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Effects of Exercise on Sleep in Neurodegenerative Disease

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Abstract

As the population ages, the incidence and prevalence of neurodegenerative disorders will continue to increase. Persons with neurodegenerative disease frequently experience sleep disorders, which not only affect quality of life, but potentially accelerate progression of the disease. Unfortunately, pharmacological interventions are often futile or have adverse effects. Therefore, investigation of non-pharmacological interventions has the potential to expand the treatment landscape for these disorders. The last decade has observed increasing recognition of the beneficial role of exercise in brain diseases, and neurodegenerative disorders in particular. In this review, we will focus on the therapeutic role of exercise for sleep dysfunction in four neurodegenerative diseases, namely Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Available data suggest that exercise may have the potential to improve sleep disorders and attenuate neurodegeneration, particularly in Alzheimer's disease and Parkinson's disease. However, additional research is required in order to understand the most effective exercise therapy for these indications; the best way to monitor the response to interventions; the influence of exercise on sleep dysfunction in Huntington's disease and amyotrophic lateral sclerosis; and the mechanisms underlying exercise-induced sleep modifications.

Keywords

Sleep; Exercise; Alzheimer's disease; Parkinson's disease; Huntington's disease; amyotrophic lateral sclerosis

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INTRODUCTION:

Neurodegenerative disorders (NDD), such as Alzheimer's disease (AD), Parkinson's disease (PD) Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), are characteristically defined by protein accumulation, synaptic loss or dysfunction of a specific group of neurons, and anatomic susceptibility leading to neuronal dysfunction and death[1,2]. Although the existing diagnostic gold standard is a neuropathological assessment at autopsy, NDD are clinically diagnosed based on their main phenotypic features. For example, AD includes problems with recent memory, word-finding, and language difficulties, with slow progression to global cognitive impairment and functional impairment[3]. In PD, diagnosis is made based on motor symptoms, which include bradykinesia, rest tremor, rigidity, and postural instability[4]. Persons with PD also experience non-motor symptoms, including cognitive decline, autonomic dysfunction, neuropsychiatric symptoms, and sleep disorders. The seminal features of HD are a triad of progressive cognitive decline, motor dysfunction (chorea, akathisia, bradykinesia, spasticity) and psychiatric symptoms and are confirmed by a genetic testing revealing a trinucleotide repeat expansion[5,6]. ALS involves degeneration of alpha motor neurons, resulting in both upper motor neuron signs (increased muscle tone, spastic paresis, and pseudobulbar palsy) and lower motor neuron signs (fasciculations, atrophy, and weakness)[7]. Sleep disorders occur in all these NDD and are correlated with a higher occurrence of both cognitive and neuropsychiatric problems affecting the quality of life of patients and their caregivers[8].

Many persons with NDD suffer from sleep disorders[8]. The exact pathogenesis underlying sleep dysfunction in NDD is unknown (Figure 1), but it can be categorized into primary and secondary mechanisms. Primary mechanisms include loss or morphological modifications of the neurons in the hypothalamus or caudal brainstem involved in sleep-wake generation, which changes the equilibrium between sleep and wakefulness and results in circadian rhythm disorders, insomnia, sleep fragmentation, hypersomnia, or parasomnia[9]. Secondary or indirect mechanisms include poor sleep hygiene, environmental factors, psychiatric co-morbidity, medication side effects, sleep-related breathing disorders, physical immobility, or increased frequency of nocturia, which results in sleep-maintenance insomnia, fatigue, irritability, and daytime somnolence[10]. Treatment of sleep disorders is complex and also important, as there is increasing evidence that inadequate sleep leads to accelerated progression of NDD and possibly plays a role in their pathogenesis[11]. Unfortunately, medications used to treat these symptoms are often not sufficiently effective and can cause intolerable adverse effects[12]. Non-pharmacologic interventions such as light therapy, cognitive behavioral therapy, behavioral modifications, and exercise have the potential to change the treatment landscape in NDD. While additional research is needed, many of these interventions have shown promise for potential to improve sleep in NDD[13–15].

The last decade has witnessed a growing appreciation of the beneficial role of exercise in NDD as a non-pharmacological therapeutic intervention. Besides preventing brain tissue loss, exercise has shown moderate improvements in subjective sleep quality in older adults with sleep problems[16]. In this review, we discuss the available evidence supporting the use of exercise for the treatment of sleep disorders in four neurodegenerative disorders.

