Revista Mexicana de Neurociencia

PERMANYER

Check for updates

ORIGINAL ARTICLE

Parkinson's disease-associated pain in a Mexican Institute

Luisa G. Lira-Juarez[1], Ariadna Domínguez-García[1], Andres Y. Regalado-Mustafá[1], Elba C. Santiago-de la Cruz[1], Maria A.G. Medrano-Delgado[1], Francisco D. Ascencio-Sanchez[3], Mayela Rodríguez-Violante[1,2], and Amin Cervantes-Arriaga[1]*

[1]Clinical Laboratory of Neurodegenerative Diseases, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery, Mexico City; [2]Movement Disorders Clinic, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery, Mexico City; [3]Faculty of Medicine, Autonomous University of Baja California, Baja California. Mexico

Abstract

Objective: *Parkinson's disease (PD) presents as a chronic condition with symptoms that worsen over time. Many PD patients experience pain at some point during their illness.This complaint is often overlooked because PD is primarily a motor disorder. The main objective is to assess the prevalence and the most frequent type of pain in this population, as well as its relation to common neuropsychiatric factors.* **Methods:** *A cross-sectional study was conducted including 196 patients diagnosed with PD. The variables analyzed included age, gender, smoking, alcohol consumption, anxiety, depression, antiparkinsonian treatment (levodopa, dopaminergic agonists, monoamine oxidase inhibitors, and amantadine), intake of antidepressants or antipsychotics, age of symptom onset, age of diagnosis, years of progression, total MDS-UPDRS 3.3 score, total MDS-UPDRS score, MDS-non-motor symptom scores, Hamilton depression and anxiety scales, and montreal Cognitive Assessment.* **Results:** *Our patient cohort consisted of 115 males (58.7%) and 81 females (41.3%), with a mean age of 63.56 ± 11.88. The mean disease duration was 7.18 ± 4.9 years. The most common type of pain was musculoskeletal pain, present in 66.7%, followed by radicular pain (24.2%), pain related to fluctuations (22.7%), chronic pain (20.7%), nocturnal pain (17.2%), discoloration, edema, or swollen pain (14.6%), and orofacial pain (5.6%).* **Conclusions:** *From the study carried out, it can be observed that the most common type of pain was musculoskeletal pain, followed by radicular pain. Pain patients had a significant association with depression and anxiety due to the intensity of pain.*

Keywords: *Parkinson's disease. Pain. Depression.*

Dolor asociado a la enfermedad de Parkinson en un Instituto Mexicano

Resumen

Objetivo: *La enfermedad de Parkinson (EP) se presenta como una enfermedad crónica con síntomas que empeoran con el tiempo. Muchos pacientes con EP experimentan dolor en algún momento de su enfermedad. Esta dolencia a menudo se pasa por alto porque la EP es principalmente un trastorno motor. El objetivo principal es evaluar la prevalencia y el tipo más frecuente de dolor en esta población, así como su relación con factores neuropsiquiátricos comunes.* **Métodos:** *Se realizó un estudio transversal que incluyó 196 pacientes diagnosticados de enfermedad de Parkinson. Las variables analizadas incluyeron edad, sexo, tabaquismo, consumo de alcohol, ansiedad, depresión, tratamiento antiparkinsoniano (levodopa, agonistas dopaminérgicos, inhibidores de la MAO, amantadina), ingesta de antidepresivos o antipsicóticos, edad*

***Correspondence:**
Luisa G. Lira-Juarez
E-mail: juarezluisa549@gmail.com

Date of reception: 08-11-2023
Date of acceptance: 16-12-2023
DOI: 10.24875/RMN.23000070

Available online: 29-02-2024
Rev Mex Neuroci. 2024;25(1):15-20
www.revmexneurociencia.com

de inicio de los síntomas, edad de diagnóstico, años de evolución, puntuación total MDS-UPDRS 3.3, puntuación total MDS-UPDRS, puntuaciones MDS-NMS, escalas de depresión y ansiedad de Hamilton y MoCA. **Resultados:** *Nuestra cohorte de pacientes estaba formada por 115 varones (58.7%) y 81 mujeres (41.3%), con una edad media de 63.56 ± 11.88 años. La duración media de la enfermedad fue de 7.18 ± 4.9 años. El tipo de dolor más frecuente fue el musculoesquelético, presente en el 66,7%, seguido del dolor radicular (24.2%), el dolor relacionado con fluctuaciones (22.7%), el dolor crónico (20.7%), el dolor nocturno (17.2%), el dolor por decoloración, edema o hinchazón (14.6%) y el dolor orofacial (5.6%).* **Conclusiones:** *Del estudio realizado se observa que el tipo de dolor más frecuente fue el musculoesquelético, seguido del radicular. Los pacientes con dolor presentaron una asociación significativa con depresión y ansiedad debido a la intensidad del dolor.*

