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Clinical management of pain and fatigue in Parkinson's disease

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SUMMARY

Pain and fatigue are part of the phenomenological spectrum of Parkinson's disease (PD). These non-motor symptoms can be as troublesome as motor symptoms, impact activities of daily living, and are often underdiagnosed.
The recognition of pain and fatigue requires a high degree of clinical suspicion and is facilitated by the use of specific questionnaires and ancillary tests. This workup is highly valuable particularly considering that pain and fatigue in PD may be treatable.
We review here the clinical manifestations and management of these non-motor symptoms. Their resolution can be challenging, as there is insufficient evidence concerning effective treatment options.

1. Introduction

Non-motor symptoms occur in over 90% of Parkinson's disease (PD) patients across all stages and include a broad range of symptoms, pain and fatigue being among the most common. In the clinical setting pain and fatigue complaints are often regarded as non-significant and usually are not systematically addressed, thus remaining underdiagnosed and therefore untreated. Still, it has been documented that pain and fatigue are highly prevalent, bothersome, may appear during the early disease stages, possibly even in the pre-motor phase, and cause a significant burden to patients. The importance of recognising pain and fatigue in PD patients is underpinned by the fact that they may be treatable.

The purpose of this article is to review the clinical manifestations and management of pain and fatigue experienced by patients with PD. Treatment of these non-motor symptoms can be challenging as the scientific evidence concerning specific treatments is insufficient. Notwithstanding, awareness that these symptoms are related to PD is a prerequisite for delivering a comprehensive modern treatment for PD.

2. Pain symptoms in PD

Pain in PD has been recognized since the first description of this movement disorder [1]. In some PD patients, pain can be even more disabling than motor dysfunction, additionally reducing the quality of life. Pain in PD is, therefore, of practical concern to clinicians, can make the diagnosis of parkinsonism more difficult, in particular when the pain precedes the clinical diagnosis, and it requires treatment.

Estimates of the prevalence of pain in PD range from 30% to 85%. This variability may be accounted for by lack of standard definition or systematic assessment of the different types of pain associated with PD. Pain in PD can have secondary causes, such as radicular problems, stiffness of shoulders and neck, muscle cramps, dystonia, or akathisia. However, PD patients can have painful sensations unrelated to any apparent disorders. Such unexplained pain is termed primary pain phenomena of central origin.

Various classifications of pain in PD have been proposed. For management purposes, it is helpful to classify PD-related pain into different categories, according to the underlying cause: musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, akathitic/restless leg syndrome discomfort, and primary or central pain [2] (Table 1). Non-pharmacological and pharmacological approaches can both be effective, but the scientific evidence is limited because there are few dedicated controlled drug trials to treat pain in PD.

2.1. Musculoskeletal pain

Musculoskeletal pain comes from problems in the muscles or skeleton, and in PD is mainly related to rigidity and akinesia. Patients with PD experience many types of musculoskeletal pain. These are aching, cramping, arthralgic, and myalgic pains commonly thought to result from muscle stiffness, limited joint mobility, arthritic changes, abnormalities of posture and gait. Muscle cramps or stiffness in PD typically affect the neck, arm, paraspinal or calf muscles; joint pains occur most frequently in the shoulders, hips, knees, and ankles. Musculoskeletal pains are often evident before diagnosis. A stiff or frozen shoulder may be an early sign of PD.

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Table 1
Etiologic classification of principal pain syndromes in Parkinson's disease and their practical management

Etiological category	Painful syndromes	Management
Primary pain	Central pain	• Dopaminergic therapy (levodopa, dopamine agonists) • Anti-inflammatory agents, opioids, antiepileptics, tricyclic antidepressants, and atypical neuroleptics
Secondary pain	Musculoskeletal pain	• Musculoskeletal examination, eventually rheumatological/orthopedic evaluation • Physical therapy and occupational therapy • Medical therapy: dopaminergic therapy (for parkinsonian rigidity and akinesia); anti-inflammatory and analgesic drugs (for rheumatological and orthopedic conditions). • Surgical therapy: orthopedic joint surgery if indicated
	Radicular/neuropathic pain	• Neurological examination, eventually electrophysiological and imaging investigations • Physical and occupational therapy • Medical therapy: antidepressants, anticonvulsants, opioids analgesic, nonsteroidal anti-inflammatory drugs, also in combination • Surgical therapy: decompressive surgery if indicated
	Dystonia-related pain	• Evaluation of painful dystonia and its relationship to dopaminergic medication: provide more continuous dopaminergic stimulation • Additional medical therapy: Anticholinergics, amantadine, injections of botulinum toxin, baclofen
	Pain related to akathisia	• Dopaminergic therapy (levodopa, dopamine agonists), opioids, clozapine
	Pain related to restless legs syndrome	• Lifestyle changes and activities: decreased use of caffeine, alcohol, and tobacco. • Eventual supplements to correct deficiencies in iron, folate, and magnesium • A program of moderate exercise and massaging the legs • Dopaminergic therapy (dopamine agonists, levodopa); benzodiazepines, opioids, anticonvulsants