EFFECTS OF EXERCISE ON SLEEP IN HEALTHY ADULTS

The basis for investigation of potential exercise-induced sleep benefit in NDD stems from prior work evaluating the influence of exercise on sleep in healthy populations. Different exercise modalities, intensities, and durations have been explored in healthy adults, and the type of exercise may shape outcomes (i.e. endurance training impacts aerobic fitness and resistance training improves strength). While cardiorespiratory (aerobic) and resistance (anaerobic) exercise are most often discussed, other modalities such as flexibility exercises or neuromotor exercises emphasizing balance, proprioception, coordination, and agility have also been explored in the research setting[17]. Incorporating a cognitive component into exercise (mind-body exercise) with exercises such as Tai chi or Qigong may have additional benefit[18]. Other considerations that influence research outcomes include duration of the intervention, ranging from acute (single bout) to regular (chronic training)[19]. Many forms of exercise, including both acute and regular exercise as well as both aerobic and resistance training improve subjective sleep quality[16,20]. Studies exploring objective sleep outcomes due to exercise are more limited than survey based analyses; however, it is known that acute exercise enhances both total sleep time and slow wave sleep, reduces REM sleep, and delays REM latency[21]. Additionally, chronic exercise training improves sleep efficiency, decreases latency to sleep onset, and increases total sleep time and slow wave sleep[19,22].

Several potential mechanisms for these beneficial sleep changes have been proposed, including exercise-induced reduction of inflammation, alterations of core body temperature, changes in neurotransmitters important for sleep regulation, increases in growth hormone and brain derived neurotrophic factor (BDNF), and changes in heart rate variability and autonomic function[19,22–25]. Additionally, exercise can promote entrainment of the circadian rhythm for improved sleep/wake regulation[26]. In mammalian models, timing of scheduled daily exercise can change the time of peak heart rate and body temperature as well as adrenal activity[27–29]. Human studies suggest that both acute bouts of exercise and chronic timed exercise interventions can modulate circadian function including shifting the onset of melatonin excretion, changing temperature regulation, and promoting phase shift of sleep-wake activity cycle[30–32]. Although there is the potential that some aspects of aging or neurodegeneration could blunt or alter the exercise-induced sleep benefit in these populations, evidence discussed in this review suggest that these benefits are maintained.

ALZHEIMER'S DISEASE

Sleep disorders in Alzheimer's disease

Sleep disorders are frequent in AD, affecting up to 45% of patients[33,34]. Sleep disturbance can be present in the early stages of AD, and its severity parallels the severity of dementia[35,36]. Sleep disorders in AD include trouble with falling or staying asleep, wandering, sleep fragmentation, and excessive daytime sleepiness[33,37]. AD patients also have alterations in sleep architecture, including prolonged REM sleep latency and decreased percentage of slow wave and REM sleep[38]. As the disease progresses, other findings include poorly formed sleep spindles and K-complexes, which makes it difficult to distinguish between stages N1 and N2 on electroencephalography[39]. Although these variations in sleep patterns can be components of the normal aging process, AD causes more degeneration of

these patterns than in age matched control subjects[40]. Sleep dysfunction in AD enhances the probability of physical and psychological morbidity in both patients and their caregivers and is correlated with increased risk of early institutionalization[41–49]. Disrupted sleep not only negatively influences the quality of life of patients, but also adversely impacts caregivers[46,50].

The cause of sleep disorders in AD is considered to be multifactorial. Proposed mechanisms (Figure 1) involve the degeneration of neural pathways controlling sleep-wake patterns, including the suprachiasmatic nucleus that regulates circadian function, as well as reduced expression of neuropeptides such as Arginine Vasopressin (AVP) and Vasoactive intestinal peptide (VIP), and changes in melatonin receptor (MT1) expression[51]. Additional mechanisms include underlying psychiatric and medical comorbidities, medication-related side effects, and altered light/dark patterns during the day or night[34,52]. Sleep interruption has also been proposed to hasten the advancement of AD through malfunctioning of the glymphatic system[53] because sleep performs a crucial function in clearing noxious protein accumulation, such as beta-amyloid, from the central nervous system[54–56].

In the forthcoming years, the aging population is expected to cause a dramatic worldwide increase in the number of people living with AD[57]. Thus, cost-effective interventions to improve disrupted sleep in individuals with AD are essential for the benefit of global economics as well as patient health. Pharmacological therapies for the treatment of sleep disorders in AD have limited efficacy and can be associated with severe adverse effects such as hypotension, dizziness, and falls[58–61]. Therefore, development of safe non-pharmacological approaches for treating sleep disorders in AD is a critical unmet need. Exercise and physical therapy are attractive treatment options for sleep dysfunction as these have already shown potential to improve cognition in AD[62].