Palabras clave: *Enfermedad de Parkinson. Dolor. Depresión.*

Introduction

Parkinson's disease (PD) presents as a chronic, long-lasting, irreversible condition with symptoms that worsen over time[1]. PD is usually considered a motor disease; less known and explored are the non-motor symptoms (NMS). These are various and arise in part due to the accumulation of Lewy bodies in regions of the nervous system distinct from the substantia nigra, which can occur even before their detection in the substantia nigra. This explains the occurrence of some non-motor manifestations before the onset of cardinal disease symptoms[2]. In this context, pain is considered a non-motor symptom.

Many PD patients experience pain at some point during their illness. This complaint is often overlooked because PD is primarily considered a motor disorder. However, for a minority of patients, pain and discomfort can be so debilitating that they dominate the clinical picture[1]. It is estimated that approximately 10% of individuals have pain as an initial symptom preceding any movement disorder. Furthermore, recently published data suggest that up to 50% of patients experience painful sensations during the course of the disease[3].

Pain in PD is often a result of inadequate dopaminergic therapy. Individuals with PD in the "on" state, when the medication is at its maximum effectiveness, report less pain than those in the "off" state[1]. Individuals with pain and PD exhibit higher scores on depression assessment scales. Therefore, it is important that any assessment of pain in an individual with PD takes into account the possibility of depression contributing to the experience. Another factor to consider is cognitive disorders, which can influence the patient's perception of pain[3].

The objective of this study is to determine the prevalence and the most frequent type of pain, as well as its relation to different motor and neuropsychiatric symptoms.

Materials and methods

A cross-sectional study was conducted involving 196 patients diagnosed with PD according to the MDS criteria[4] seen at the Movement Disorders Clinic of the National Institute of Neurology and Neurosurgery. A structured questionnaire was administered to all participants after giving informed consent. Data collection spanned from 2021 to 2023, involving expert-led directed interviews during outpatient visits. The variables collected included age, gender, smoking habits, alcohol consumption, anxiety, depression, antiparkinsonian treatment (levodopa, dopaminergic agonists, monoamine oxidase [MAO] inhibitors, and amantadine), intake of antidepressants or antipsychotics, age at symptom onset, age at diagnosis, disease duration, MDS-Unified PD Rating Scale (MDS-UPDRS) item 3.3 score (rigidity item)[5], and total MDS-UPDRS score[6], where scores were assigned as follows: 0: Never, 1: Rarely (≤ 10% of the time), 2: Sometimes (11–25% of the time), 3: Frequently (26–50% of the time), and 4: Most of the time (≥ 51% of the time).

The MDS-UPDRS consists of four parts, namely I: Non-motor experiences of daily living; II: Motor experiences of daily living; III: Motor examination; IV. Each question is based on five responses that are linked to commonly accepted clinical terms: 0 = normal, 1 = mild, 2 = mild, 3 = moderate, and 4 = severe. The full MDS-UPDRS contains questions/assessments, divided into Part I (13), Part II (13), Part III (33 scores based on 18 items, several with right, left, or other body distribution scores), and Part IV (6). The MDS-UPDRS scores 65 items compared to 55 in the original UPDRS, 48 that had 0-4 options and 7 with yes/no responses.

The MDS Non-Motor Rating Scale (MDS-NMS) L1, 2, 3, and 4 scores (pain-related items)[7] were also applied; scores were assigned as follows: L1: muscular, joint, or back pain; L2: deep or dull pain; L3: pain due to abnormal twisting movements of arms, legs, or body; L4: other types of pain (e.g., nocturnal pain and orofacial pain).

The MDS-NMS instrument consists of 30 questions with dichotomous responses, items are grouped into nine domains: Gastrointestinal, urinary tract, sexual function, cardiovascular, apathy/attention/memory, hallucinations/delusions, depression/anxiety/anhedonia, sleep/fatigue, pain, and miscellaneous[7].

