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# Chronic pain and pain processing in Parkinson's disease

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ABSTRACT

Pain is experienced by the vast majority of patients living with Parkinson's disease. It is most often of nociceptive origin, but may also be ascribed to neuropathic (radicular or central) or miscellaneous sources. The recently validated King's Parkinson's Disease Pain Scale is based on 7 domains including musculoskeletal pain, chronic body pain (central or visceral), fluctuation-related pain, nocturnal pain, oro-facial pain, pain with discolouration/oedema/swelling, and radicular pain. The basal ganglia integrate incoming nociceptive information and contribute to coordinated motor responses in pain avoidance and nocifensive behaviors. In Parkinson's disease, nigral and extra-nigral pathology, involving cortical areas, brainstem nuclei, and spinal cord, may contribute to abnormal central nociceptive processing in patients experiencing pain or not. The dopamine deficit lowers multimodal pain thresholds that are amenable to correction following levodopa dosing. Functional brain imaging with positron emission tomography following administration of $H_2{}^{15}O$ revealed abnormalities in the sensory discriminative processing of pain (insula/SII), as well as in the affective motivational processing of pain (anterior cingulate cortex, prefrontal cortex). Pain management is dependent on efforts invested in diagnostic accuracy to distinguish nociceptive from neuropathic pain. Treatment requires an integrated approach including strategies to lessen levodopa-related response fluctuations, in addition to other pharmacological and non-pharmacological options such as deep brain stimulation and rehabilitation.

## 1. Introduction

Patients living with Parkinson's disease (PD) can literally suffer from the condition. Long before the advent of levodopa, various pain manifestations, dysesthesias, and cramps had been described in one-half of patients (Sigwald and Solignac, 1960). Pain was recognized long ago as a possible premotor symptom, and its intensity could be severe enough to become the chief complaint. The pre-levodopa literature suggested that pain may be revealed or aggravated by therapeutics. In the last 30 years, increased awareness of pain as a nonmotor symptom in a large fraction of PD patients with levodopa-related fluctuations has generated an extensive body of research into the causative mechanisms and management strategies. Nonetheless, the mechanisms of abnormal nociceptive processing and modulation by supraspinal mechanisms, as well as the influence of levodopa replacement therapy, remain unclear. The pain threshold, brain network of regional changes associated with pain in PD, and relationship of pain with depression, sleep deprivation, and quality of life, have been examined. Pain in PD may be difficult to treat and may require an interdisciplinary approach for proper management and wise prescription of analgesic drugs.

## 2. Prevalence and types of chronic pain

Chronic pain is prevalent with age in the general population, but figures vary according to the criteria used for duration and level of pain intensity. Moderate to severe pain lasting at least 6 months is reported by 19% of the general population (Breivik et al., 2006), but more inclusive criteria raise the prevalence rates up to 40% (Verhaak et al., 1998), further doubling among nursing home residents (Fox et al., 1999). Pain is highly heterogeneous in the PD population, and many syndromes have been delineated (Ford, 1998; Wasner and Deuschl, 2012). The reliance on clinical judgment alone, lack of standardized tools to determine whether or not a given pain source is considered a feature of PD, and disparity in pain descriptions, have complicated the subclassification of pain as directly related (caused by PD only), indirectly related (aggravated by PD), or unrelated (attributed to any other health problem) to PD (Lee et al., 2006; Nègre-Pagès et al., 2008) (Table 1).

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**Table 1**
Classification of parkinsonian pain (after Ford, 1998).

| Pain type | Etiology | |
|---|---|---|
| Nociceptive | Musculoskeletal | |
| | Related to PD | Due to rigidity, cramps, shoulder disturbances, spinal or hand/foot deformity |
| | | Non-radicular back pain |
| | | Dystonic pain (OFF-period, early morning dystonia, beginning-of-dose, peak-dose, end-of-dose dystonia) |
| | Not related to PD | Due to rheumatic disease or trauma |
| Neuropathic | Peripheral | Radicular |
| | | focal or peripheral neuropathy |
| | Central | Emergence of pain before PD diagnosis |
| | | Otherwise unexplained pain often worse in the most parkinsonian limbs |
| | | Rare, unexplained oral, abdominal or genital pain non-dystonic feature of daily motor fluctuations |
| Miscellaneous | Akathisia | OFF-period |
| | | drug-induced |
| | Restless legs syndrome | May be augmented by medication |
| | Depression | |

Pain in PD has been assessed by different methods, including home-made surveys, clinical interview and evaluation, Short Form McGill Pain Questionnaire, Leeds Assessment of Neuropathic Symptoms and Signs, Brief Pain Inventory, the body pain items of the 36-Item Short Form (SF-36) Health Survey, and the pain item of the Non-Motor Symptoms Scale (Chaudhuri et al., 2007). Recently, the specific King's PD Pain Scale (KPPS) was validated to assess pain (Chaudhuri et al., 2015). Fourteen items in 7 domains encompass recognized categories of pain in PD, including musculoskeletal pain, chronic body pain (central or visceral), fluctuation-related pain, dyskinetic-dystonic pain, nocturnal pain (linked to immobility or restless legs), oro-facial pain, discolouration/oedema/swelling, and radicular pain. This classification falls into the broad nociceptive, neuropathic, and miscellaneous sources of chronic pain in PD proposed by others (Wasner and Deuschl, 2012), but does not allow a physiopathological classification of pain. The Movement Disorder Society's review in pain rating scale in PD does not recommend this scale for syndromic classification and suggests it only (Perez Lloret et al., 2016).

