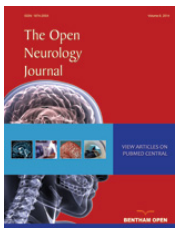

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RESEARCH ARTICLE

Chronic Pain And Levodopa Therapy in Parkinson's Disease Patients

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Abstract:

Background:

Pain is a frequent non-motor symptom in patients with Parkinson's disease (PD) and appears to be related to low levels of dopamine. This study describes the characteristics of chronic pain in a group of PD patients undergoing levodopa therapy.

Methods:

This was a cross-sectional study. The pain was assessed in 21 selected PD patients with chronic pain using several scales and instruments. Changes in pain response from levodopa use (wearing-off phenomenon) were monitored.

Results:

The most prevalent type of pain was nociceptive (71.4%), musculoskeletal and dystonic, but neuropathic pain accounted for the highest pain score according to the Parkinson's Disease Pain Classification System (45.5±30.08). Patients with neuropathic, nociplastic, or nociceptive pain upon wearing-off were those who responded to levodopa (p=0.999). According to the McGill questionnaire, patients with pain upon wearing-off had higher scores in the affective/motivational dimension (p=0.022).

Conclusion:

Using a new pain classification and scoring tool, this study corroborates a good response to levodopa in PD-related pain.

Keywords: Parkinson's disease, Pain, Antiparkinson agents, Levodopa, Pain Classification, Parkinsonism.

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1. INTRODUCTION

The prevalence of pain in Parkinson's disease (PD) can range from 34% [1] to 83% [2]; this early symptom can precede motor symptoms by years [3]. In individuals who have had the disease for less than six years, pain can be the most disturbing non-motor symptom. Although it is common in any stage of the disease [4], around 40.5% of patients may not report this complaint in routine visits to a physician [5].

Chronic pain is defined as pain that persists after the normal period of injury healing and continues for at least three months [6]. There is no consensus on assessment, classification, or duration of pain in PD patients. The first classification, published by Ford [7], is most commonly used and classifies PD-related pain into five groups (musculoskeletal, dystonic, neuropathic/radicular, central or primary, and akathisia), but this classification is not complete enough to characterize the various aspects of pain in PD. A new classification associated with a novel scale, the Parkinson's Disease Pain Classification System (PD-PCS), was recently proposed, defining PD-associated pain as nociceptive, neuropathic, or neuroclastic and generating scores by multiplying intensity by the frequency and impact of pain on activities of daily living [8]. In nociceptive pain, nociceptors are activated by stimuli related to actual or potential lesion to

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nonneural tissues. It includes most of inflammatory conditions where tissue lesion or inflammation predominates. Neuropathic pain is associated to a lesion or disease of the peripheral or central somatosensory system, with specific characteristics (tingling, burning, or electric-shock-like sensations) and location (neurologically plausible). Nociplastic pain syndromes comprise instances where the nociceptive system is overactive without any evidence of somatosensory system lesion or peripheral activation of nociceptors due to actual or potential tissue damage [7 - 9].

PD pain may be related to low levels of dopamine and dysfunction in the nigral and extranigral pathways [2, 4]. Dopamine is secreted in several central nervous system structures involved in pain and analgesia such as periaqueductal gray matter, hypothalamic paraventricular nucleus, amygdala, and substantia gelatinosa in the spinal cord [10]. There is a state of hyperalgesia with a reduced pain threshold in PD patients that is reversed with dopaminergic medications [11]. Levodopa is still the most widely used and effective dopaminergic medication for treating motor signs of PD, but long-term management of chronic patients on levodopa is hampered by the occurrence of motor fluctuations and dyskinesias, which tend to become major causes of disability and reduced quality of life as the disease progresses [12]. Although non-motor fluctuations have only been recently recognized, they occur similarly [13]. Pain is frequently reported during the "off" phases when treatment loses effectiveness and motor fluctuations appear, and occurs in around 50% of patients [14, 15]. The clinical characteristics of pain during off phases are not well established [16, 17], and investigating pain in these phases can help improve the understanding of this symptom in PD patients and contribute to the study of chronic pain in individuals without this disease [9]. This study describes the characteristics of chronic pain in a group of PD patients, analyzing the difference between pain in the "on" and "off" phases of levodopa therapy.

