TREATMENT AND REHABILITATION IN NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease. The cardinal clinical features of PD are motor and include bradykinesia, rigidity, and resting tremor with an asymmetric pattern. Apart from these, various nonmotor symptoms (NMS) also occur in PD and constitute a major clinical symptoms. NMS can present at any stage of the disease including early and pre-motor phase of PD. Management of PD requires recognition of both motor and nonmotor symptoms as well as an understanding of the relationship between these symptoms and how they can be affected by treatments for PD. Therapy should be individualized for each patient, as treatments for the motor symptoms of PD can improve some nonmotor symptoms while they can worsen others. Some non-motor symptoms, including depression, constipation, pain, genitourinary problems, and sleep disorders, can be improved with antiparkinsonian drugs . Other non-motor symptoms can be more refractory and need the introduction of novel non-dopaminergic drugs in association with rehabilitation programs . In the future, development of treatments that can slow or prevent the progression of Parkinson's disease and its multicentric neurodegeneration are the best hope of ameliorating non-motor symptoms

Key Words: Parkinson disease, non-motor symptoms, treatment, rehabilitation

Parkinson's disease (PD) is the second most common neurodegenerative disease. The prevalence of PD is estimated to be 329 per 100,000 people, with an annual incidence ranging from 16 to 19 per 100,000 people. The prevalence of PD increases with age, affecting about 1% to 2% of adults 60 years and older, and greater than 4% of adults 80 years and older. As the elderly population grows, the incidence is expected to double by 2030. (1)

PD is considered to be a movement disorder defined by the presence of motor symptoms, such as bradykinesia, tremor and rigidity. However, it is nowadays widely accepted that PD is associated with a wide variety of non-motor features, which affect the vast majority of patients during the course of the disease and may even precede the onset of motor symptoms. Non-motor symptoms (NMS) are practically always present during the course of the disease and some of them (constipation, depressive status, hyposmia and anxiety) could even exist before the onset of classical motor symptoms (2). Although Parkinson's disease (PD) is generally considered a predominantly motor movement disorder, a majority of PD patients also suffer from non-motor symptoms increasing the disability and influencing the quality of life.

Non-motor symptoms in PD are present in 88% of patients (3)(4) and include different categories of symptoms (5) :

- Neuropsychiatric conditions:
  - Mood and affect disorders: depression, anxiety , panic attacks, apathy, and fatigue
  - Cognitive dysfunctions: executive dysfunctions, PD dementia
  - Hallucinations and psychosis
  - Medication-related impulse controls disorders and other compulsive behaviors
- Disorders of sleep-wake cycle regulation
  - Sleep fragmentation and insomnia
  - RBD (Rapid eye movement sleep behavior disorder)
  - Restless legs syndrome
  - Periodic limb movements of sleep
  - Daytime sleepiness and sudden onset of sleep
- Autonomic dysfunctions:

* Cardiovascular dysfunction: ortostatic hypotension, dyspneea on exertion, fatigue
* Gastrointestinal dysfunction : constipation, sialorrhea / drooling, fecal incontinence
* Genitourinary dysfunction: urinary urgency, urinary incontinence, sexual dysfunction
* Sweating

- Pain and sensory dysfunction:
  * Olfactory dysfunction
  * Paresthesias
  * Joint pain, limb pain, visceral pain

NMS can present at any stage of the disease including early and pre-motor phase of PD. Several NMS such as olfactory dysfunction, constipation, REM behaviour disorder, depression may antedate the motor signs, symptoms and diagnosis of PD by a number of years. They become increasingly prevalent and obvious over the course of the illness, and may become the chief therapeutic challenge in advanced stages of PD. Despite the high prevalence and associated disability of non-motor symptoms in PD, many of the non-motor symptoms may not have effective treatment options. Many other NMS and in particular hallucinations, cognitive impairment, sleep disorders and difficulty in swallowing strongly affect the advanced stage of disease, and represent a real therapeutic challenge. (2), (4).

