REVIEW

Prevalence of Pain in Parkinson's Disease: A Systematic Review Using the Modified QUADAS Tool

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ABSTRACT: Pain has been studied more intensely as a symptom of Parkinson's disease (PD) in recent years. However, studies on the characteristics and prevalence of pain in PD have yielded conflicting results, prompting us to do a systematic review of the literature. A systematic review of the literature was conducted, using different databases. The last inclusion date was March 15, 2011. The modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used, which is especially designed for judging prevalence studies on their methodological quality. Only articles that met the predefined criteria were used in this review. We found 18 articles, of which only 8 met the methodological criteria. Prevalence frequency ranges from 40% to 85% with a mean of 67.6%. Pain is most frequently located in the lower limbs, with almost one-half of all PD patients complaining about musculoskeletal pain (46.4%). The pain fluctuates with on-off periods. Surprisingly, only 52.4% of PD patients with pain used analgesics, most often nonopioids. PD patients seem to be predisposed to develop pain and physicians should be aware of pain as a common feature of PD. As many as one-half of PD patients with pain may be missing out on a potentially useful treatment, and proper treatment could increase quality of life in PD patients.

Key Words: pain; Parkinson's disease; prevalence

Parkinson's disease (PD) prominently affects motor function, characterized by symptoms such as rigidity, bradykinesia, postural instability, and resting tremor. In addition, PD causes non-motor manifestations, including problems with cognition, behavior, and pain. Although Parkinson described the first symptoms of the disease, Charcot was the first to notice a relationship between PD and pain.[1,2] Like other non-motor symptoms of PD,[3] pain contributes to severe disability[4] and adequate pain treatment may improve quality of life.[5] There has been a growing interest in the association between pain and PD and the reported prevalence varies widely: from as low as 11%[6] up to 85%.[7] To inventory the existing knowledge in this field, we systematically reviewed the literature on the prevalence and characteristics of pain in PD.

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Materials and Methods

Literature Search and Selection of Articles

A systematic literature search was carried out covering articles published from January 1966 till March 2011 using the databases Medline, PubMed, and Cochrane library. We used the Medical Subject Headings (MeSH) terms "Parkinson" and, "Parkinson's disease" in combination with "Pain," "Prevalence," "Quality of Life," and "Non-motor symptoms" in the title. Subsequently, we analyzed the abstract for relevant articles and searched the reference list of each appropriate article for other relevant articles. Studies addressing pain in PD available in full text and written in English, French, German or Dutch were included.

Quality Assessment

With regard to the reported prevalences, the quality of the studies was assessed with epidemiological

TABLE 1. Modified QUADAS tool: quality criteria for prevalence studies

A		The final sample should be representative of the target population
	1	At least 1 of the following should apply for the study (2 points):
		An entire target population
		Randomly selected sample
		Sample stated to represent the target population
	2	At least one of the following (2 points):
		Reasons for nonresponders described,
		Nonresponders described
		Comparison of responders and nonresponders
		Comparison of sample and target population
	3	Response rate $\geq$ 90% (2 points)
		Response rate 70% to 90% (1 point)
		Response rate $\leq$ 70% (0 point)
B		Quality of data
	4	Were the data primary from a prevalence study (2 points) or was it taken from a survey not specifically designed for that purpose (1 point)
	5	The same mode of data collection should be used for al subjects (2 points), if not: 1 point
	6	The data have been collected directly from the patient by means of a validated questionnaire/interview (3 points)
		No validated questionnaire/interview patient (2 points)
		Data have been collected from proxies of retrospectively from medical record (1 point)
C		General description of the method and results should include:
	7	Description of target population and setting where patients were found (2 points)
	8	Description of stage of disease, sex, age (all 2 points, 1 or 2: 1 point)
	9	Final sample size (1 point)
D		Definitions of pain prevalence
	10	Prevalence recall periods should be stated (1 point)

quality criteria. We modified the previous formulated criteria by Leboeuf-Yde et al.[8] and adjusted them for this review into a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, including 10 criteria in which the reliability of the prevalence study is evaluated (Table 1).[9,10] The quality score ranges from 0 to 19 points, with a cutoff level for methodological acceptability set at 14 points, which is 75% of the total points that can be achieved.[11] All studies were reviewed independently by 2 researchers (M.P.G.B., M.M.B.) and differences between interpretations were resolved using a discussion and consensus approach.