In addition, the following assessments were performed: QUICK questionnaire 18[8] for pain presence or improvement after medication dose, Montreal Cognitive Assessment (MOCA)[9], Hamilton Depression Scale, Hamilton Anxiety Scale (HAS), King's Parkinson's Disease Pain Scale (KPPS), MDS-UPDRS 4.3 (time in off, and MDS-UPDRS 4.6 (on-dystonia).

Regarding the HAD scale[10], scores were assigned as follows: 0-7 points: Normal, 8-13 points: Mild depression, 14-18 points: Moderate depression, 19-22 points: Severe depression, ≥ 23 points: Very severe depression.

For the HAS[11], the scores were as follows – 0-17 points: Mild anxiety, 18-24 points: Mild-to-moderate anxiety, 25-30 points: Moderate-to-severe anxiety, and 31-56 points: Very severe anxiety. For the Hamilton Depression and Anxiety scales, obtained scores were classified as follows: Scores < 8 as normal, scores < 14 as mild depression, scores < 19 as moderate depression, scores < 23 as severe depression, and scores > 23 as very severe depression. Similarly, for the anxiety scale, scores < 18 were categorized as mild anxiety, scores < 25 as mild-moderate anxiety, scores < 31 as moderate-severe anxiety, and scores < 57 as very severe anxiety. MOCA questionnaire scores were divided into < 26 for probable mild cognitive impairment and < 16 for probable severe impairment.

The Levodopa Equivalent Dose (LED) was calculated using the formula: (dose in mg of L-dopa × 1) (dose in mg of L-dopa × 0.33 (entacapone) or 0.5 (tolcapone or opicapone) to obtain the COMT inhibitor LED)) + (dose in mg of controlled-release L-dopa × 0.75) + (dose in mg of extended-release L-dopa × 0.5) + (dose in mg of pergolide × 100) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66) + (dose in mg of cabergoline × 66. mg of cabergoline × 66. 77) + (dose in mg of bromocriptine × 10) + (dose in mg of pramipexole × 100) + (dose in mg of ropinirole × 20) + (dose in mg of lisuride × 100) + (dose in mg of dihydroergocryptine × 5) + (dose in mg of lisuride × 100) + (dose in mg of dihydroergocryptine × 5) + (dose in mg of bromocriptine × 5) × 5) + (mg dose of oral selegiline × 10 or sublingual × 80) + (mg dose of rasagiline × 100) +(mg dose of subcutaneous apomorphine × 10 or sublingual apomorphine × 1. 5) + (dose in mg rotigotine × 30) + (dose in mg rotigotine × 30)(dose in mg of piribedil × 1) + (dose in mg of amantadine immediate release × 1 or prolonged release × 1.25) = L-dopa daily dose equivalents[12].

The KPPS[13] is an evaluator-based scale that assesses pain in PD patients through an interview. It consists of 14 items divided into seven separate domains. Each item is scored for severity (from 0 [no pain] to 3 [very intense pain]) multiplied by frequency (from 0 [never] to 4 [all the time]), resulting in sub-scores ranging from 0 to 12. The sum of these sub-scores gives the total score with a theoretical range of 0-168. The domains and score ranges are as follows: (1) Musculoskeletal pain (range, 0-12); (2) chronic pain (range, 0-24); (3) fluctuation-related pain (range, 0-36); (4) nocturnal pain (range, 0-24); (5) orofacial pain (range, 0–36); (6) discoloration, edema/swelling (range, 0-24); and (7) radicular pain (range, 0-12)[14].

Statistical analysis

Patients were categorized according to the MDS-UPDRS item 1.9 (pain)[6], patients with pain (Group 1) and non-pain (Group 2). Normality testing was conducted using the Shapiro–Wilk test, resulting in a non-normal distribution. The categorical variables included smoking, alcohol consumption, current treatment, intake of antipsychotics or antidepressants, and self-perceived anxiety or depression, categorized with values of 0 (absence) or 1 (presence). The continuous variables encompass age of onset, age of diagnosis, years of progression, equivalent dose per medication group, equivalent dose of medications per day, NMS-UPDRS total, and NMS-UPDRS 3.3 total.

For the nominal variables, the Chi-squared test was used, and for continuous variables, the T-test or Mann–Whitney U test was used as needed. The statistical analyses were conducted using SPSS software. Statistical significance was set at $p < 0.05$.