The cause of nonmotor manifestations of PD is multifactorial, but to a large extent, these manifestations are related to the nature of the neurodegenerative process and the widespread nondopaminergic neuropathological changes associated with the disease (3). The motor symptoms are neuropathologically associated with accumulation of alpha-synuclein with Lewy body formation and neurodegeneration of the nigrostriatal dopamine system. Postmortem evaluation of PD brains has revealed more widespread degeneration in non-dopaminergic systems including several

brainstem nuclei (raphe nucleus, locus ceruleus, dorsal vagal nucleus), limbic and neocortical structures, as well as the peripheral autonomic system (6). Some motor symptoms, such as tremor and postural instability, and most non-motor symptoms, however, are not fully levodopa-responsive, and suggested to manifest extranigral pathology. (7).

The non-motor symptoms (NMS) of PD are the clinical manifestations of this extensive degeneration, which suggests that NMS are an intrinsic and fundamental features of PD.

Assessment of NMS could be made using specific scales. The most commonly used patient-administered questionnaire is the Non-Motor Symptoms Questionnaire (NMS-Q),which was designed as a screening tool. This 30-item questionnaire in yes/no format is used to determine if NMS are present . Formal assessment of the nonmotor dimensions of PD can be accomplished clinically with a 30-item scale called the Nonmotor Symptoms Scale (NMSS). The NMSS has 9 dimensions, including cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal tract abnormalities, urinary tract abnormalities, sexual dysfunction, and miscellaneous symptoms.

The high costs associated with PD, the expected rise in frequency, and the increasingly recognized importance of associated nonmotor symptoms highlight the necessity for increased understanding of all aspects of the disease and treatment options. (1). Early recognition and treatment of NMS will improve the quality of life of PD patients and will decrease the economic burden on the caregivers.(8)

Therapy should be individualized for each patient, as treatments for the motor symptoms of PD can improve some nonmotor symptoms while they can worsen others. In many cases, symptom-specific treatments are necessary to control nonmotor symptoms of PD. (1)

Some non-motor symptoms, including depression, constipation, pain, genitourinary problems, and sleep disorders, can be improved with available treatments (9). Other non-motor symptoms can be more refractory and need the introduction of novel non-dopaminergic drugs. Inevitably, the development of treatments that can slow or prevent the progression of Parkinson's disease and its multicentric neurodegeneration provides the best hope of curing non-motor symptoms.

For mood disorders (anxiety disorders and apathy) treatment consist in use of selective serotonin reuptake inhibitors (SSRIs) as first-line therapy, despite the fact that they were no randomized clinical trials to sustain the efficacity of this treatment.

For depression, the strongest evidence supports the use of pramipexole and of tricyclic antidepressants (nortriptyline, desipramine). There is insufficient evidence for amitriptyline, SSRIs or repetitive transcranial magnetic stimulation (rTMS).

Treatment of fatigue is controversial: some guidelines sustain the use of methylphenidate and modafinil. For patients with advanced PD, a recent study shows that intrajejunal levodopa infusion (IJLI) ameliorates fatigue and sleep disorders comparative to subcutaneous apomorphine infusion (10). Currently insufficient evidence exists to support the treatment of fatigue in PD with any drug or nondrug treatment, other trials are needed. (11)

Psychosis and dementia, in particular, greatly affect quality of life for both patients and caregivers and are associated with poor outcomes. Antipsychotics with dopamine-blocking properties can worsen parkinsonian motor features and have been associated with increased morbidity and mortality in old patients. In the treatment of PD psychosis, a first step is identification of producing factors, as infections, or toxic-metabolic disturbancies. Next step will be simplification of parkinsonian medications, with decreasing dopamine therapy, if possible. If these

strategies failed, antipsychotic treatment with clozapine or quetiapine can be implemented at the lower dose levels. Olanzapine should be avoided because of safety concerns.

For dementia occurring in PD, the strongest evidence supports the use of rivastigmine; however, there is wide use of all of the central cholinesterase inhibitors. Rivastigmine is the only Food and Drug Administration approved medication for PD dementia and is a reasonable first choice. Other cholinesterase inhibitors and memantine have not yet achieved recommendation status in evidence-based medicine reviews but are well tolerated in studies of PD dementia patients (12). For mild cognitive impairment, rasagiline is under study. Non-pharmacological treatments have also been shown to improve cognition in parkinsonian patients.

For medication-related impulse control disorders and related behaviors there are no treatment recommendations, and there were no randomized control trials to support treatment alternatives; amantadine is useful for the treatment of pathological gambling.