Impact of Exercise on Sleep in Alzheimer's disease

Similar to findings in healthy adults, exercise has shown potential for improving sleep dysfunction in AD as well. Most published research on this topic describes observational studies evaluating the relationship between physical activity and sleep in AD. In 59 patients with dementia evaluated cross-sectionally with the Mini-Sleep Questionnaire, those who participated in regular physical activity had fewer sleep complaints compared to those who had lower levels of physical activity[63]. Another observational, cross-sectional study in 184 participants with dementia examined the influence of exercise (defined as number of hours per week of walking) on sleep quality and sundowning[64]. The findings showed that walking with relatives as compared to non-relatives and walking more hours per week was associated with less sundowning and with improved sleep quality in AD[64]. One limitation of this study was its reliance on caregiver recall[64]. Exercise has also been shown to delay or prevent the onset of behavioral problems in demented frail older people living in nursing homes. For example, one pilot longitudinal study showed that the combination of aerobic/endurance activities, strength training, balance, and flexibility training statistically reduced behavioral problems, including sleep disorders in dementia patients[65].

Although additional study is needed, there have been a few randomized, controlled trials (RCT) investigating effects of exercise on sleep outcomes in AD. One RCT examined the

benefits of physical activity (N=32), light exposure (N=34), and combination treatment (walking, light exposure, and guided sleep education) (N=33) for improving sleep dysfunction in AD compared to a contact control group (N=33). The primary outcome included actigraphically-measured total wake time at night. The exercise intervention included 30 minutes of continuous walking every day. Compared to the contact control group, participants in each active treatment arm had shorter actigraphic total wake time post-intervention. Patients in the exercise group were awake 33.1 fewer minutes per night compared to the control, suggesting that exercise improved objectively measured sleep[66]. Another RCT, the nighttime insomnia treatment and education for Alzheimer's disease (NITE-AD) trial, included thirty-six community-dwelling patients with AD and their caregivers. Caregivers in both the active treatment arm (N=17) and the control arm (N=19) received specific suggestions regarding establishing and employing sleep hygiene programs. The caregivers in the active treatment arm were also encouraged to have patients walk 30 minutes daily and increase daytime light exposure. Patients in the NITE-AD active arm showed a significant reduction in the number of nighttime awakenings, total time awake at night, and depression. These benefits were continued up to six months of follow-up[67]. A pilot study revised the NITE-AD program and analyzed the intervention in a group rather than individual format with caregivers. The time frame in the modified NITE-AD program was six weeks instead of two months in the original NITE-AD program. While this program was pilot and only included seven participants, all showed reduced frequency, severity, and distress on the Sleep Disorder Inventory[68]. Another controlled study evaluated the effects of multimodal exercise conducted regularly over six months on instrumental activities of daily living (IADL) and subjective sleep disturbances, measured with the Mini-Sleep Questionnaire, in persons with AD[69]. Participants in the active exercise arm (N=19) had one-hour exercise sessions three times per week for six months compared to no exercise in the control group (N=16). Those in the exercise group showed improvement in IADLs and subjective sleep quality compared to the control group[69].

In summary, several studies suggest that exercise has the potential to improve sleep in persons with AD. However, to our knowledge, there are no RCTs or observational studies investigating the relationship between physical activity and polysomnographically-measured sleep outcomes in this patient population. More study is needed to fill this gap and to determine the potential mechanisms underlying exercise-induced changes in sleep (Figure 2) as well as the optimal exercise modality, duration, and intensity to better optimize sleep in persons with AD.

PARKINSON'S DISEASE

Sleep Disorders in Parkinson's Disease

Sleep disorders are nearly universal among patients with PD and include sleep fragmentation, REM sleep behavior disorder, insomnia, excessive daytime sleepiness (EDS), periodic limb movements of sleep, and circadian rhythm dysregulation[70,71]. In contrast to studies in AD, persons with PD have reduced amplitude of the circadian rhythm without any significant shift in circadian phases[72]. Compared to healthy older adults, persons with PD also have changes in sleep architecture, with reduced sleep efficiency and total sleep time

and decreased amounts of REM and slow wave sleep[71,73,74]. Motor symptoms occurring during the night, as well as nocturia, constipation, mood disorders, and other non-motor symptoms of PD also contribute to insomnia and sleep fragmentation[75]. However, treatment of motor symptoms with dopaminergic therapy can also contribute to sleep dysfunction and daytime somnolence. For example, dopaminergic medications can alter circadian physiology. In one analysis of medication naïve patients with PD, introduction of levodopa caused an increase in melatonin production while concurrently delaying sleep onset[76]. Unfortunately, sleep dysfunction contributes to impaired quality of life and is associated with worse motor, cognitive, autonomic, and neuropsychiatric dysfunction in PD[71,74,77–79].