Patients complain of aching shoulder pain on the side initially affected by rigidity and loss of dexterity, not uncommonly leading to orthopaedic referrals and occasionally even shoulder surgery for suspected impingement or lesions to the rotator cuff. Spinal deformities, mainly of the thoracolumbar region which produce trunk postural abnormalities, and arthritis are described especially in advanced disease stages.

Treatments of musculoskeletal pain in PD usually involve physical therapy, medications, or both, depending on the cause. If pain is due primarily to parkinsonian rigidity, dopaminergic therapy, physiotherapy, and a regular exercise program are indicated. The goal of treatment is to restore mobility, and an exercise program for most patients is an important way to prevent further musculoskeletal problems. Non-steroidal anti-inflammatory drugs and analgesics are helpful for rheumatological and orthopedic conditions, in tandem with physical therapy. Orthopedic joint surgery may be indicated.

2.2. Radicular or neuropathic pain

Radicular or neuropathic pain is localized to the territory of a nerve root or nerve. It may be associated with paresthetic sensations of coolness, numbness, or tingling that may be erroneously attributed to a central pain in PD patients, but when further investigated can reveal a compressive root or nerve lesion. Hyperkinetic movement disorders in PD patients, such as neck chorea or dystonic movements, can cause cervical radiculopathy.

The clinical approach includes neurological, electrophysiological and imaging investigations when required. Treatment may include avoidance of overuse or poor posture, physical and occupational therapy, or may require decompressive surgery. Many different medications are used for neuropathic pain, including antidepressants at low doses (e.g., tricyclics and selective serotonin-norepinephrine reuptake inhibitors), anticonvulsants (e.g., pregabalin, gabapentin), opioid analgesics (e.g., morphine, codeine), and nonsteroidal anti-inflammatory drugs (e.g., ibuprofen). Sometimes combinations of drugs work better than a single drug.

2.3. Dystonia-related pain

Pain associated with dystonic movements or postures is among the most painful symptoms that a patient with PD may experience. Parkinsonism associated with dystonia may be seen in some genetic disorders, including parkin and PINK1 diseases, where dystonia may be the presenting sign, mainly localized in the lower limb [3]. Dystonia and related pain in these patients may be reduced by effective treatment of the underlying PD with dopaminergic agents.

Most frequently dystonia in PD is a complication of dopaminergic treatment. Among patients under levodopa or dopamine agonist therapy dystonia usually occurs as an off-period dystonia but can present as peak dose dystonia, or diphasic dystonia [4]. The most frequent site for off-period dystonia is the foot, whereas the neck and face are more commonly involved in peak-dose dystonia. Diphasic dystonia usually affects both distal and proximal lower limb, as well as the ipsilateral arm. Patients tolerate on-period dystonia better than dystonia occurring in the off-periods, because of the associated good motor state and lack of pain or discomfort [4].

When painful dystonia occurs during the off-period, the treatment approach is aimed at reducing or preventing the frequency and duration of off-periods. If a patient notices that high-protein meals interfere with the absorption of levodopa, a low-protein diet should be introduced. Therapies aim to provide more continuous dopaminergic stimulation throughout the day. Adding or increasing the dose of direct-acting dopamine receptor agonists, especially the extended-release dopamine agonist formulations, or of catechol-O-methyl transferase (COMT) inhibitors is the best first-line strategy. Other approaches include increasing the frequency of immediate-release levodopa preparations or using controlled-release preparations. Overnight subcutaneous apomorphine infusion is reported to be effective in reducing nocturnal off periods, pain and dystonia in patients with PD [5]. More technological approaches should be considered when simpler methods fail. These include deep brain stimulation of the

pallidum [6] or the subthalamic nucleus [7], or direct duodenal continuous infusion of levodopa in patients who are unable to undergo surgery [8]. A beneficial effect of deep brain stimulation, pallidotomy and continuous duodenal levodopa administration in reducing off-period dystonia and pain has been proved in PD patients. Additionally, injections of botulinum toxin may be helpful to treat focal dystonia in PD [9], while intrathecal baclofen has shown little effect on dystonia associated with PD [10]. A recent report showed that repetitive transcranial magnetic stimulation over the primary motor area significantly reduced the painful off-period dystonia in a PD patient [11]; this treatment option needs to be further verified.