2. MATERIALS AND METHODS

2.1. Selection of Patients

Patients with (a) idiopathic PD according to the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS**)** [18], (b) receiving levodopa therapy regularly for at least 6 months, (c) who also had chronic pain, and (d) over 50 years of age were included in this cross-sectional study. Patients with (a) other forms of Parkinsonism, (b) Mini Mental State Examination [19] score <16, or (c) who were unable to cooperate were excluded. Informed consent was obtained from all patients and the local ethics committee approved the study. A total of 22 patients, 11 men and 10 women (mean age 68.04±9.09 years), were recruited from an outpatient neurology clinic of the Hospital Universitário Regional dos Campos Gerais.

2.2. Pain Assessment

All patients had chronic pain (persisting for at least three months) and were subjected to a semi-structured questionnaire to assess their PD and pain. Pain characteristics were evaluated with the Portuguese version of the multidimensional McGill Pain Questionnaire (MPQ) [20]; this instrument consists of 78 words describing pain grouped into 20 subclasses and assesses three major dimensions of pain (sensory-discriminative, affective-motivational, and evaluative-cognitive). Different types of scores can be obtained from this questionnaire. The simplest score is the number of words chosen (NWC), which has a range of 0–78, and the rank values for each word are added to obtain a pain rating index (PRI) for each dimension as well as a total score. Pain intensity was assessed using a 1–10 visual analog scale (VAS), and the location of the pain was marked on an image depicting the patient's body.

We also applied the Ford classification of pain in PD (musculoskeletal, dystonic, neuropathic/radicular, and central or primary) [7]. To diagnose neuropathic pain, we used the Portuguese version of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale [21].

A post hoc analysis was performed on the data obtained to fit them into PD-PCS, which was published in April 2021 [8]. This classification framework differentiates PD-related pain from non-PD-related pain and classifies PD-related pain into 3 groups based on validated mechanistic pain descriptors (nociceptive, neuropathic, or nociplastic) that encompass all the previously described PD pain types. From Ford's classification, patients with musculoskeletal and dystonic pain were reclassified as nociceptive pain. Patients with central pain were reclassified as neuropathic pain. Those with neuropathic pain were reclassified as neuropathic or nociplastic pain according to evidence of peripheral nerve damage. Severity of PD-related pain syndromes was scored by ratings of intensity, frequency, and interference with daily living activities. The VAS score data were used to classify intensity (0–10). Frequency was classified into three categories: (1) up to two days a week; (2) 3–5 days per week; and (3) 6–7 days per week. Interference in activities of daily living was classified using the answers from item 16 of the MPQ [20]: (1) annoying pain that has little impact on daily activities; (2) troublesome or miserable pain that has a moderate impact on activities; (3) intense or unbearable pain that has a considerable impact on activities. Assessment of pain during the off period and response to levodopa on a previously scheduled day, the patients were asked to suspend use of dopaminergic agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase B inhibitors (MAO-B), or amantadine to document any decline in the duration of their motor symptoms and benefit from each levodopa dosing cycle, a phenomenon known as wearing-off [9]. Each patient was given a greater equivalent dose of levodopa that usually was taken in one dose (125 to 500 mg). The patients were evaluated during three stages: 1–2 hours after a new dose of levodopa (ON), 3 hours after the usual dose of levodopa (OFF1), and 4 hours after this dose (OFF2). Parkinsonism was assessed using the Hoehn and Yahr scale [22] as well as sections III and IV of the MDS-UPDRS [18].