Although poor sleep is a common source of morbidity in PD, interventions for treatment are limited. Available medications such as sedatives/hypnotics, antipsychotics, and antidepressants can have an intolerable side effect profiles in this population of patients who are at risk for balance and cognitive dysfunction. The sleep benefits of non-pharmacologic interventions are therefore of proportionally greater interest. Cognitive-behavioral therapy is recommended for treatment of insomnia by the American Academy of Sleep Medicine and may be beneficial in patients with PD[13,80]. Further, light therapy for circadian reconditioning demonstrates benefits on both sleep and mood in PD[13].

Exercise is emerging as a beneficial nonpharmacologic aspect of PD care[81–83]. The effects of exercise on PD are wide ranging and include improvements in quality of life, motor symptoms, balance, strength, and endurance as well as skeletal muscle adaptions[83,84]. Non-motor symptoms also improve, with benefits on cognition, depression, constipation, and anxiety[82,85]. Similarly, the effects of exercise on sleep symptoms are beginning to be recognized.

Impact of Exercise on Sleep in Parkinson’s Disease

Several studies have evaluated the impact of exercise on subjective sleep quality in PD. One study retrospectively analyzed subjective sleep quality, as measured by the Parkinson’s Disease Sleep Scale (PDSS), in patients with PD who underwent multidisciplinary intensive rehabilitation treatment (MIRT) in an inpatient setting over 4 weeks compared to patients who did not undergo rehabilitation. The MIRT group had 3 one-hour sessions per day, five days per week, over four weeks. These sessions included a wide range of exercises including aerobic exercises, relaxation techniques, stretching, stabilometric platform exercises focusing on balance and gait, occupational therapy, and other exercises tailored to the individual patient such as speech therapy, hydrotherapy, and robotic-assisted walking training. The persons with PD in the MIRT group (N=89) demonstrated significant improvement in PDSS scores in all items except for two, which were in normal ranges prior to the intervention (distressing hallucinations during the night and daytime sleepiness) compared to patients who were kept on pharmacologic therapy only without rehabilitation (N=49)[86].

Similar exercise-induced sleep quality improvement was found in a trial in which PD participants were assigned either to a no-exercise control group (N=19) or an intervention group (N=23) with three times weekly, 1-hour multimodal exercise sessions administered by physical education professionals over a 6-month intervention period[69]. The exercises were

of moderate intensity aerobic exercise achieving 60 – 80% of maximal heart rate and utilizing multimodal exercises designed to benefit balance, resistance, and flexibility. The intervention arm demonstrated marked improvement in the Brazilian version of the Mini-Sleep Questionnaire while the control group did not change[69].

Other less intensive interventions with more emphasis on cognitive outcomes have also been reported. One such therapy, Qigong, is a form of mild intensity exercise which incorporates mindfulness as well as balancing. In a pilot study, 7 patients with PD were compared before and after an 8-week program incorporating twice daily sessions of 15 – 20 minutes of Qigong exercise as well as weekly one-hour class-based interventions with an instructor. Participants showed a small but non-significant improvement in the PDSS[87]. A more robust analysis of this intervention was performed with an RCT comparing daily walking for 30 minutes (N=44) to an intervention with 4 instructor-led sessions of 45 minutes duration followed by four times weekly home-based Qigong sessions lasting approximately 20 minutes (N=45). After 6 months, the Qigong intervention group reported significant improvement in their PDSS-2 while controls did not experience a change[88]. A small pilot study[89] investigated the effects of Qigong exercise on pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α, which have been found to be increased in PD and have also been implicated in sleep-wake regulation[90–93]. Participants with mild to moderate PD were enrolled into either the control group (n=5) or the intervention group (n=5), which performed Qigong exercises twice daily at home for 15–20 min and also attended a group exercise session weekly for 45 – 60 min for a duration of 6 weeks. The control group maintained the same schedule with sham-Qigong which consisted of the same physical activities without the deep breathing or meditative components. Sleep quality was assessed subjectively with PDSS-2 which found statistically significant improvement in PD symptoms at night as well as improved overall PDSS-2 score in the intervention group compared to the control group. Additionally, TNF-α levels were found to be statistically lower in the intervention group[89].

