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Review

Possible management of non-motor symptoms of Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed but not halted, by treatment. The goal of the medical management of Parkinson's disease is to provide control of signs and symptoms for as long as possible while minimizing adverse effects. Parkinson's disease (PD) is classically considered as a motor disease, with tremor, rigidity, bradykinesia and gait problems as the classic motor features. However, non-motor manifestations (NMM) of PD have become increasingly recognized – they can often be more disabling than the motor symptoms. Non-motor manifestations of PD result from neuronal degeneration in widespread areas of the brainstem. Unfortunately, NMM is often underrecognized, and therefore, undertreated. The goal of this article is to provide a guide to recognizing and managing these NMM so that the quality of life of a patient with PD can improve.

INTRODUCTION

Parkinson's disease is recognized as one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years.[1] Most NMM falls into one of three major categories: autonomic dysfunction, cognitive and psychiatric symptoms, and sleep disorders. They can occur throughout PD; some of them, such as olfactory dysfunction, constipation, depression, and rapid eye movement sleep behavior disorder (RBD) can precede the motor symptoms of PD. Others, especially cognitive symptoms such as hallucinations and dementia, tend to occur late in PD.

Olfactory & Taste Dysfunction [2,3]

Prevalence: up to 90% of patients

Patients experience:

Olfactory dysfunction (hyposmia or anosmia) and sometimes taste alterations occur in PD.

Since these changes occur gradually, it is difficult for the patient to recognize them. Hyposmia often precedes the motor symptoms of PD, and therefore, it may be useful in the future as a screening tool to identify those at risk of PD. These symptoms are not serious, but in some cases, they may cause decreased appetite.

Why does it happen?

Olfactory dysfunction occurs due to the degeneration of the anterior olfactory nucleus and olfactory bulb, one of the first brain areas to degenerate in PD. Furthermore, sniffing, which enhances olfaction, is impaired in patients with PD. Olfactory dysfunction may also be caused by smoking, rhinitis, head trauma, and other neurodegenerative conditions.

Screening:

There are two principal options for testing olfaction.

1. UPSIT (The University of Pennsylvania Smell Identification Test). This test consists of 40 scratch and sniff pads (or 12 in a brief version) which release odors when scratched with a pencil; patients choose the correct odor from four available options. Some odors may be foreign to some patients, and this may affect their test scores.

2. Sniffin Sticks which are felt-tip pens infused with odors and are used to detect the patient's olfactory threshold.

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Possible Treatments:
No treatments are currently available for olfactory or taste dysfunction in PD.

Choking and Swallowing Difficulties [4,5]

Prevalence: Approximately 50% of patients
Patients experience:
Although mild swallowing problems can be experienced early in the disease, severe dysphagia usually occurs only in advanced PD. The patient may have trouble swallowing food, liquids, or pills. Complications include malnutrition, aspiration pneumonia, and choking.
Why does it happen?
Swallowing difficulties are due mainly to dysfunction in the oral and pharyngeal phases. Oropharyngeal dysphagia may be associated with poor activation of tongue and cheek muscles, cricopharyngeal dysfunction, and incomplete relaxation and in the coordination of the upper esophageal sphincter. Most swallowing difficulties in PD are due to impaired bolus transport across the pharynx.
Possible Treatments:
Non-pharmacological:
1. Advise the patient to avoid hard, dry foods that are difficult to swallow.
2. Ensure that the patient follows correct eating habits: proper posture while eating, smaller portions, clear mouth before speaking.
3. In some cases, increasing the patient's antiparkinson drug dosage may improve mouth movements and swallow.
Special interventions:
Occupational/speech therapy. In most cases, patients with swallowing problems should be referred to as an occupational/speech therapist for assessment and therapy. Barium swallow examinations are commonly performed to localize the deficit (oral, pharyngeal, esophageal), and to rule out alternative causes. Consider the referral to a gastroenterologist if the patient is more symptomatic.
A gastric feeding tube may be required in severe cases.