Management of sleep disorders in PD patients usually starts with optimization of dopaminergic therapy followed by specific treatment of the sleep disturbances, treatment choice depends on patient's symptoms. For excessive daytime sleepiness (EDS) most authors recommends modafinil. Insomnia should be treated with levodopa/carbidopa controlled release (CR), eszopiclone, melatonin 3 to 5 mg and melatonin 50 mg (3), (4).

RBD (REM sleep behavior disorder), characterized by enactment of dream content during REM sleep, occurs mainly in old and parkinsonian patients. Development of RBD may be one of the first symptoms of Parkinson's disease. Clonazepam is the treatment of choice for patients with RBD. The drug is efficacious and has a low incidence of adverse effects. Melatonin is a viable second-line or adjunctive treatment. (13)

Restless legs syndrome (RLS), actually called Willis-Ekbom disease (WED) alters quality of life in parkinsonian patiens; iron deficiency should be treated with iron supplements, and pharmacological treatment includes dopaminergic drugs : pramipexole, ropinirole, and rotigotine - which have been established as effective for up to 6 months in treating RLS/WED, levodopa or calcium channel alpha 2 delta ligands: gabapentin or pregabalin (14). Other drugs with limited efficacity are opioids and clonazepam.

For autonomic dysfunction manifested as orthostatic hypotension, the most common treatment plan is to begin with nonpharmacologic interventions such as increased fluid/salt intake and compressive stockings, followed by pharmacologic treatments such as fludrocortisone, midodrine, or indomethacin (5). No evidence sustain treatment with dihydroergotamine, etilefrine hydrochloride, yohimbine and L-threo-3.4-dihydroxyphenylserine (4).

Sildenafil is recommended for the treatment of erectile dysfunction, but with insufficient evidence.

Sialorrhea should be treated with botulinum toxin A (BTX-A) and BTX-B injections, as well as with glycopyrrolate. There is insufficient evidence for ipratropium bromide spray treatment.

For constipation, evidence supports the use of isosmotic macrogol (polyethylene glycol). There is insufficient evidence for cisapride, which have a risk of cardiovascular ischemic events.

For the treatment of anorexia, nausea and vomiting associated with l-dopa and/or dopamine agonist treatment, domperidone is efficacious, while there are still insufficient data for metoclopramide, which has an unacceptable risk in patients with PD because it can aggravate motor symptoms (4).

Pharmacological interventions mentioned before have limitted efficacy for a category of non-motor symptoms, like impulse-control disorders, fatigue or mood

disorders. There is still a place left for non-pharmacological treatments and neuro-rehabilitation strategies. Few studies have been done regarding the influence of rehabilitation programs on non-motor symptoms.

Recent studies demonstrate improvement of mobility and balance after training of muscular strength and endurance, trunk control, and amplitude and rhythmicity of movements (treadmill) (15). Attentional and cognitive strategies were found to enforce body awareness and improve movement sequences. Dance, sensory (auditory, visual, tactile) and cognitive training are effective for problems of gait and balance.. Parkinsonian patients should continue physical exercise as long as possible. There is hope that regular sport activities may modify PD risk and progression.

Recent evidence suggests that music-based movement therapy may be a promising intervention to improve gait and gait-related activities in Parkinson's disease patients, because it combines cognitive movement strategies, balance exercises and physical activity (16)

Physiotherapy aims to maximise functional ability and minimise secondary complications through movement rehabilitation. The overall aim is to optimise independence, safety and wellbeing, thereby enhancing quality of life. Benefit for physiotherapy was found in most outcomes over the short term (less than 3 months) but was significant only for speed, balance freezing and UPDRS score. No evidence of differences in treatment effect was noted between the different types of physiotherapy interventions being used (17), (18).

In conslusion, some of the non-motor symptoms, including depression, constipation, pain, genitourinary problems, and sleep disorders, can be improved with antiparkinsonian drugs, but others are more refractory and need the introduction of novel non-dopaminergic drugs in association with rehabilitation programs In the future, development of treatments that can slow or prevent the progression of Parkinson's disease and its multicentric neurodegeneration are the best hope of ameliorating non-motor symptoms.

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