Another study investigated the effects of Tai Chi, a low intensity form of exercise focusing on slow smooth movements with concurrent breathing and meditative tasks, on subjective sleep quality in persons with PD. Participants were randomized to one of two interventions over 12 weeks: 1) three weekly sessions of Tai Chi supplemented by 2 weekly sessions of multimodal exercises including both aerobic and resistance training (N=19) or 2) five weekly sessions of multimodal exercise alone (N=22). Both groups demonstrated improvement in PDSS and PD motor symptoms, though there was no difference in outcomes between the intervention groups[94].

Other forms of exercise have also been studied. A small RCT studied the effects of resistance training three times weekly for 12 weeks on subjective sleep quality. The intervention group (N=11) demonstrated improved sleep quality as measured by the PSQI compared to controls (N=11). In fact, at the end of this intervention, they reported better sleep quality than a group of age matched healthy controls[95].

Many exercise trials are confounded by the social aspect of the study design. There is a potential bias if patients are actually experiencing benefit because of the cognitive

stimulation that a group setting provides. In another study utilizing Tai Chi, the relative value of group setting compared to individual tutelage was evaluated in a small randomized controlled trial. Patients with PD received the exercise either individually (N=17) or in a group setting (N=19) three days a week for 13 weeks. There was significant though similar improvement in their questionnaire-based sleep evaluation in both groups compared to baseline. Though there was a trend toward more improvement in the group-based intervention, improvement was not statistically different between groups. The group-based intervention did have significantly better compliance[96].

Most published studies of sleep outcomes incorporate only questionnaire-based assessment tools. However, a subanalysis of a trial of persons with PD incorporated activity monitoring with a triaxial accelerometer[97]. In this intervention lasting 6 months, an exercise group received twice weekly, hour-long exercise sessions (30 minutes resistance training plus 30 minutes of endurance training) (N=29) compared to a control group assigned to a handwriting task designed to mimic the cognitive tasks involved in exercise (N=36). The quality of sleep was evaluated both by analysis of sleep related questions from UPDRS parts I and II, as well as accelerometer data during periods of rest and activity. There was no improvement subjectively on questionnaires in either group, but both groups demonstrated decreased accelerometry-measured motor activity during sedentary times, thought to represent improved sleep quality with decreased restlessness or awakenings[97].

We recently reported the first RCT investigating the impact of exercise on objective sleep outcomes measured with polysomnography in PD[98]. Persons with PD were randomized to either high-intensity progressive resistance training rehabilitation (N=27) or a no-exercise, sleep hygiene control group (N=28). Participants in the exercise group had supervised exercise training 3 times per week for 16 weeks, with a combination of resistance training (RT) and bodyweight functional mobility exercises with limited rest intervals designed to challenge strength, power, balance, and endurance. The sleep hygiene group received suggestions for improving sleep hygiene through discussion with a board-certified sleep medicine physician and were provided written materials. The exercise group had significant improvement in sleep efficiency (primary outcome), as well as total sleep time, wake after sleep onset, and time spent in slow wave sleep, compared to the sleep hygiene group[98].

In summary, multiple different exercise modalities have potential to improve sleep quality in PD. However, more study is needed with dedicated RCTs addressing sleep as a primary outcome. The exercise modality, frequency, duration, and intensity needed for optimization of sleep is not known. Additionally, more investigations of objective sleep outcomes measured with polysomnography as well as additional study on influence of exercise on circadian rhythms in PD are needed.

HUNTINGTON'S DISEASE

Sleep Disorders in Huntington's disease

HD is an autosomal dominant trinucleotide repeat neurodegenerative disorder that causes motor dysfunction (chorea, bradykinesia, rigidity, spasticity, tics, akathisia), progressive cognitive decline, and psychiatric symptoms. Persons with HD also have significant sleep

and circadian dysfunction[99]. Mechanisms underlying circadian abnormalities in HD are largely unknown, and there is conflicting evidence for how melatonin secretion changes in HD. In one study, there was no difference in mean daytime melatonin level between HD patients and controls, but persons with HD had delayed onset of the diurnal melatonin rise[100]. Another study found reduced and flattening of the circadian rhythm of the 24-hour melatonin concentration[101]. Some of these circadian changes may be related to neurodegeneration within the hypothalamus and suprachiasmatic nucleus[102]. In addition to circadian changes, sleep disturbances are present in up to 90% of persons with HD and include insomnia, frequent awakenings, and daytime sleepiness[99]. In a meta-analysis of 7 studies that have measured laboratory-based polysomnography (PSG) in HD and control participants, a pooled sample of 152 HD and 144 controls were evaluated[103]. This analysis showed that, compared to controls, persons with HD had reduced sleep efficiency, lower percentage of slow wave sleep and REM sleep, increased latency to sleep onset, and increased light sleep and wake after sleep onset[103]. Some of these abnormalities were influenced by advanced age, longer CAG repeat length, and lower BMI[103]. In some cases, sleep disturbances measured by polysomnography in HD are often not concordant with subjective sleep complaints[104]. These changes in sleep architecture have been noted even in pre-manifest HD (mutation carriers prior to onset of subjective symptoms) and early HD[105]. Findings of REM sleep behavior disorders have also been reported in HD[105]. Sleep complaints in HD have been associated with worse depression, anxiety and disinhibition compared to those without sleep complaints and waking later in the morning is associated with worse cognitive impairment[106,107]. Treatments for sleep dysfunction in HD are limited.

