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Sleep Disorders in Parkinson's Disease

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Abstract
Sleep disturbances are common problems affecting the quality life of Parkinson's disease (PD) patients and worsen their symptoms. Impaired sleep can have a severe impact on health, general well being. Sleep disturbances includes various causes such as nocturnal motor disturbances, depressive symptoms, and medication use. Co-morbidity of PD with sleep apnoea syndrome, restless legs syndrome, rapid eye movement sleep behaviour disorder, or circadian cycle disruption also results in impaired sleep. Sleep disorders in PD may occur during the day or at night and which can be before or during the disease. Patients with PD should be asked about their symptoms related to sleep disturbances. Treatment strategies should be based on physical examinations which need to be tailored to the individual and reviewed regularly.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system that causes loss of cells in the part of brain that controls movement characterized by the cardinal motor symptoms of bradykinesia, rigidity resting tremor, and a range of frequent non-motor symptoms such as sleep disturbances, depression and chronic fatigue [1].

Many people with PD have trouble falling asleep or staying asleep at night. Some sleep problems are caused by Parkinson's symptoms, while others may be the result of medications. Rapid eye movement sleep behavior disorder and Excessive day time sleepiness can be observed in the early phase and even in the premotor phase [2].

Each of the sleep disorders in PD can be seen individually or more than one sleep disorder can be seen in the same patient at the same time. It is difficult to recognize symptoms of sleep disturbances in PD as it may occur due to various factors such as stress, medications or environmental causes, etc [3].

Classification of sleep disorders in Parkinson's disease [4]

Sleep problems may be an early sign of Parkinson's disease, even before motor symptoms have begun. Some of the common sleep problems for Parkinson's patients include:

1. Insomnia
2. Sleep apnea

3. Excessive daytime sleepiness
4. Restless Legs Syndrome (RLS)
5. Narcolepsy
6. Rapid eye movement sleep Behavior Disorder (RBD)

1. Insomnia

Definition: Insomnia produces sleep fragmentation and sleep latency characterised by difficulty in either falling asleep, remaining asleep or feeling refreshed from sleep [5]. Insomnia occurs when there is destabilisation of the "sleep-wakefulness" [6].

Symptoms[7]: Difficulty falling asleep, awakenings, breathing problems (snoring, gasping, coughing), fatigue, mood changes, restlessness, irritability.

Treatment [8]: Pharmacological treatment

I. Non benzodiazepines
II. Benzodiazepines
III. Melatonin receptor agonist
IV. Antihistamines
V. Sedative antidepressants

Table: 1 Treatment of Insomnia

Drug	Strength	Doses	Indication
NONBENZODIAZEPINES			
CYCLOPYRROLONES			
Eszopiclone	1,2,3mg	2-3mg HS 1mg HS in elderly; max 2 mg 1mg HS in severe hepatic impairment; max 2mg	Sleep onset and maintenance insomnia
IMIDAZOPYRIDINES			
Zolpidem	5,10mg	5 mg HS; in elderly or hepatic impairment 10 mg HS	Sleep onset insomnia
Zolpidem (controlled released)	6.25 mg 12.25mg	6.25 mg HS in elderly or in hepatic impairment 12.25mg HS	sleep onset and maintenance insomnia
PYRAZOLOPYRIMIDINES			
Zaleplon	5,10mg	5mg HS in elderly, mild to hepatic impairment 10mg HS; max 20 mg	Sleep onset and maintenance insomnia
BENZODIAZEPINES			
Estazolam	1,2 mg	1-2 mg HS	Insomnia
Temazepam	7.5, 15,30mg	7.5 mg HS in elderly 15-30 mg HS	Insomnia
Triazolam	0.125, 0.25mg	0.125 mg HS in elderly, max 0.25 mg 0.25 mg HS, max 0.5 mg	Short acting insomnia
Flurazepam	15,30 mg	15 mg HS in elderly 30 mg HS	Long acting insomnia
MELATONIN RECEPTOR AGONIST			
Ramelteon	8 mg	8 mg HS	Sleep onset insomnia
ANTIHISTAMINES			
Diphenhydramine	25, 50 mg	25 mg PO ,IM ,IV every 8-12 hrs 50 mg HS	Mild insomnia
Promethazine	25-50 mg	25 mg PO HS	Mild insomnia
SEDATIVE ANTIDEPRESSANTS			
Amitriptyline	50-100mg	50 – 100 mg HS	Non restorative sleep
Doxepin	3-6 mg, 10-150 mg	75-150 mg OD HS	
Trazodone	25-100mg	25-100 mg HS	

I. Non benzodiazepines[9]

Mechanism of action - Selectively binds to $GABA_A$ receptors and effectively induces sleepiness.

Adverse effects – Drowsiness, amnesia, dizziness, headache and GI problems.