Constipation [6,7]

Prevalence: Approximately 75% of patients
Patients experience:
Constipation is defined as fewer than 3 bowel movements per week or straining to pass stools.
Constipation often precedes motor symptoms. Aside from the distress, it adds to daily life, complications include megacolon, pseudo-obstruction, volvulus, and a bowel perforation. Therefore, severe constipation should not be neglected.
Why does it happen?
Constipation is a symptom of dysautonomia and is mainly due to reduced colonic motility and occasionally anorectal dysfunction. Peripheral and brainstem autonomic nuclei degeneration causes increased intestinal transit time and constipation. Parasympathetic cholinergic denervation can lead to sphincter dyssynergia, in which the coordinated relaxation of the anal sphincter is impaired, leading to the inability to defecate normally.
Possible Treatments:
Non-pharmacological:
Exercise & Diet is the first line of treatment for constipation.
1. Adequate hydration
2. Dietary fiber (bran, prunes, etc.)
3. Physical exercise
Pharmacological:
1. Bulking agents (Psyllium, Metamucil) and stool softeners (Colace 100 mg BID). In most cases, bulking agents are not sufficient, and stimulants/osmotic are needed.
2. Stimulant laxatives & osmotic agents:
a) Senokot: is a natural laxative available in tea or pill form.
b) Isosmotic macrogol solution/polyethylene glycol 3350 (1-3 standard doses/d) or Lax-a-day (17g/day)
c) Lactulose 30-60 cc BID
d) Lubiprostone 24 ug QD to BID
Note: Classic laxatives may lead to an atonic colon and cause electrolyte imbalance (hypokalemia). Although they are generally not recommended for

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extended periods, many patients nevertheless require daily laxatives.

3. Cholinomimetics: Pyridostigmine Bromide (30-60 mg TID-QID). Consider the option to treat constipation associated with PD when patients also suffer from orthostatic hypotension, because it can treat both symptoms.

4. Suppositories (e.g. Glycerine) and enemas may be required in resistant cases.

5. Reduce or discontinue drugs with anticholinergics activity.

6. Add Domperidone.

Bladder Dysfunction [8,20]

Prevalence: Over 50% of patients

Patients experience:

A diverse range of bladder symptoms is experienced by PD patients. The commonest are related to detrusor hyperreflexia, including nocturia, urinary urge, urinary frequency, and incontinence. Urinary retention/detrusor hyporeflexia is less common. Mild bladder symptoms are common in early PD, incontinence occurs in more advanced PD. In some cases, it is difficult to diagnose the nature of the impairment (or combination of impairments) on history alone, if this is the case, consider urodynamic studies.

Why does it happen?

Bladder dysfunction is due to the degeneration of autonomic bladder neurons, motor areas, and higher control areas. Furthermore, degeneration of the substantia nigra (SN), which inhibits urination, also leads to bladder dysfunction.

Possible Treatments:

Non-pharmacological:

General measures for treating urinary urgency and incontinence include avoiding coffee and limiting water ingestion before bedtime, etc.

Pharmacological:

A. Detrusor hyperreflexia (urgency, frequency):

1. Dopamine therapy: Levodopa generally improves detrusor hyperreflexia and urgency

2. Anticholinergics: The first line of treatment for an overactive bladder.

- Oxybutynin (5mg 3-4 times/day or 1 patch twice/week) may have more central anticholinergic effects than the others in this class
- Tolterodine (2mg -3 times/day)
- Solifenacin (Vesicare) (5-10mg/day)
- Darifenacin (7.5-15mg/day)
- Trospium Chloride/Trosec (20-40mg/day)

Note: Anticholinergic medications such as these can worsen constipation, impair memory, and cause hallucinations, therefore be cautious when prescribing to patients with dementia.

3. Alternative treatments:

- Botox injection (serotype A) injection in detrusor muscle may reduce bladder overactivity.

B. Nocturia:

Desmopressin nasal spray (10-40mcg/night nasal spray) - decreases urine production. It can also be used to treat orthostatic hypotension. Caution should be given to avoiding excessive fluid intake when taking desmopressin. Drinking too much water causes decreased sodium in the blood (rare) and electrolyte imbalance.