Impact of Exercise on Sleep in Huntington's disease

Although exercise has been investigated as an intervention for HD motor symptoms and quality of life, few studies have evaluated how exercise influences sleep in HD[108,109]. One controlled study explored the impact of a 9-month multimodal intervention (exercise, cognitive and dual task training, and social events) on sleep, daytime sleepiness, hypothalamic volume, melatonin, cortisol, and BDNF levels in patients with premanifest and prodromal HD[110]. Eighteen HD participants received the intervention and were compared to 11 HD participants in the control group. The exercise component of the intervention included twice weekly exercise sessions with 30 minutes of aerobic training and 30 minutes of resistance training. Sleep was measured subjectively with questionnaires including PSQI, Epworth Sleepiness Scale (ESS), and Consensus Sleep Diary. The results showed the hypothalamic volume loss was less in the intervention group compared to the control group and serum BDNF decreased in the control group but not in the intervention group[110]. There were no differences between groups in terms of changes in melatonin or cortisol levels. There was no difference between groups in change in PSQI-assessed subjective sleep quality or ESS-assessed daytime sleepiness. Participants in the control group reported increases in diary-recorded total sleep time and time spent in bed, while there were no changes in sleep habits in the intervention participants[110]. Given the lack of concordance between objective and subjective sleep in HD, this study would have been strengthened by inclusion of polysomnography or actigraphy[104]. Another cross-sectional study by the same group showed that, although persons with premanifest HD had lower physical activity levels compared to controls, there was no relationship between reported physical activity levels and

subjective sleep quality[111]. In an uncontrolled study of influence of aquatherapy (one-on-one, individually-tailored sessions offered twice weekly for 6 weeks) on quality of life in mid- to late-stage HD, some of the 6 participants reported improvement in sleep quality in a 30-minute, structured post-intervention interview with open ended questions[112].

In summary, available information about the impact of exercise on sleep dysfunction in HD is sparse. Additional studies, particularly RCTs with objective outcome measures, are needed to determine the impact of exercise and rehabilitation interventions on sleep and circadian function in HD.

AMYOTROPHIC LATERAL SCLEROSIS

Sleep Disorders in amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative illness, which involves a wide-ranging clinical continuum, affecting both upper and lower motor neurons[7,113]. In a subcategory of patients, cognitive and behavioral defects or overt frontotemporal dementia is associated with the motor system deterioration[114]. Persons with ALS also have significant sleep disorders, which are often under-diagnosed or under-reported. Recent recognition of their significant role in affecting the quality of life in ALS patients has prompted increased attention to sleep dysfunction in these patients[115,116]. Sleep disorders are present in up to 59% of persons with ALS[117] and include increased time spent awake during the sleep period, excessive daytime sleepiness, sleep-disordered breathing, and a substantial reduction in the quantity of deep sleep and REM sleep[118]. Insomnia (65%) and sleep-disordered breathing (52.5%) were the two most common sleep disorders reported in one observational study[117]. These disturbances are due to an extended range of considerations including nocturnal hypoventilation, restless legs syndrome, obstructive sleep apnea, difficulty positioning in bed due to lack of mobility, cramps, depressed mood, psychological stress, excessive secretions, and choking[115,119,120]. Nocturnal hypoventilation results from weakness of respiratory, bulbar, or diaphragmatic musculature, a challenge which is likely intensified by supine posture and failure of accessory respiratory muscle function during REM sleep. Unfortunately, ALS is demoralizing and fatal[121], with limited treatment options. A recent review showed that endurance and/or resistance exercise have potential beneficial effects to improve quality of life in ALS, but without any known extension of life expectancy[122]. However, to our knowledge, no research to date has explored the impact of conventional exercise on sleep disorders in ALS. Hence, further investigations are necessary to determine any role of exercise in treating sleep dysfunction in ALS patients.