Results

The final sample consisted of 115 males (58.7%) and 81 females (41.3%), with a mean age of 63.56 ± 11.88. The mean disease duration was 7.18 ± 4.9 years. All patients were receiving antiparkinsonian treatment, with 184 on levodopa, 27 on MAO inhibitors, 91 on dopaminergic agonists, and 26 on amantadine (Table 1). Regarding the intake of antidepressants or anxiolytics, 13 were taking anxiolytics and 56 were taking antidepressants.

Upon conducting the analysis, the following observations were made: Regarding the group of 139 patients with pain, 83 were male and 56 were female (p = 0.645). Group G1 had 92 patients with negative smoking status and 47 with positive smoking status, whereas G2 had 47 with negative smoking status and 10 with positive smoking status (p = 0.23). Positive alcohol consumption was observed in 13 patients and negative in 44 for G2 and 90 were negative with 49 positive for G1 (p = 0.89).

For the self-perceived anxiety variable, we found that in G1, 78 did not have anxiety and 61 did (p = 0.364). On the anxiety scale, for G1, 125 had mild anxiety, 10 had mild-moderate anxiety, and four had moderate-severe anxiety. For G2, 55 had mild anxiety, two had mild-moderate anxiety, and none had moderate-severe anxiety (p = 0.25).

In the self-perceived depression variable, we noted that 79 patients in G1 did not present anxiety and 60 did, whereas in G2, there were 20 patients with anxiety and 37 without it (p = 0.296). In the analysis of the depression scale, for G1, 59 had no depression, 61 had mild depression, 10 had moderate, five had severe, and four had very severe. In G2, 38 had no depression, 15 had mild, four had moderate, and no patient had severe or very severe depression (p = 0.20).

Regarding the analysis of the MOCA questionnaire score, for G1, 29 patients had no impairment, 90 had a mild impairment, and 20 had severe impairment. In G2, 15 had no impairment, 37 had mild impairment, and 5 had severe impairment (p = 0.464).

When performing the analysis of the MDS-UPDRS variable on dystonia and time off, no association was found between groups, detailed information is shown in Table 2. Out of the 139 patients who reported self-perceived pain at the time of the QUICK 18 questionnaire, 83 confirmed again that they were experiencing fluctuating pain. Regarding the improvement in pain with doses of medication, it was found that 55 patients mentioned improvement.

In the MDS-NMS variable L, the most frequently self-perceived types of pain reported by the patients were muscular/joint pain (p < 0.001) and deep/dull pain in the body (p < 0.001).

To compare the total score of the different scales between the groups, we used the Student's t-test where we obtained a significant relationship between depression, anxiety, and the presence of pain. More information is shown in Table 3.

The mean KPPS score was 8.62 ± 10.2. The most associated type of pain in our population was musculoskeletal pain, present in 66.7% of the population, followed by radicular pain (24.2%), pain related to

Table 1. Description of the type of drug in the sample

Medication type		G1 (n = 139)	G2 (n = 57)	p-value
Levodopa	Levodopa/ Carbidopa Levodopa/ benserazida	124 7	48 5	0.565
MAOI	Rasagiline	20	7	0.697
Dopaminergic agonist	Bromocriptine Pramipexole Rotigotine	3 45 19	2 14 8	0.805
Amantadine	Amantadine	21	5	0.235

G1: Parkinson's disease and pain; G2: Parkinson's disease with no pain; MAOI: Monoamine oxidase inhibitor.

Table 2. Comparison between groups about dystonia and time off

Variable	G1 (n = 139)	G2 (n = 57)	p-value
Dystonia			
No dystonia	126	52	0.316
Minimum	3	4	
Mild	5	2	
Moderate	4	0	
Serious	1	0	
Off time			
No periods	99	39	0.843
< 25%	22	10	
26-50%	12	4	
51-75%	6	4	

G1: Parkinson's disease and pain; G2: Parkinson's disease with no pain.

Table 3. Comparison of scales applied between groups

Variable	GROUP 1 (n = 139)		GROUP 2 (n = 57)		p-value
	Mean	SD	Mean	SD	
MDS-UPDRS 3.3	34.17	14.67	32.40	15.51	0.452
MDS-UPDRS TOTAL	61.08	25.69	57.82	28.41	0.436
MOCA	20.88	5.72	21.77	4.66	0.297
HAD	9.37	5.69	5.77	4.75	0.000
HAS	9.36	6.04	6.02	4.89	0.000

MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale; MOCA: Montreal cognitive assessment; HAD: Hamilton depression scale; HAS: Hamilton anxiety scale; G1: Parkinson's disease and pain; G2: Parkinson's disease with no pain.

fluctuations (22.7%), chronic pain (20.7%), nocturnal pain (17.2%), discoloration, edema, or swollen pain (14.6%), and orofacial pain (5.6%).