The Wearing-Off Questionnaire (WOQ-19) [23] was applied during all three stages, and improvement in at least one symptom during the ON phase was considered a diagnosis of wearing-off. We compared UPDRS-III scores for the ON and OFF2 stages to avoid errors in identifying motor improvement.

A reduction of 2 or more points was also considered to diagnose wearing-off [24].

Pain is one of the WOQ-19 items [23]; patients in whom wearing-off was diagnosed who reported pain in the OFF1 or OFF2 stages were included in the wearing-off pain group (WOFFP), and pain relief in the ON stage was considered to demonstrate a positive response to levodopa. Patients without pain during all "off" stages were included in the non-wearing-off pain group (NWOP).

2.3. Statistical Analysis

All data were tested for normality with the Shapiro-Wilk test. Statistical differences between the means of the groups were measured with the one-tailed Student's t-test and ANOVA for normal distribution, and the Mann-Whitney and Kruskal-Wallis tests for non-normal distribution. Correlations were measured using Spearman correlation coefficients, and Fisher's exact test was used to analyze the qualitative variables. All statistical analyses were performed using MedCalc v15.8 software. Differences were considered significant when $P<0.05$.

3. RESULTS

The mean scores for the Hoehn and Yahr staging (2.35±1.19), MDS-UPDRS-III during the ON stage (17.95±10.03), and MDS-UPDRS-IV (6±3.17) indicate a group in the intermediate stage of the disease with treatment complications. Demographic and clinical data are summarized in Table **1**.

3.1. Chronic Pain in PD

The legs (47.6%) and arms (23.8%) were the most frequent sites of pain in our sample (Table **1**). Nociceptive, musculoskeletal (66.7%), and dystonic (4.8%) pain were the most common clinical types. No differences were seen in scores for intensity, frequency, or impact on activities of daily living measured by the PD-PCS among patients with neuropathic, nociceptive, or neuroplastic pain. The characteristics of the pain in our sample are shown in Table **2**.

There was a weak correlation between PD-PCS scores and UPDRS-IV scores (r_s=0.34187, p=0.12931), and inversely with UPDRS-III scores when patients were in the ON phase (r_s=-0.29375, p=0.1962). There was no correlation between PD-PCS scores and disease duration (r_s=-0.05886, p=0.79993), levodopa use time (r_s=-0.06029, p=0.79517), pain duration (r_s=-0.14584, p=0.52817), MDS-UPDRS-III scores with patients during the OFF phase (r_s=-0.07178, p=0.75718), or Hoehn-Yahr scores (r_s=-0.3181, p=0.15994).

Table 1. Characteristics of patients with parkinson's disease.

Characteristic
Sex (M/F)
Age
Duration of disease (years)
Duration of levodopa therapy (years)
MDS-UPDRS-III score
ON phase
OFF1 phase
OFF2 phase
MDS-UPDRS-IV score
Modified Hoehn and Yahr stage
Frequency of pain episodes (per week)
Intensity of pain episodes (VAS)
Location of pain
Neck
Lower back
Arms
Legs
Thorax/Abdomen

Abbreviations: MDS-UPDRS=Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; VAS=visual analog scale; PD=Parkinson's disease.

Table 2. Pain characteristics in parkinson's disease according to the pd-pcs.

Variables
Patients (n)
Pain (Ford Classification)
Musculoskeletal
Dystonic
Neuropathic/Radicular
Central or Primary
Intensity of pain (0–10)
Frequency of pain (1–3)
Impact of pain on activities of daily living (1–3)
PD-PCS
Worse pain reported during OFF periods
Pain observed during wearing-off
Improvement of wearing-off pain with levodopa

Abbreviations: VAS=visual analog scale; PD-PCS=Parkinson's Disease Pain Classification System. #Fisher's exact test, *ANOVA parametric test

Table 3. Differences between patients with and without wearing-off pain.