II. Benzodiazepines

Mechanism of action- It works through $GABA_A$ receptors to promote sleep by inhibiting brain stem monoaminergic arousal pathways, resulting on hyperpolarisation of neuronal membranes. Traditional benzodiazepines have sedative, anxiolytic, muscle relaxant and anticonvulsant properties.

Adverse effects-Drowsiness, confusion, dizziness, vision problems and feelings of depression.

III. Melatonin receptor agonist

Mechanism of action – It is selective for MT1 and MT2 melatonin receptors that regulate circadian rhythm and sleep onset.

Adverse effects– Headache, dizziness, somnolence.

IV. Antihistamines

Mechanism of action –It suppresses histamine induced swelling and vasodilatation response by blocking the binding of histamine to its receptors or reducing histamine receptor activity on nerves , vascular smooth muscles, glandular cells, endothelium and mast cells.

Adverse effects- Dry mouth, dizziness, nausea, vomiting.

V. Sedative antidepressants

Mechanism of action – Inhibit reuptake of neurotransmitters through selective receptors thereby increasing the concentration of specific neurotransmitter around the nerves in the brain.

Adverse effects- Headache, insomnia, fatigue, GI disturbances.

Non pharmacologic therapy [10]

1) Establish regular times to wake up and to go to sleep (including weekends).
2) Go to bed only when sleepy. Avoid long periods of wakefulness in bed. Use the bed only for sleep or intimacy; do not read or watch television in bed.
3) Avoid trying to force sleep; if you do not fall asleep within 20–30 minutes, leave the bed and perform a relaxing activity (e.g., read, listen to music, or watch television) until drowsy. Repeat these as often as necessary, avoid daytime naps.
4) Discontinue or reduce the use of alcohol, caffeine and nicotine.
5) Avoid drinking large quantities of liquids in the evening to prevent night time trips to the restroom, do something relaxing and enjoyable before bedtime.

2. Sleepapnoea*[11]*

Sleep apnoea is serious sleep disorder characterised by repetitive episodes of cessation of breathing during sleep followed by brief arousal from sleep to restart breathing. Hence blood oxygen desaturation can occur with these apnoeic episodes.

There are two types of sleep apnoea

- **Obstructive sleep apnoea (OSA):** It is caused by upper airway collapse and obstruction.
- **Central sleep apnoea (CSA):** It involves impairment of respiratory drive.

Obstructive sleep apnoea- Is characterized by partial or complete closure of upper airways.

Symptoms [12]: Loud snoring, occasionally waking up with a choking or gasping sensation, apnoea [complete cessation of air flow], daytime sleepiness, sleepiness while driving, morning headaches, forgetfulness, mood changes and decreased interest in sex, recurrent awakenings or insomnia.

Treatment [13]:

1. Continuous positive airway pressure (CPAP)- It is the gold standard treatment for OSA. It reduces the number of nocturnal obstructive events and number of nocturnal arousals, improves sleep

parameters and nocturnal oxygen saturation.

2. Positive airway pressure (PAP)- It functions as a pneumatic support and allows to maintain upper airway by increasing upper airway pressure. Alternative to PAP therapy include positional therapy and oral appliances.
3. Surgery – Surgical therapy (uvulopalatopharyngoplasty) opens the upper airway by removing the tonsils, trimming and reorienting the posterior and anterior tonsillar pillars, and removing the uvula and posterior portion of the palate. In very severe cases tracheostomy can be necessary.

Pharmacologic treatment:

- The most important pharmacologic intervention is the avoidance of all CNS depressants (e.g., alcohol, hypnotics) and drugs that promote weight gain.
- There is no drug therapy for OSA.

Non pharmacologic treatment: Weight reduction, avoid smoking, alcohol, sedatives and hypnotics.

Central sleep apnoea [14]

1. CSA causes fragmented sleep and consequent daytime somnolence.
2. CSA can be idiopathic but more commonly is caused by underlying autonomic nervous system lesions (e.g., cervical cordotomy), neurologic diseases (e.g., poliomyelitis, encephalitis, and myasthenia gravis), high altitudes, and congestive heart failure.
3. Currently, the primary treatment approach for CSA is PAP therapy with or without supplemental oxygen.

3. Excessive Daytime Sleepiness (EDS)[15]

It is first described as "sleep attack" characterised by sudden and irresistible overwhelming sleepiness without awareness of falling asleep.

Excessive daytime sleepiness in Parkinson Disease is mainly due to arousal system damage [16].

Symptoms [17]: Anxiety, increased irritation, decreased energy, restlessness, slow thinking, slow speech, Anorexia, hallucinations and memory difficulty.