Data Extraction and Analyses

After estimating pain prevalence, articles were first assessed on distribution of pain, second for description of different pain types, and third on whether they mention influence of on-off phases and if they report use of analgesics. We calculated weighted averages using SPSS 16.0 (SPSS, Chicago, IL, USA) and the percentages followed by a standard deviation (SD) are given. Additionally, general study characteristics were extracted from each article.

Results

Trial and Study Characteristics

In total 68 studies were found. However, 31 assessed only treatment of pain in PD and 9 focused on the pathophysiology of pain. Fourteen articles discuss other subjects such as the relation between pain and depression, repercussion on quality of life, or commentaries on previous studies. The remaining 14 articles[6,7,12–23] are included and from their reference listings we included 4 more articles.[24–27] After reviewing all 18 articles we decided to exclude the articles by Koller[24] and Brefel-Courbon et al.[13] Koller[24] did not specifically focus on pain, but on overall sensory symptoms in PD. The study by Brefel-Courbon et al.[13] compares pain prevalence using analgesic prescription in PD patients, in the general population, and in 2 samples of pain-suffering patients. However, it is unclear if all patients had PD or used analgesics for only pain, and if drug prescriptions correlated with drug consumption and pain. Consequently, 16 articles were evaluated with the modified QUADAS tool. The study quality of all 16 articles are listed in Table 2, 8 articles scored more than 14 points (37%).[7,12,14,15,19,21–23] A combination of shortcomings in representativeness, data collection, and response rate of <70% was the main reason for not reaching the required score of >14 points. General characteristics of the 8 studies are listed in Table 3. All studies were retrospective and all but 1 (Tinazzi et al.[23]) used validated questionnaires. Four studies compared PD patients with a control group.[14,15,19,21]

Pain Prevalence and Distribution of Pain

The pain prevalence reported in the 8 studies[7,12,14,15,19,21–23] varies between 40% and 85% with a weighted average prevalence of 67.6% (SD = 11.5). Three studies[7,12,19] asked patients whether they thought the pain was related to PD, which resulted in a PD-related pain prevalence of 57.6% (SD = 6.2). Four articles[7,15,19,23] report different locations of pain, and we classified them into neck/shoulder-region, upper limbs, lower limbs, and back pain. Pain in the lower limbs is reported most frequently in 47.2% (SD = 21.5). Back pain was reported by 14.3% (SD = 2.0) of the PD population, whereas pain in the upper limbs and neck/shoulder region is reported in 13.8% (SD = 7.4) and 12.4% (SD = 3.9) of PD patients, respectively.

Type of Pain

Articles were then reviewed on the 5 different types of pain previously described by Ford[28,29]; musculoskeletal, radicular-neuropathic, dystonic, central neuropathic pain, or akathisia. In one-half of the