Since Souques (1921), central parkinsonian pain has been accepted as a separate entity. The following criteria have been applied (Ford, 1998): emergence of pain before the onset of motor symptoms; first appearance of pain on the side the motor symptoms appeared; unexplained abdominal or genital pain; pain unexplained by other causes, either related or unrelated to PD (arthritis, musculoskeletal or dystonic pain). Its prevalence is estimated between 4.5% and 22% of cases (Defazio et al., 2008a, 2008b; Valkovic et al., 2015; Buhmann et al., 2017). Other unusual and uncommon pain descriptions involving the oral area have also been thought to have a central origin (Ford et al., 1996). Central Parkinsonian pain is probably underestimated because the diagnostic criteria are not well defined and overlap with those of musculoskeletal pain.

Pain is highly prevalent in PD and occurs in 30–95% of patients (Beiske et al., 2009; Broen et al., 2012; Valkovic et al., 2015; Buhmann et al., 2017). In a dataset of 198 PD patients (Bonenfant et al., 2016), the prevalence of body pain regardless of distribution and type was 74.2%. In a cross sectional French survey conducted in 278 PD patients experiencing chronic pain, 65% had PD-related pain (Nègre-Pagès et al., 2008). In comparison, chronic pain occurs in 30% (11–55%) of stroke victims (Paolucci et al., 2016). A pharmacoepidemiological approach has also been used to estimate the prevalence of pain in PD patients from the chronic consumption of analgesic drugs collected from a French Health Insurance database (Brefel-Courbon et al., 2009). This study, carried out in more than 11,000 patients with PD, showed that the chronic analgesic prescription was higher in PD patients compared to the general population (33% versus 20%) and was remarkably identical to that of patients with osteoarthritis. Pain assessed through the SF-36 was experienced much more commonly in PD patients (83%) than in controls (30%) (Beiske et al., 2009). In one study, the prevalence (%) of the different pain types was as follows: musculoskeletal (70), central (10), dystonic (40), radicular-neuropathic (20) (Beiske et al., 2009). In another, prevalence figures were: musculoskeletal (41), central (22), dystonic (17), radicular-neuropathic (27), or others (31) (Valkovic et al., 2015). In comparison, neuropathic pain (often radicular in origin) is estimated to affect 7–10% of the general population (Colloca et al., 2017). Nearly 30% of patients reported more than one pain type (Beiske et al., 2009), a proportion found to be 51.5% in our dataset, and as high as 71% in another report (Valkovic et al., 2015). Musculoskeletal pain is common in PD. Patients may experience unexplained, non-traumatic shoulder pain as a presenting feature of the illness, before motor symptoms become apparent in the ipsilateral arm. In retrospective reports, this was the case in 2% (Stamey et al., 2008) and 8% (Riley et al., 1989) of patients diagnosed with PD. Back pain is nearly 3-fold more prevalent in PD affecting 74% of patients, is more intense, and more commonly associated with radicular pain and deficits than in the general population (Broetz et al., 2007), possibly due to changes in posture and muscle tone. Using clinical assessment, others have concluded that only dystonic and central pain types distinguished PD patients from age-matched healthy volunteers (Defazio et al., 2008a, 2008b). Of note, BMS is infrequent in PD according to a dedicated survey on the issue, with a prevalence of nearly 4% comparable to that reported in the general population, and its occurrence does not correlate with PD duration and severity, or levodopa equivalent daily dosing (Bonenfant et al., 2016).

Pain can appear early in the course of PD, even as a pre-motor symptom (before the onset of motor symptoms). Anatomo-clinical study in 433 PD patients showed that 21% of patients had exclusive non-motor symptomatology during the prodromal phase, and pain was the most frequently reported symptom (O'Sullivan et al., 2008). A study based on a Taiwanese cohort follow-up reported that subjects with moderate to severe pain had a higher incidence of developing PD with a hazard ratio of 2.88 (Lin et al., 2013). According to Braak's hypothesis, lesions of Parkinson's disease follow a caudo-rostral progression within the central nervous system. Early documented pathology in the locus coeruleus and nuclei of the raphe, before substantia nigra involvement and clinical onset of motor symptoms, could play a role in the pre-motor occurrence of pain in PD (Hawkes et al., 2010). Another study, based on a questionnaire proposed to newly diagnosed untreated PD patients ($N$ = 109) and controls ($N$ = 107), found unexplained pain reported by 20% of patients in a time period of 2 to 10 years before the onset of motor symptoms (Pont-Sunyer et al., 2015). Pain is not only an early symptom and even a pre-motor in PD, but it is also more prevalent with disease progression (Barone et al., 2009).

Predictive factors for pain development in PD have been examined in few studies reaching no consensus. Differences in sample size, patient population, assessment methods, and study design, may underlie these discrepant results. In a survey ($N$ = 123), pain did not correlate with age, disease stage or duration, or depression (Lee et al., 2006). In other studies, female gender (Beiske et al., 2009), younger age (Goetz et al., 1986; Nègre-Pagès et al., 2008), presence of motor response fluctuations (Goetz et al., 1986; Quinn et al., 1986; Nègre-Pagès et al., 2008), longer disease duration (Valkovic et al., 2015), and depression (Starkstein et al., 1991; Nègre-Pagès et al., 2008; Ehrt et al., 2009), have been proposed as significant predictors.