C. Hyporeflexia (urinary retention): Bethanechol Chloride (25-75mg/d)

Cognitive Dysfunction and Dementia [9,10]

Prevalence: Up to 70 % of patients

Patients experience:

Patients with early disease demonstrate subtle changes in neuropsychiatric tests of mental flexibility and executive function, but these changes are usually asymptomatic. Parkinson's Disease Dementia (PDD) usually occurs in patients in later stages who are above 65 years of age. Predominant symptoms include bradyphrenia (slow thought process), impaired memory (due to retrieval more than encoding problems), impaired attention, visuoperceptual/visuospatial dysfunction, and dysexecutive syndrome (poor planning, rigidity, etc.).

Why does it happen?

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Lewy Body degeneration of cortical structures is the major underlying cause of PDD, but Alzheimer-like changes and vascular lesions may contribute in many cases. Probable risk factors for PDD include age (>65), hallucinations and delusions, family history of dementia, depression, advanced disease, and REM sleep behavior disorder.

Diagnosis:

Commonly used screening tests for cognitive dysfunction include:

1. Mini-Mental Status Examination (MMSE): a test score of 25/30 or less indicates with functional impairment is considered within the demented range in PD. Note that it is notably insensitive to the cognitive abnormalities of PD.
2. The Montreal Cognitive Assessment (MoCA) tests more completely the visuospatial and executive dysfunctions that occur in PD. Scores <21 may indicate dementia, and <26 indicate mild cognitive impairment.
3. Other potential instruments include the Mattis Dementia Rating Scale.

Possible Treatments:

Non-pharmacological:

1. Remain cognitively active.
2. Regular exercise: PD risk in humans is probably reduced by midlife exercise. No studies have addressed whether exercise influences dementia risk in PD, however, PD patients who exercise vigorously may improve cognitive scores.
3. Healthy diet.
4. Control vascular risks: Blood pressure, Diabetes, Cholesterol levels.
5. Control other reversible factors: sudden onset cognitive impairment can be a sign of a superimposed acute medical process (sepsis).

Pharmacological:

Medication review: ensure there are no medications that cause cognitive impairment, such as anticholinergic medications (including tricyclic antidepressants), benzodiazepines, etc.

Cholinesterase Inhibitors: Rivastigmine (1.5-6mg BID) and Donepezil (5-10mg QD) have had randomized trial evidence of benefit in PD. Side-effects of cholinesterase inhibitors include nausea, vomiting, and diarrhea (often these are less of a problem in PD patients who already suffer from constipation). Tremor can occasionally worsen with cholinesterase inhibitors, but this is rarely a practical problem.

Dopamine therapy is limited in treating PDD, but it may improve subtle cognitive deficits seen in early PD.

Orthostatic Hypotension [11,12]

Prevalence: Seen in 30-58% of patients

Patient experience:

Orthostatic hypotension (OH) is formally defined as a drop in systolic blood pressure by > 20 mmHg or diastolic pressure >10 mmHg from supine to standing. Due to cerebral autoregulation, many patients with OH are asymptomatic. Symptoms can include lightheadedness, fatigue, headache, shoulder-ache (coat-hanger pain) and cognitive slowing after standing up or occasionally after large meals. Falls and blackouts may occur if the OH is severe.

Why does it happen?

OH in PD occurs due to the failure of the baroreceptor reflex (both its cardiovagal and sympathetic branches) and to cardiac sympathetic denervation. Dopamine therapy may also cause OH.

Possible Treatments:

Non-pharmacological:

1. Encourage water intake
2. Increase salt intake
3. Avoid big meals
4. Head of bed elevated at night
5. Compressive stockings

In practise, these measures can be complex in the context of motor disability, and are often poorly tolerated by PD patients.

Other recommendations which can be useful:

1. Advise the patient to stand up slowly and carefully.

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2. Leg exercises before standing may prevent OH by bringing pooled blood back into circulation.
3. Dehydration should be avoided.
Pharmacological:
1. Re-assess antihypertensives: Because of orthostatic hypotension, the typical 24 hours BP in PD 10 mm lower than in age-matched controls. In general, medications for orthostasis have not been thoroughly studied in PD.
Options include:
2. Domperidone (10 mg TID): A peripheral D2 receptor antagonist blocks OH effects of dopaminergic therapy. It does not cross the BBB, and therefore, does not affect dopamine levels in the brain. It may be useful even in the absence of dopaminergic therapy.
3. Physostigmine 30-60mg QID can help OH and has the added benefit of treating constipation. Increased drooling and exacerbation of urinary dysfunction can occur.
4. Midodrine (2.5-10mg TID): An alpha-adrenergic agent and a vasopressor. Like options 5 and
6, it can cause supine hypertension. Other side-effects include piloerection, scalp pruritus, paresthesia, urinary retention or urgency.
5.Fludrocortisone (0.1-0.3mg/day): A mineralocorticoid that treats OH by increasing renal sodium absorption and plasma volume.
6. Desmopressin (10-40ug nasal spray or 100-400ug orally at bedtime): Desmopressin treats OH as well as nocturia. It increases plasma volume by acting on the renal tubule V2 receptors.
Midodrine and Fludrocortisone may cause hypertension in the supine position. In patients on dopaminergic therapy, Domperidone may be the first-line option.

Sexual Dysfunction [13,14]

Prevalence: Approximately 50% of patients
Patients experience:
Sexual dysfunction (SD) in PD includes erectile dysfunction (ED), difficulty reaching orgasm, decreased libido, and decreased genital sensitivity. On the other hand, patients can occasionally have increased sex drive (hypersexuality), usually related to dopamine agonists. Sexual dysfunction is reported more commonly by men than women, perhaps because it is more easily identified in men.
Why does it happen?
Erectile dysfunction occurs as part of autonomic degeneration, with parasympathetic and sympathetic denervation. Sexual dysfunction can also be due to motor dysfunction, medications, or mood disorders. Testosterone deficiency can be implicated in some cases. Aberrant sexual behavior and drive including hypersexuality are impulse control disorders, which in susceptible patients is linked to dopaminergic drug treatment.
Possible Treatments:
Pharmacological:
First-line therapies for erectile dysfunction involve phosphodiesterase inhibitors. These include:
1. Sildenafil Citrate 50mg-100mg before intercourse
2. Vardenafil 10mg before intercourse
3. Tadalafil 20mg before intercourse
Hormone Replacement Therapy can help some women with certain sexual dysfunction. However, the risk/benefit ratio must be carefully determined.

Insomnia [15, 16]

Prevalence: up 60-80% of patients
Patients experience:
There are two major types of insomnias:
Sleep-onset insomnia: trouble falling asleep
Sleep-maintenance insomnia: trouble staying asleep and waking too early
In general, PD patients tend to be more troubled by sleep-maintenance insomnia. Many patients notice that they have become increasingly 'early to bed, early to rise'.
Why does it happen?
Insomnia can be due to many causes. Motor symptoms such as bradykinesia, tremor, dyskinesia, restless legs syndrome frequently interfere with sleep. All antiparkinson medications can cause insomnia, particularly evening Selegiline, which has

amphetamine metabolites. Neuropsychiatric symptoms such as hallucinations and delusions often disrupt sleep. Nocturia is common in PD. Finally, the degeneration of sleep-promoting and circadian regions of the brain is an important cause of insomnia.

Possible Treatments:

Non-pharmacological:

1. Sleep hygiene measures: These include having regular sleep hours, avoiding excess time in bed and daytime naps, having regular get-up time, using the bed for sleep only, scheduling time to relax before bedtime, being physically active during the day, ensuring adequate sun exposure, making the bedroom quiet, dark, and comfortable, minimizing stimulants during the evening, and avoiding large evening meals. Sleep hygiene may be especially useful when used with other strategies.
2. Cognitive-behavioral therapy (CBT): Although not studied in PD, CBT is a proven and highly effective treatment of primary insomnia. Goals include alteration of patient's dysfunctional beliefs and misconceptions about sleep and insomnia. CBT also helps to reformulate anxiety-provoking thoughts regarding sleep. Different approaches can be used to improve sleep including sleep hygiene training, relaxation training, stimulus control, and sleep restriction.