DISCUSSION

Persons with NDD frequently report sleep dysfunction, which is challenging to manage and decreases quality of life for both patients and caregivers. Physical activity, even at low intensities, has been reported to improve sleep quality, reduce time to fall asleep, and increase the duration of sleep in the elderly[123,124]. The precise mechanisms through which exercise benefits sleep-related disorders are still being explored, but evidence indicates that exercise increases total sleep time and slow-wave sleep, reduces REM, and delays REM sleep onset[125]. It is thought that these beneficial effects on sleep architecture are achieved in

part by enhancement of numerous neurotransmitter systems, including norepinephrine and serotonin afferents to the hippocampus, and also by exercise-induced BDNF upregulation (Figure 2)[126,127].

There is growing evidence that interrupted sleep accelerates progression of neurodegenerative disease. In this review, we discuss the evidence for potential exercise-induced improvements in sleep dysfunction, particularly in AD and PD. Unfortunately, there are considerations specific to persons with these NDD that may limit participation in exercise. For example, specific symptoms such as motor symptoms of PD and the risk of falls, cognitive impairment, excessive daytime sleepiness, depression, apathy, cardiac sympathetic denervation, and fatigue can decrease involvement in physical activity and lead to a more sedentary lifestyle[128–132]. Devising approaches to increase commitment to routine exercise poses a challenge for both researchers and caregivers. A few methods to enhance physical activity involvement include establishing community-based programs; treating depression; designing interventions to accommodate motor symptoms of PD (i.e., stationary bicycle); and reviewing obstacles to physical activity with both the patient and caregivers. Future studies could evaluate the influence of environmental, interpersonal, or physical attributes of patients and caregivers as well the amount of instructor contact that is required to develop sustainable physical activity programs in order to optimize sleep, motor, and cognitive outcomes in persons with NDD.

Although exercise has proven to be a low risk and beneficial intervention to improve overall health and sleep disorders in AD and PD; several questions remain unanswered. For example, the modality of exercise, as well as the frequency and session duration needed for the maximum benefit are still unknown. Additionally, while there is evidence supporting the benefits of exercise on subjective sleep quality in AD and PD, the impact of exercise on objective sleep outcomes in these disorders is underexplored. Finally, factors that may predict responsiveness to specific exercise interventions are undetermined. Future studies investigating potential biomarkers of exercise efficacy and predictors of exercise response could lead to a more personalized approach to treatment for these conditions.

For other NDD, such as ALS and HD, available evidence about the effects of exercise on sleep dysfunction is scant. In persons with ALS, although some early data indicated a possible connection between a vigorously active lifestyle and a heightened risk of ALS[133–135], the latest research suggests that physical activity is not a risk factor for ALS[136–138]. In fact, there is substantial data indicating that several exercise modalities, including resistance, stretching, endurance or a combination, can have positive impact on quality of life and physical functionality[139–145], muscle strength[143,146], and cardiorespiratory function[140,143,144] in ALS. Exercise has also been shown to slow disease progression and reduce caregiver burden in ALS[147]. While there is a lack of data about the effects of physical activity on sleep disorders in both HD and ALS patients, this is an exciting potential avenue for future studies.

The beneficial effects of exercise and physical activity on overall health and well-being are well documented. Due to the increasing prevalence of NDD in our aging population and the potential for adverse effects of pharmacological treatments for sleep disorders in these

patients, there is a critical need to expand our understanding of the influence of nonpharmacological interventions such as exercise on sleep dysfunction in NDD.