Characteristics
Duration of pain (months)
Duration of pain episodes (hours)
Frequency of pain episodes (1–3)
Intensity of pain episodes (0–10)
Impact of pain episodes on activities of daily living (1–3)
PD-PDS
Pain (pathophysiological classification)
Nociceptive
Neuropathic
Neuroplastic
Pain (Ford classification)
Musculoskeletal
Dystonic
Neuropathic/Radicular
Central or Primary

Abbreviations: VAS=visual analog scale; WOFFP=wearing-off pain group; NWOP=non-wearing-off pain group. #Fisher's exact test, *Mann-Whitney non-parametric test, **Student's t parametric test.

3.2. Chronic Pain and off Periods

The wearing-off phenomenon was diagnosed in 20 patients (95.23%), 13 (61.9%) presenting both motor and non-motor associated symptoms, 5 (23.8%) only motor symptoms, and 3 (14.28%) only non-motor symptoms.

Among the 21 patients with chronic pain, 16 (76.19%) reported pain only or worsening during the OFF phase. During the tests, only 10 (47.6%) experienced pain during the wearing-off phase (WOP group). Despite previous reports of pain during the off phase by 6 patients, because they did not present pain during wearing-off testing, these patients were included in the NWOP group. For this reason, a significantly higher number of patients in the WOFFP group reported pain relief from levodopa (10, 100%) compared to the NWOP group (6, 54.5%; p=0.035). We did not identify any differences in demographic, PD, or pain characteristics between the WOFFP and NWOP groups, except for the duration of the pain symptom, which was shorter in the WOFFP group (p=0.025), exhibiting more recent onset, as well as pain intensity, which was higher in patients diagnosed with WO (p=0.024). (Table **3**).

In the MPQ scores, no statistically significant differences were found in relation to the total number of words chosen and the total pain rating index, but the WOFFP group chose more words in the affective-motivational dimension ($p<0.05$).

4. DISCUSSION

The pain was not influenced by sex or age in our sample, although recent data from the literature indicate predominance in women [11]. An increase in the prevalence of pain should also be expected throughout the clinical and neurodegenerative progression of the disease, in line with the findings of Sung *et al*. [11], even though previous isolated studies indicated otherwise [2, 25].

The legs were the most frequent location for pain reported by our study participants. In the review by Rana *et al*. [26], the lumbar region and legs were most affected. The DoPaMiP study [27] found leg pain in 67% of patients with pain directly related to PD, while lumbar pain was most prevalent in the group with pain related to a cause other than PD and not aggravated by PD. Some cases of spontaneous leg pain with normal lumbosacral spine imaging and no association with motor fluctuations could be a variant of PD central pain [9, 28].

As in other studies, the most common type of pain in our sample was musculoskeletal [2, 25, 29, 30]. However, our study found neuropathic and central pain more prevalent than dystonic pain. We revisited our results to fit them into the new Parkinson's disease pain classification tool developed by Mylius *et al*. [8], the PD-PCS. We found a similar number of patients with neuropathic pain as described in the study by Mylius *et al*. [8] (19.1% *vs*. this group's 16%), but we found more patients with nociceptive pain (71.4% *vs*. 55%) and fewer patients with neuroplastic pain (9.5% *vs*. 22%). Our scores for nociceptive pain (25.26±21.26 *vs*. 22.6±29.1) were similar to those found by Mylius *et al*. [8], and the lowest scores were also found in patients with nociplastic pain (13±7.07 *vs*. 6.0±16.4). However, the results for neuropathic pain (45.5±30.08 *vs*. 7.3±19.1) were quite different, which may be justified by the use of a specific tool to diagnose neuropathic pain (LANSS) [21]. Furthermore, the small sample size in our study was a limitation that may have distorted the results.

The higher MDS-UPDRS-IV score observed in the patients in our sample with chronic pain was related to a higher frequency of levodopa complications in this group and reinforces the association between pain and motor complications, as reported by other authors [29 - 31]. Most patients with wearing-off had associated motor and non-motor symptoms, and 90% of the patients presented pain during this phenomenon. Cheon *et al*. [14] described similar findings in this group's assessment of symptoms during wearing-off, reporting that approximately 70% of patients with motor fluctuations exhibited associated non-motor symptoms, with diffuse pain the most common complaint in 51% of patients.