The correlation coefficients for KPPS: Bivariate correlation of the total scores of the KPPS scale and anxiety yielded a Pearson correlation coefficient of 0.320, indicating a moderate correlation (p = 0.000). Similarly, when compared to the depression scale, the Pearson correlation coefficient was 0.381, also indicating a moderate correlation (p = 0.000).

Discussion

The mechanisms underlying pain in PD are unclear. Although some studies have reported that PD patients may have a low pain threshold and tolerance and that they tend to decrease as PD progresses, which may predispose to the development of pain, when we performed our analysis, there was no significant difference in the years of evolution[15]. Pain can occur at any time during the disease and may be present before diagnosis[16].

"KPPS" is a questionnaire with 14 questions covering seven domains: (1) Musculoskeletal pain; (2) chronic pain; (3) pain related to fluctuation; (4) nocturnal pain; (5) orofacial pain; (6) discoloration and edema/swelling; and (7) radicular pain. This is a new approach to pain in PD, which will allow for more in-depth testing in clinical trials for treatments for this aspect of PD[17].

It has been observed that all motor symptoms fluctuate, presenting more severe symptoms in the "off" state than in the "on" state but at the time of our analysis, no relationship was found because the patients did not spend so much time in off, although they did report that they noticed an improvement in pain with their medication doses according to the analysis carried out[18].

According to several studies, as well as in our population, musculoskeletal pain has been reported to be the most prevalent due to in our population was present in 98 patients[19,20]. All types of pain were more prevalent in patients with PD in advanced stages than in early stages[21], Although in our population, pain in early stages was seen more frequently, this may be due to the fact that patients in advanced stages are often difficult to follow-up.

No association between dystonic or non-dystonic pain has been found in other studies, nor was any association found in this one[22]. The risk factors for pain in PD include early age of onset, comorbid depressive symptoms, and associated diseases[23], we did not take into account the associated diseases but we can see that in the age of our population is no association with early age but there is an association with depressive symptoms.

Although most studies report that pain related to PD is significantly more common in women than in men[24], some articles state the opposite[25], and this was observed in our study since it was more common in men and no association was found.

Pain patients had significantly more severe depressive symptoms than pain-free patients and pain intensity was associated with more severe depression[26], in our study also had an association with depression and anxiety. Some studies mention that as pain intensity increases, quality of life decreases significantly in PD patients[27].

Diagnosing the cause of pain requires skill and clinical experience. The most important diagnostic tool is the patient's medical history. Perhaps, the most crucial task for individuals with Parkinson's who experience pain is to describe with the utmost precision whether medications induce, exacerbate, or alleviate their pain[1].

The limitations of this study were the lack of information on whether the patient was taking any treatment for pain, the sample was not so large, and most of our patients were in the intermediate stages of the disease so we do not know how it presents in advanced stages, the variables of education or socioeconomic level were not included.