Treatment: Pharmacological treatment **[18]**

Table 2 : Medications commonly used to treat EDS

Medications	Usual daily dosage range	MOA	Adverse effects
Dextroamphetamine and methamphetamine	5-60mg	They increase dopamine and nor epinephrine in synaptic space and also block their reuptake into presynaptic neuron by competitive inhibition	Tremor, palpitations, headache, irritability, sweating, insomnia, anorexia, HTN, cardiac arrhythmias
Methylphenidate	10-60mg	It inhibits reuptake of dopamine and nor epinephrine, increased dopaminergic and noradrenergic activity in the prefrontal cortex	Insomnia, anorexia, headache, irritability, sweating
Pemoline	56.25-75mg	Exact MOA is unknown but used in attention deficit hyperactive disorder	Hepatic toxicity not common but may be life threatening
Modafinil	100-400mg	It binds to dopamine transporter and inhibits dopamine reuptake	Headache, nausea
Gamma hydroxybutyrate (GHB)	3-9 g (in divided doses, BD, HS	Binds to receptors for major inhibitory neurotransmitter GABA	Nausea, vomiting, weight loss, occasional sedation

Non pharmacological treatment

- Good sleep hygiene, bright light therapy

4. Restless Leg Syndrome [RLS]

Definition: RLS is an abnormal involuntary movement during sleep such as nocturnal

myoclonus, termed as periodic limb movements during sleep have been associated with RLS [19].

It is also called as Willis-Ekbom [WED] which refer to an overwhelming urge to move the legs, usually associated with unpleasant sensations. The urge to move the legs is worse at rest and at night and relieved by movement.

Depending upon the time of day it occurs, RLS can interfere with falling asleep at night. It is one of the Side effects of Parkinson's medication or a medical condition associated with iron deficiency anaemia, chronic kidney disease and pregnancy [20].

Symptoms [21]: Unpleasant sensation between the ankle and knee that extends and involve whole lower limbs, creeping, crawling and tingling, burning or pain in the lower limbs, difficulty falling asleep and sleep disturbances.

Treatment:

Pharmacological treatment

I. Dopamine precursors
II. Dopamine agonist
III. Anticonvulsants
IV. Opioids
V. Benzodiazepines

Table 3: Treatment of RLS

S.No	Drugs	Dose
1	**Dopamineprecursors:** Carbidopa/levodopa	25/100 mg carbidopa/levodopa, 30 mins or 1 hr before bedtime
2	**Dopamine agonist:**	
	Ropinirole	0.25 mg OD 1-3 h before bedtime
	Pramipexole	0.125 mg OD 2-3 h before bedtime
3	**Anticonvulsants:** Gabapentin	100 – 300 mg TID
4	**Opioids:**	
	Oxycodone	2.5 – 10 mg 4 – 8 h
	Tramadol	50 mg QID
	Oxycodone SR	10- 40 mg every 12 h
5	**Benzodiazepines**	
	Clonazepam	0.5 – 2 mg/day
	Alprazolam	0.25 – 1 mg/day

I. Dopamine agonist[22]

Mechanism of action - Activates receptors in the brain that produces dopamine,a chemical that helps to regulate movement and mood.

Adverse effects- Nausea, hallucinations, somnolence.

II. Opioids[23]

Mechanism of action- Act on both central and peripheral nervous system and produces effects on neuron acting on receptors located on the neuronal cell membrane.

Adverse effects- constipation, tolerance, dependence.

III. Anticonvulsants[24]

Mechanism of action - They act either by decreasing excitation or enhancing inhibition by altering electrical activity in neurons by affecting ion channels in the cell membrane.

Adverse effects- Abdominal pain, anxiety, dizziness and mood changes.

Non pharmacological treatment [25]

- It includes life style modifications such as avoidance of alcohol, nicotine and caffeine, stretching exercises for posterior leg muscle, take warm baths
- Iron replacement therapy – ferrous sulphate 325 mg TID for patients with less than 50 ng/ml serum ferritin levels.

5. Narcolepsy

Definition: It is a chronic neurological sleep disorder considered as a hypersomnia, characterized by excessive daytime sleepiness with potentially disabling symptoms. [26].

There are 3 types of narcolepsy

1) Narcolepsy with cataplexy
2) Narcolepsy without cataplexy, Involves excessive day time sleepiness
3) Secondary narcolepsy: This can result from an injury to Hypothalamus, part of brain involved in sleep.

Symptoms[27]: Excessive daytime sleepiness, cataplexy, sleep paralysis, hypnogogic hallucinations dream like hallucinations that occur while falling asleep.

