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 2mg | Sleep onset and maintenance insomnia          |
|                       |          | 1mg HS in severe hepatic impairment; max 2mg |                                                 |
| **IMIDAZOPYRIDINES**  |          |                              |                                                 |
| Zolpidem              | 5,10mg   | 5 mg HS; in elderly or hepatic impairment 10 mg HS | Sleep onset insomnia                             |
| Zolpidem (controlled released) | 6.25 mg | 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 | Short acting insomnia                         |
|                       |          | 0.25 mg, max 0.5 mg          |                                                 |
| 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\cite{9}
Mechanism of action - Selectively binds to GABA\textsubscript{A} receptors and effectively induces sleepiness.
Adverse effects – Drowsiness, amnesia, dizziness, headache and GI problems.

II. Benzodiazepines
Mechanism of action- It works through GABA\textsubscript{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\cite{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. Sleep apnoea\cite{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\cite{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\cite{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\textsuperscript{[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 \textsuperscript{[20]}.

Table 3: Treatment of RLS

| S.No | Drugs                     | Dose                                    |
|------|---------------------------|-----------------------------------------|
| 1    | **Dopamine precursors:**  | 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                      |
| 5    | **Benzodiazepines**       | Clonazepam 0.5 – 2 mg/day               |
|      |                           | Alprazolam 0.25 – 1 mg/day              |

I. Dopamine agonist\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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 \textsuperscript{[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.\textsuperscript{[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 |
|      | Venlafaxine | 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 sleep atonia 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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