future investigations of sleep in HD would benefit from multimodal assessments that combine self-assessment methods with objective measurements. Such investigations would ideally include larger cohorts and longitudinal assessments. The studies would include at-risk individuals as well those with pre-manifest and symptomatic disease and unaffected relatives. PSG may provide a wealth of potential biomarkers, and when possible two or more nights pf PSG recordings may be considered to allow for more reliable results, although this may be a challenging task for symptomatic HD patients. Use of mobile technologies to measure sleep at home rather than in a sleep laboratory is much needed in order to overcome challenges related to access, cost, and burden off PSG testing, while allowing for long term monitoring of sleep and alertness.

Available studies on circadian rhythm in humans have mainly relied on measurements of circadian biomarkers (see Table 1). These studies remain challenging due to the need for demanding circadian-based protocols. Investigations that center on patients' and caregivers' reports in combination with non-invasive monitoring of rest-activity rhythms (e.g., actigraphy) may bypass some of the challenges of rigorous experimental designs, especially if complemented with less demanding and feasible assessments of circadian rhythms (e.g., measurements of salivary melatonin and urinary melatonin metabolites).

Circadian-based interventions such as melatonin pharmacotherapy, timed light exposure and physical activity as well as social engagement/structuring are widely-available ways that may have significant beneficial impact on sleep and circadian health of PD patients.

CONCLUSIONS

Disrupted sleep and excessive sleepiness are common in the HD population. The most frequent sleep abnormalities in HD patients are fragmented sleep and reduced REM and slow-wave sleep. These findings have been observed in studies of HD animal models.

Progressive circadian dyssynchronization and diminished response to light entrainment characterize animal models of HD. Comprehensive assessments of circadian function in HD patients are needed. Most clinical investigations have evaluated indirect biomarkers of circadian dysfunction, influenced by exogenous factors, due to the challenge posed by demanding circadian experimental protocols.

Sleep and circadian abnormalities are underdiagnosed and undertreated problems in HD patients. Available investigations of sleep in HD patients are sparse, with small cohorts and various methodologies. Future clinical studies should include assessment of motor, cognitive and psychiatric disease burden, as they are highly prevalent in HD and have important implications in the interpretation of sleep and circadian function. More robust studies employing objective measurements of sleep and alertness such as video-PSG, Multiple Sleep Latency Test (MSLT), and actigraphy are needed. The utility of other rapidly developing mobile technologies should be explored in the assessment of sleep and circadian physiology in HD.

Treatment of sleep and circadian disturbances in HD represents a big unmet need in HD. Well-designed intervention studies aimed at the treatment of poor sleep associated with HD are very much

needed. Non-invasive and low-cost circadian-based therapies such as light therapy may be promising for the management of sleep-wake disturbances in HD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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