Treatment [28]:

Pharmacological treatment

I. Stimulants
II. Sodium oxybate
III. Antidepressants

Table 4: Treatment of Narcolepsy

S.No	Drug	Dose
1	**Stimulants**	
	Modafinil	200-400mg PO
	Methylphenidate	10-20mg BID
	extroamphetamine	10mg BID
2	**Sodium oxybate**	
	SSRIs	3-9g Given at bed time BID
	Venlafixine	37.5-150mg each morning
	Fluoxetine	10-40mg each morning
3	**Antidepressants**	
	Protriptyline	10-40mg/day
	Clomipramine	25-50mg/day

I. Stimulants[29]

Mechanism of action-It act through stimulation of hypocretin-containing neurons in the hypothalamus or through inhibition of dopamine reuptake. It is the first line therapy for excessive daytime sleepiness.

Adverse effects-Anxiety, nervousness, insomnia, headache.

II. Sodium oxybate

Mechanism of action-It is a metabolite of gamma-amino butyric acid (GABA) that works as a partial agonist at GABA-B receptors that may contribute to promoting slow-wave sleep and decreasing cataplexy.

Adverse effects- Confusion, dizziness, headache, incontinence.

Selective Serotonin Reuptake Inhibitors (SSRIs) [30]

Mechanism of action- SSRIs affects brain chemicals that may be unbalanced in people with depression.

Adverse effects - Gastrointestinal upset, asthma, hypertension.

III. Antidepressants

Mechanism of action-They inhibit reuptake of catecholamine, increases muscle tone and REM sleep.

Adverse effects- Dry mouth, constipation, urinary retention.

Non pharmacological treatment [31]

- Good sleep hygiene, avoid large meals before bedtime, exercise regularly and maintain a healthy diet, avoid alcohol and caffeine consumption, limit exposure to light in the evenings.

6. Rapid Eye Movement Sleep Behavior Disorder (RBD)

Definition[32]: It involves unusual actions or behaviours during the rapid eye movement (REM) sleep phase. REM sleep is a phase of sleep cycle which starts 90 minutes after falling asleep during a normal sleep cycle. During the REM phase of sleep, the muscles in the body enter in a state of temporary paralysis, but in persons with RBD this paralysis is incomplete or completely absent, so the person "acts out" their dreams, in dramatic or violent ways. Hence lack of muscle paralysis temporarily causes people with RBD to become physically distressed. The episodes tend to occur in morning hours when REM sleep is more frequent.

Symptoms [33]: Dream-enactment behaviours — It is repeated episodes of sleep-related vocalization

and/or complex motor behaviours during REM sleep, correlating with dream mentation. Reduced motor abilities, mild cognitive impairment, impairment in colour vision, orthostatic hypotension and depression.

Treatment

Pharmacological treatment

I. Benzodiazepines
II. Melatonin
III. Dopamine agonist
IV. Selective serotonin reuptake inhibitors (SSRIs)
V. Acetyl cholinesterase inhibitors
VI. Tricyclic antidepressants

Table 5: Treatment of RBD

S.No	Drugs	Dose
1	Clonazepam	0.25-4.0 mg HS
2	Melatonin	3mg
3	Pramipexole	0.7 mg TID
4	Paroxetine	10-40 mg
5	**Acetyl cholinesterase Inhibitors**	
	Donepezil	10-15 mg
	Rivastigmine	4.5-6 mg BID
6	Zopiclone	3.75-7.5mg HS
7	**Benzodiazepines**	
	Temazepam	10 mg
	Alprazolam	1-3mg
8	Desipramine	50mg qHS

I. Melatonin

It is an endogenous hormone normally secreted by pineal gland in response to evening darkness, entraining circadian rhythms. Melatonin at high doses at bedtime augments REM sleepatonia and improves RBD symptoms [34].

Adverse effects- Mild to moderate sleepiness, fatigue, dizziness, cognitive alteration [35].

II. Selective Serotonin Reuptake Inhibitors (SSRIs) [36]

Mechanism of action- It increases the levels of serotonin by limiting its reabsorption into presynaptic cells, increasing levels of serotonin in synaptic cleft.

Adverse effects- Dry mouth, insomnia, nervousness, headache.

III. Acetyl cholinesterase Inhibitors

Mechanism of action-Reduces dream - enactment behaviour episodes in patient with PD and RBD. Works by inhibiting enzyme from breaking down acetylcholine when it travels from one cell to another [37].

Adverse effects – Low blood pressure, loss of appetite, diarrhea and dizziness.

IV. Tricyclic Antidepressants (TCAs)

Mechanism of action – Act predominantly as serotonin and nor epinephrine reuptake inhibitors that has inhibitory effect on pontine REM – on neurons [38].

Adverse effects- Blurred vision, dry mouth, constipation, weight gain.

Non pharmacological treatment [39]

Good sleep hygiene, limit exposure to light in the evenings. Establish regular times to wake up and to go to sleep (including weekends).

Diagnosis such as Physical findings, polysomnography, actigraphic findings, Epworth Sleepiness Scale, Multiple Sleep Latency Test, Immobilization Test, Chin or limb electromyography is common for all sleep disorders[40]

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