The main goal of treatment for on-period painful dystonia is to reduce excessive dopaminergic stimulation. Reducing the dosage or discontinuing adjunctive drugs, such as MAO-B inhibitors, direct-acting dopamine agonists, and COMT inhibitors, is usually the first step. Levodopa reduction may be necessary, but may result in increased off-period. Amantadine is currently the only drug considered efficacious in the treatment of peak dose dyskinesias [12].

2.4. Primary pain syndromes

Primary pain in PD is presumed to be of central origin: a direct consequence of the disease itself not due to secondary causes. The spectrum of primary pain symptoms in PD includes unexplained painful, burning, stabbing, aching, itching, or tingling sensations that occur in undefined and peculiar body regions, or a vague overall sensation of tension and discomfort [13]. Primary central pain may also be a pre-motor feature of PD. There are several reports of unusual pain syndromes involving the face, head, pharynx, epigastrium, abdomen, pelvis, rectum, and genitalia. Pain of central origin may have a relentless, obsessional, distressing quality that overshadows the motor symptoms. Furthermore, some patients with motor fluctuations experience fluctuations of painful sensations that may have a distinctly autonomic or visceral character.

Central pain in PD might be dopamine-mediated and might respond to dopaminergic therapy (levodopa and dopamine agonists) that may be considered the first treatment option. The effective use of central pain suppressant or analgesics is anecdotal and difficult to verify. Individual reports of response to non-steroidal anti-inflammatory agents, opioids, antiepileptics such as carbamazepine and gabapentin, tricyclic antidepressants, and atypical neuroleptics, including clozapine, for the treatment of generalized and nonspecific pain syndromes have been published.

2.5. Akathisia/restless legs syndrome-related pain

Akathisia in PD is a subjective inner urge to move, producing an intolerance of remaining still, and manifesting as a constant need to move or change position. The discomfort of akathisia primarily involves the lower limbs, can be severe and is relieved by motor activities, such as walking around the room or just getting out of bed. Akathisia is common in treated PD, and it has also been reported in untreated PD. It is unclear from existing reports whether akathisia in fluctuating PD is related to on- or off-periods or whether it has a biphasic pattern, since many patients see no clear relationship to medication patterns.

Akathisia can respond to dopaminergic treatment when it presents during an off-period, but might need the additional prescription of more specific drugs such as clozapine [14].

Symptoms of akathisia may mimic the clinical picture of restless legs syndrome, making it difficult to distinguish. The classical clinical restless legs syndrome is characterized by an urge to move the legs, accompanied by uncomfortable and unpleasant sensations that worsen at rest or during periods of inactivity, with peaks in the evening or at night, and are relieved by movement. In contrast to akathisia, patients with restless legs syndrome are able to control voluntary movements in spite of unpleasant sensations and urge to move. In addition, akathisia is not associated with a circadian rhythm.

Although ropinirole and pramipexole are approved to treat restless legs syndrome in the general population, there are no controlled trials of the use of dopamine agonists in patients with PD and restless legs syndrome apart from a small placebo-controlled study. This study of six patients reported that continuous apomorphine infusion given subcutaneously overnight resulted in significantly reduced nocturnal discomfort and decreased leg movements.

3. Fatigue in PD

The recognition of fatigue in PD is relatively recent. Fatigue is a common problem in PD, occurring in about 50% of patients, and it is often the most troubling of all symptoms of PD; however fatigue in PD is poorly understood, generally under-recognized, and has no identified treatment.

One of the major problems in studying fatigue is the lack of a universally accepted definition. It is commonly referred to as a constant lack of energy, feeling of exhaustion or tiredness. Fatigue can be either mental, physical or both; however, severity of mental fatigue does not correlate well with physical fatigue, suggesting that the two conditions are caused by independent mechanisms [15].