Conclusions

In recent years, nonmotor symptoms in PD have received increasing attention from physicians and researchers. Pain is a heterogeneous symptom in PD. Pain is affected by several factors, e.g., age, sex, depression, severity or duration of illness. Of the disease From the conducted study, it can be observed a significant association between depression and anxiety due to the intensity of pain. In our analysis we found musculoskeletal pain to be the most frequent as seen in the literature. Increased awareness of pain symptoms in PD would provide greater understanding. Further research is needed assessing patients in advanced stages of the disease, including socioeconomic status, pain management, to give a specific analysis that will help us in the majority of PD patients.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Rotondo J, Toro M, Bolívar M, Seijas ME, Carrillo C. Dolor en la enfermedad de Parkinson. Una mirada a un aspecto poco conocido de esta patología. Rev Soc Esp Dolor. 2019;26:184-98.
2. Simon Perez E, Aguilera Pacheco OR, Nunez Lahera I, Colina Avila E. Síntomas no motores en pacientes con enfermedad de Parkinson. MEDISAN. 2017;21:681-7.
3. Alemán Pullas SL, Montero Balarezo CX, Díaz Recalde EX, Jarro Sanchez CM. Enfermedad de Parkinson. Diagnóstico y tratamiento. RECIMUNDO. 2022;6:250-66.
4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591-601.
5. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A, et al. Expanded and independent validation of the movement disorder society-unified Parkinson's disease rating scale (MDS-UPDRS). J Neurol. 2013;260:228-36.
6. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder society- sponsored revision of the unified Parkinson's disease rating scale (MDS- UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129-70.
7. Palacios Sánchez E, Silva Soler MA, Vergara Aguilar JP, Perdomo Rivera CJ, Patiño Rodríguez HM. Non-motor symptoms in Parkinson's disease, relationship to laterality at the beginning of the disease? Acta Neurol Colomb. 2015;31:261-6.
8. Martinez-Martin P, Tolosa E, Hernandez B, Badia X, ValidQUICK Study Group. Validation of the "QUICK" questionnaire--a tool for diagnosis of "wearing-off" in patients with Parkinson's disease. Mov Disord. 2008;23:830-6.
9. Kandiah N, Zhang A, Cenina AR, Au WL, Nadkarni N, Tan LC. Montreal cognitive assessment for the screening and prediction of cognitive decline in early Parkinson's disease. Parkinsonism Relat Disord. 2014;20:1145-8.
10. Trajković G, Starčević V, Latas M, Leštarević M, Ille T, Bukumirić Z, et al. Reliability of the hamilton rating scale for depression: a meta-analysis over a period of 49 years. Psychiatry Res. 2011;189:1-9.
11. Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, et al. Reliability and validity of a structured interview guide for the hamilton anxiety rating scale (SIGH-A). Depress Anxiety. 2001;13:166-78.
12. Cervantes-Arriaga A, Rodríguez-Violante M, Yescas P, Alonso-Vilatela E. Fluctuaciones motoras en enfermedad de Parkinson. Rev Méd Inst Mex Seguro Soc. 2012;50:141-6.
13. Stoyanova-Piroth G, Milanov I, Stambolieva K. Translation, adaptation and validation of the Bulgarian version of the King's Parkinson's Disease Pain Scale. BMC Neurol. 2021;21:357.
14. Rodríguez-Violante M, Alvarado-Bolaños A, Cervantes-Arriaga A, Martinez-Martin P, Rizos A, Chaudhuri KR. Clinical determinants of Parkinson's disease-associated pain using the king's Parkinson's disease pain scale. Mov Disord Clin Pract. 2017;4:545-51.
15. Zambito Marsala S, Tinazzi M, Vitaliani R, Recchia S, Fabris F, Marchini C, et al. Spontaneous pain, pain threshold, and pain tolerance in Parkinson's disease. J Neurol. 2011;258:627-33.
16. Fil A, Cano-de-la-Cuerda R, Muñoz-Hellín E, Vela L, Ramiro-González M, Fernández-de-las-Peñas C. Pain in Parkinson disease: a review of the literature. Parkinsonism Relat Disord. 2013;19:285-94, discussion 285.
17. Young Blood MR, Ferro MM, Munhoz RP, Teive HA, Camargo CH. Classification and characteristics of pain associated with Parkinson's disease. Parkinsons Dis. 2016;2016:6067132.
18. Storch A, Schneider CB, Wolz M, Stürwald Y, Nebe A, Odin P, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology. 2013;80:800-9.
19. Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. Mov Disord. 2012;27:480-4.
20. Rana AQ, Kabir A, Jesudasan M, Siddiqui I, Khondker S. Pain in Parkinson's disease: analysis and literature review. Clin Neurol Neurosurg. 2013;115:2313-7.
21. Valkovic P, Minar M, Singliarova H, Harsany J, Hanakova M, Martinkova J, et al. Pain in Parkinson's disease: a cross-sectional study of its prevalence, types, and relationship to depression and quality of life. PLoS One. 2015;10:e0136541.
22. Tinazzi M, Del Vesco C, Fincati E, Ottaviani S, Smania N, Moretto G, et al. Pain and motor complications in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77:822-5.
23. Tai YC, Lin CH. An overview of pain in Parkinson's disease. Clin Park Relat Disord. 2020;2:1-8.
24. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. Pain. 2009;141:173-7.
25. Ha AD, Jankovic J. Pain in Parkinson's disease. Mov Disord. 2012;27:485-91.
26. Ehrt U, Larsen JP, Aarsland D. Pain and its relationship to depression in Parkinson disease. Am J Geriatr Psychiatry. 2009;17:269-75.
27. Prange S, Klinger H, Laurencin C, Danaila T, Thobois S. Depression in patients with Parkinson's disease: current understanding of its neurobiology and implications for treatment. Drugs Aging. 2022;39:417-39.