Recent evidence supports an association between the off phase and the development of chronic pain; dopamine-depleted patients seem to have an increased sensitivity to pain [11].

Patients in the WOFFP group had more recent onset of pain, 12 months *versus* 36 months in the NWOP group. The DoPaMiP study [27] reported similar findings; the subgroup with pain directly related to PD reported a shorter time to pain onset than the groups with pain indirectly related to PD and pain not related to PD. The group with pain directly related to PD presented similar characteristics to the patients in this study in the WOFFP group: a higher prevalence of patients with motor complications and exacerbation of pain during the off phase, in addition to a good response to antiparkinsonian medication, regardless of the type of pain (nociceptive, nociplastic, or neuropathic). Storch *et al*. [16] observed that most episodes of pain were intensified or restricted to the off phase in patients with motor fluctuations. Martinez-Martin *et al*. [31] reported an interesting finding that nocturnal pain (when the off phase is commonly expected) is significantly more frequent in PD patients than controls.

A relevant finding of this study was the greater number of words chosen in the affective/motivational dimension of the MPQ pain evaluation by the individuals in the WOFFP group; this was also observed in the pain rating index for this dimension. In the DoPaMiP study, the group with PD-related pain scored higher in this dimension than the group with non-PD-related pain [27]. This finding may be related to the hypothesis of dopaminergic dysfunction in the mesocorticolimbic pathway, which is associated with the affective/motivational dimension of pain, the ascending reticular activator system, the central modulation of pain perception, and the reward system [9, 10]. A study utilizing positron emission tomography found increased activation in the insula, prefrontal cortex, and anterior cingulate cortex during the off phase [32]; these areas of the limbic system are associated with the affective/motivational dimension of pain. In other words, degeneration of dopaminergic neurons in the ventral tegmental area may reduce pain thresholds and simultaneously activate structures in the limbic system associated with the unpleasant perception of pain [9, 10].

CONCLUSION

Although our sample was small, we could corroborate a good response to levodopa in Parkinson's disease-related pain by using a new pain classification and scoring tool. These results are expected to stimulate further studies to clarify the role of dopaminergic and non-dopaminergic pathways in nociception, central modulation of pain, and the affective/motivational dimensions of pain perception.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

- Carlos Henrique F. Camargo, MD, MSc, Ph.D., FAAN: conception and design of the study, data acquisition, data analysis and interpretation, and drafting/critical revision of the manuscript.

Marcelo Resende Young-Blood, MD, MSc: conception and design of the study, data acquisition, data analysis and interpretation, and drafting/critical revision of the manuscript.

Camila Medik, MD: conception and design of the study, data acquisition, data analysis and interpretation, and drafting/critical analysis of the manuscript.

Matheus Gomes Ferreira, MD: data interpretation, and drafting/critical revision of the manuscript.

Hélio Afonso Ghizoni Teive, MD, MSc, PhD: critical revision of the manuscript.

Marcelo Machado Ferro, PhD: conception/design of the study, and drafting/critical revision of the manuscript.

LIST OF ABBREVIATIONS

PD	=	Parkinson's Disease
PD-PCS	=	Parkinson's Disease Pain Classification System
MDS-UPDRS	=	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
MPQ	=	McGill Pain Questionnaire
VAS	=	Visual Analog Scale
NWC	=	Number Of Words Chosen
COMT	=	Catechol-O-Methyl Transferase
PRI	=	Pain Rating Index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of State University of Ponta Grossa - 572,605 – March 27, 2014.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. This research was conducted on humans in accordance with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent was obtained from all patients.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

Dr. Carlos Henrique Camargo is the Editorial Advisory Board Member of The Open Neurology Journal. However, the other author declares no conflict of interest, financial or otherwise.

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Declared none.

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