Fatigue is often considered a warning sign of oncoming PD, since it may antedate the development of motor symptoms by several months. In most studies, the presence and severity of fatigue does not correlate with disease duration or degree of motor disability. Conversely, the presence of depression, nocturnal sleep disturbance and autonomic impairment are all thought to exacerbate the subjective experience of fatigue. However, fatigue in PD is only partially associated with these factors, being common in non-depressed patients and also in patients with no complaint of sleep disorders. Fatigue cannot be explained by this comorbidity alone and the major contributors remain to be identified. The etiology of fatigue in PD has often been discussed and the idea that fatigue may be associated with the basal ganglia is gaining acceptance. Fatigue is ameliorated by administration of dopamine in some patients with PD, which suggests that dopamine deficiency itself may be involved in causing fatigue.

In clinical practice, physicians do not pay sufficient attention to fatigue as a symptom of PD that remains under-recognized. Fatigue unquestionably is one of the most disabling features in PD and is associated with reduced activity and poorer quality of life, therefore correct recognition of fatigue and appropriate countermeasures constitute important steps in the management of PD.

Little information is available about the management of fatigue in PD. A first approach might be to search for contributing factors that are treatable (Table 2). It is of importance to pay attention

Table 2
Management of fatigue in Parkinson's disease

1. Screening and early identification of fatigue
2. Search for contributing factors that are treatable (e.g., lack of sleep, excessive stress, depression, anxiety, orthostatic hypotension)
3. Non-pharmacological therapy: Physical exercise
4. Pharmacological therapy:
a. Methylphenidate (Level C)
b. Antiparkinsonian medications: dopaminergic agents
c. Antidepressant treatment
d. Modafinil

to lack of sleep, excessive stress, anxiety or depression, because, by appropriately managing them, episodes of fatigue might be reduced. Treating orthostatic hypotension in PD patients may prevent fatigue.

Physical exercise is also beneficial on fatigue and quality of life in patients with different chronic diseases, such as multiple sclerosis. Although exercise might seem to be incompatible with fatigue, aerobic exercise has a potentially beneficial role on fatigue in PD, and many cases have been reported in which fatigue has totally disappeared after exercise. Therapeutic exercise may be worth trying in PD patients with mild motor symptoms.

The only drug that has shown significant improvement of fatigue in patients with PD in controlled studies is the dopamine transporter blocker, methylphenidate, at a dose of 10 mg three times a day (Level C) [16]. Open label studies have indicated a beneficial effect of some dopaminergic agents such as levodopa and apomorphine infusion. A recent prospective open-label observational study evaluated the effect of intrajejunal levodopa infusion and confirmed a significant improvement of motor symptoms and dyskinesias, but also observed a benefit on non-motor features, including fatigue and pain [17]. One study has shown that bromocriptine, which mainly has a D2 activating function, does not ameliorate fatigue, while pergolide, which has both D1 and D2 activating functions, reduces fatigue. This may suggest a possible correlation between fatigue and the D1 receptor.

One controlled trial of antidepressant treatment in PD reported the impact on fatigue. A small study reported that fatigue improves with nortriptyline, a tricyclic antidepressant. Selective serotonin reuptake inhibitors are commonly used in the treatment of chronic fatigue syndrome and can be used in PD patients with a history of fatigue. However, according to recent findings that fatigue in PD is associated with relative serotonergic denervation in the basal ganglia and associated limbic circuits, selective serotonin reuptake inhibitors are less likely to be efficacious in these patients. Alternative strategies to increase the brain level of serotonin and serotonergic transmission in non-depressed patients with PD with fatigue should be tested. A recent small double-blind controlled study of modafinil, a central nervous system stimulant that is effective in treating hypersomnia and narcolepsy, demonstrated that although modafinil may be effective in reducing physical fatigability in PD, it did not improve fatigue symptoms.

4. Conclusions

Pain and fatigue are an integral part of PD. These non-motor symptoms can be as troublesome as motor symptoms and impact activities of daily living, though they are often under-recognized by health care professionals [18]. There is insufficient scientific evidence concerning specific treatments for pain and fatigue in PD [16].

A concerted and multidisciplinary effort needs to be made toward finding treatments not only for pain and fatigue, but for all non-motor symptoms in PD. The NMS Quest study [19] established a valid and reliable questionnaire to identify non-motor symptoms in PD. Additionally, a revised version of the Unified Parkinson's Disease Rating Scale will include an expanded section to assess non-motor symptoms [20]. These tools should assist in screening and early identification of non-motor symptoms in PD. Moreover, a careful analysis of these symptoms with the use of specific questionnaires and ancillary tests should be done to allow designing an appropriate treatment plan using various medical and non-medical options (multimodal therapy), and will thus help improving the quality of life of the patients.

Conflict of interests

The authors report no conflict of interest.

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