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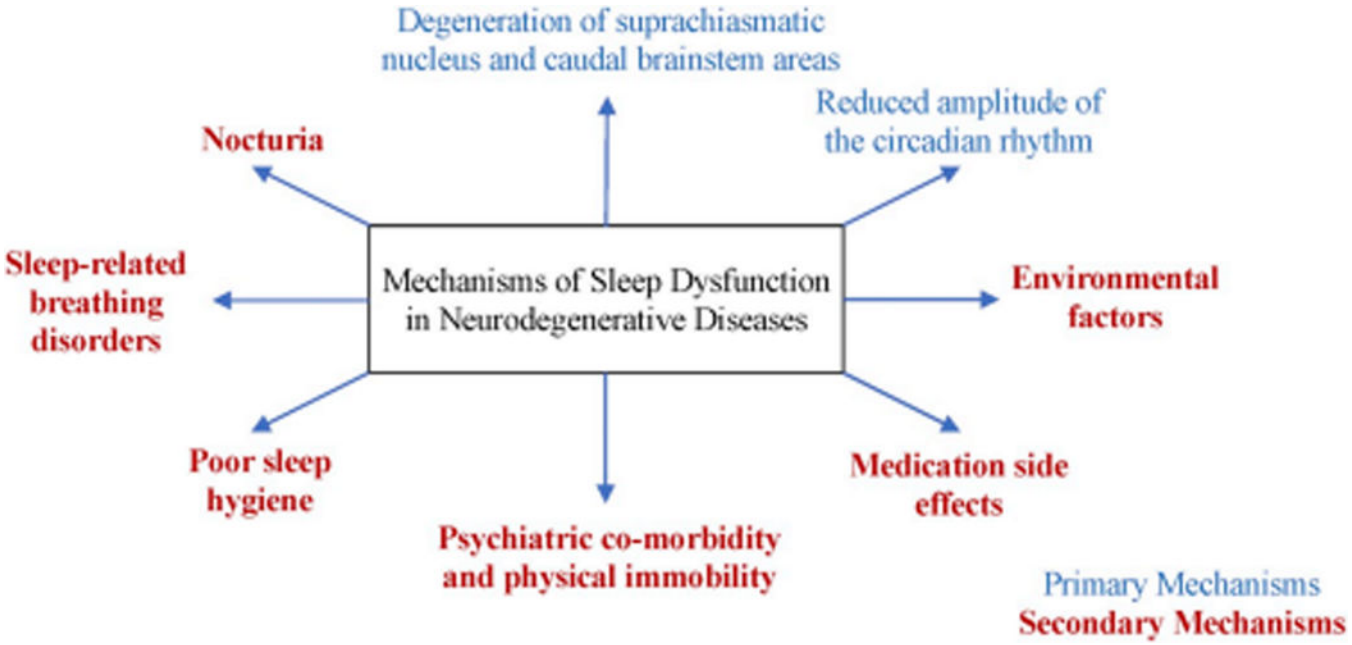

Fig. 1.
Potential mechanisms of sleep dysfunction in neurodegenerative disease

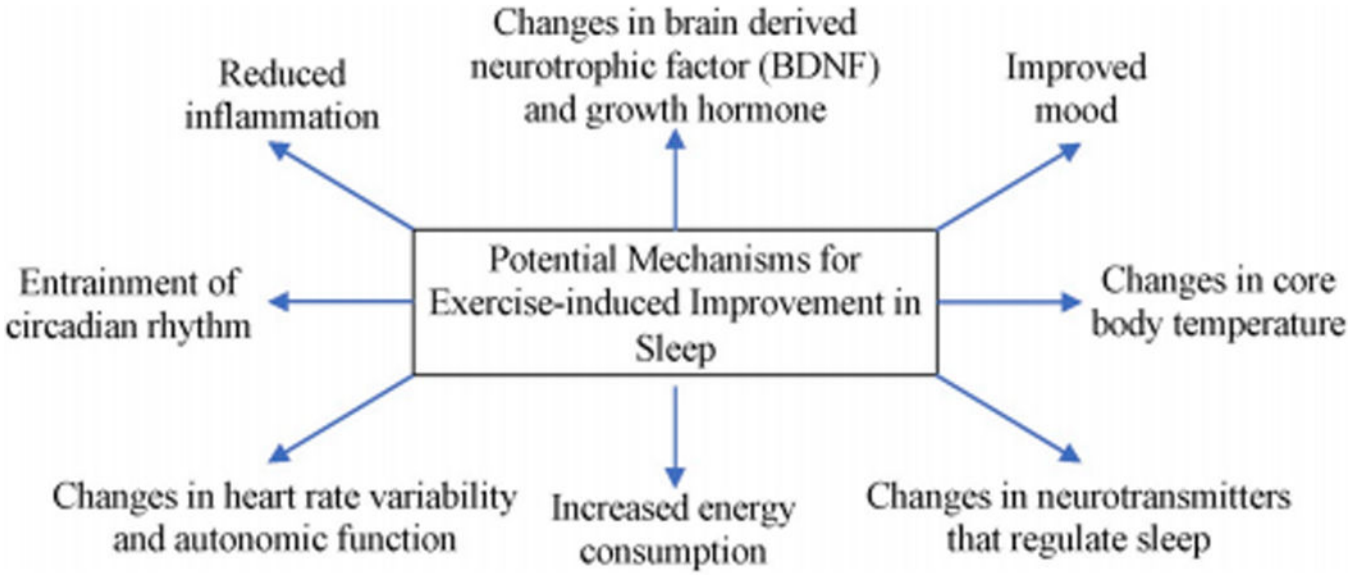

Fig. 2.
Potential machanisms for exercise-induced improvement In sleep.