Pharmacological:

1. Assess if medications are a cause. If Selegiline is being taken in the afternoon or evening, move it to a.m. and noon. Sedative drugs that cause drowsiness during the day should be avoided.
2. Nonbenzodiazepine cyclopyrrolones: Selectively bind GABA receptors, inducing a hypnotic affect. They decrease latency to sleep initiation, increase the duration of sleep, and reduce episodes of awakening. Examples include Zopiclone (7.5 mg hs) and Eszopiclone (2-3 mg hs).
3. Histaminergic: Doxepin (5-10 mg hs) is classified as a tricyclic antidepressant, it has selective histaminergic antagonistic action at low doses. In pilot studies, it has been particularly effective in sleep maintenance insomnia in PD.
4. Melatonin: in pilot studies, it has improved perception of sleep quality but the effect on total sleep time is small.
5. Dopaminergic medications: If motor manifestations such as tremor or pain secondary to rigidity are disrupting sleep, the addition of dopaminergic therapy may be useful. In some patients, dopaminergic agents (especially dopamine agonists) can promote sleep. Options include controlled-release levodopa at bedtime, levodopa upon awakening in the early morning, or addition of long-acting agents to the daily regimen.
6. Sedating antidepressants: Trazodone, low dose Desipramine, have sedating properties. These may be especially useful if there is associated depression but watch for anticholinergic effects.
7. Benzodiazepines are short-term options only, can be useful in some, but caution is needed in patients with cognitive impairment. Habituation must be avoided.

REM Sleep Behaviour Disorder (RBD) [17,18]

Prevalence: Found in 50% of patients with PD

Patients experience:

Rapid Eye Movement Sleep Behaviour Disorder (RBD) is characterized by the absence of muscle atonia during REM sleep. Patients act out their dreams, resulting in talking, limb jerking or screaming during their sleep. Patients may fall out of bed, injure themselves, or hurt their bed partner. Patients often note that dreams have become more violent. In many cases, RBD precedes motor symptoms and can be a marker of other problems, especially cognition.

Why does it happen?

Degeneration of lower brainstem nuclei is probably involved in RBD, particularly in the perilous ceruleus area.

Possible Treatments:

Non-pharmacological:

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Warn the patient about injury and consider bed-safety measures (e.g. moving sharp objects away from the bed, using bed rails, placing pillows or mattresses at the side of their bed, sleeping apart from a spouse, etc.).

Pharmacological:

1. Remove triggers: antidepressants, including SSRIs and tricyclics, can trigger or worsen RBD.
2. Clonazepam (0.25-2 mg at bedtime). The first described treatment of RBD, it helps up to 90%. As with any benzodiazepine, caution needs to be used in patients with cognitive impairment, excessive daytime somnolence, and falls.
3. Melatonin (3mg-12mg at bedtime): Melatonin works by directly restoring REM atonia. It is recommended as first-line therapy for patients at risk of cognitive dysfunction or excessive daytime somnolence. If clonazepam and melatonin alone or in combination therapy fail, additional drugs may occasionally help, including dopaminergic therapy, donepezil, etc.

Pain [19,20]

Prevalence: Approximately 33-66% of PD patients

Patients experience:

Pain in PD presents as stiffness, cramps, spasms, or muscle pain, usually occurring in the calves, neck, or back. Both primary PD pain and secondary pain exist in PD. Primary pain often occurs during off periods (i.e. when antiparkinson medications 'wear off' in patients who fluctuate). Pain can also be associated with dyskinesias and early morning dystonia. PD also can decrease pain thresholds, so that other secondary pain syndromes worsen in the presence of PD.

Why does it happen?

Decreased pain thresholds in PD can be due to the degeneration of dopamine-dependent centers that regulate pain inhibition. Norepinephrine degeneration in the locus coeruleus is also associated with pain in PD. Cramping, dystonia, and muscle rigidity due to the primary manifestations of PD can also be painful.

Possible Treatments:

Non-pharmacological:

Stretching, massage, a warm bath, and over-the-counter pain medications may help.

Pharmacological:

Adjust antiparkinson medication: Increasing dopaminergic therapy may help both primary and secondary pain in PD. If the pain is occurring during off periods, reducing fluctuations may be helpful. Therefore, pain may be a signal that dopaminergic medications should be adjusted. Dystonic pain mostly responds to PD drugs or Botulinum Toxin.

Anti neuropathic treatment (Gabapentin, Pregabalin, Lamotrigine and tricyclic antidepressants) may be useful. Tricyclic antidepressants or selective serotonin and noradrenaline reuptake inhibitors can be useful especially if the pain is linked to depression.

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