TABLE 2. Study quality according to the modified QUADAS tool

Article/score[a]	A-1	A-2	A-3	B-4	B-5	B-6	C-7	C-8	C-9	D-10	Total
2009 Beiske et al.[12]	2	2	1	2	2	3	2	2	1	1	18
2008 Defazio et al.[15]	2	0	2	2	2	3	2	2	1	0	17
2008 Negre-Pages et al.[19]	2	2	0	2	2	3	2	2	1	1	17
2008 O'sullivan et al.[20]	2	0	0	2	2	1	2	1	1	0	11
2008 Silva et al.[22]	2	0	0	2	2	3	2	2	1	1	15
2008 Stamey et al.[6]	0	0	0	1	2	1	2	2	1	0	9
2007 Broetz et al.[14]	2	2	0	2	2	3	2	2	1	1	17
2006 Lee et al.[7]	2	2	1	2	2	3	2	2	1	1	18
2006 Tinazzi et al.[23]	2	2	2	1	2	2	2	2	1	1	17
2005 Giuffrida et al.[16]	2	0	1	2	2	2	2	2	1	0	14
2004 Mott et al.[18]	2	0	0	2	2	2	2	1	1	0	12
2004 Quittenbaum et al.[21]	2	2	1	2	2	3	2	2	1	1	18
1986 Goetz et al.[17]	1	0	0	2	2	2	1	2	1	0	11
1976 Snider et al.[26]	0	2	2	1	2	2	2	2	1	0	14
1970 Zsiboy-Gisinger et al.[27]	0	0	0	1	2	0	0	0	0	0	3
1960 Sigwald et al.[25]	2	0	2	1	1	0	0	0	1	0	7

[a]Studies in bold meet quality criteria.

studies[12,15,22,23] pain is classified accordingly; in the remaining 4 articles pain is classified otherwise, most of them providing only a subdivision in dystonic or musculoskeletal pain. Additionally, 3 articles[7,12,19] investigated different pain types in pain thought to be PD-related. Musculoskeletal pain is recalled most frequently in 46.4% (SD = 18,0) of PD patients[12,15,21–23] and in up to 55.6% (SD = 12.2) of patients reporting PD-related pain.[7,12,19] Second most frequent is dystonic pain in 19.6% (SD = 9.2) of both patients with pain and PD-related pain, followed by radicular[12,15,22,23] and central neuropathic pain[12,15,23] in 9.1% (SD = 6.3) and 5.6% (SD = 2.6) of PD patients, respectively. Inconsistent reports on akathisia make it difficult to compare results thoroughly, but it seems that akathitic discomfort is apparent in only a small number of PD patients.

On-Off Fluctuations

Six out of 8 articles[12,14,15,19,22,23] mention on-off fluctuations, but only 2 report quantitative results.[19,22] Silva et al.[22] describes a significant improvement during antiparkinsonian medication in 28.6%, with pain increasing during off periods. In addition, Negres-Pages et al.[19] notes aggravation of pain during *off* periods with improvement on antiparkinsonian drugs, especially in PD-related pain. On the contrary, Broetz et al.[14] did not find a relationship between pain and the number of hours per day in *off* phase but did not provide quantitative data. Defazio et al.[15] and Tinazzi et al.[23] hypothesized that other mechanisms than dopaminergic deprivation might contribute to pain experience, suggested by the apparently poor response of nondystonic pain to levodopa and the lack of association between pain and motor complications.

Medication

Five articles mention analgesic use.[7,12,14,19,22] Of the PD patients with pain, 52.4% (SD = 14) used some kind of analgesic medication. Only 3 studies[7,12,19] provided sufficient data to classify medication according to the World Health Organization (WHO).[30] Doing so, 37.6% (SD = 15.4) use nonopioid analgesics, 13.5% (SD = 6.2) either weak or strong opioids,

TABLE 3. Study characteristics

	Number of PD patients	Population	Pain prevalence (%)	Quality score	Distribution of pain	Pain dimension	Pain medication	On/off fluctuations
2009 Beiske et al.[12]	176	Outpatient	83	18	NR	R	R	NR
2008 Defazio et al.[15]	402	Outpatient	69.9	17	R	R	NR	NR
2008 Negre-Pages et al.[19]	450	Outpatient	61.8	17	R	R	R	R
2008 Silva et al.[22]	50	Outpatient	56	15	NR	R	R	R
2007 Broetz et al.[14]	101	Inpatient and outpatient	74	17	NR	R	R	NR
2006 Lee et al.[7]	123	Outpatient	85	18	R	R	NR	NR
2006 Tinazzi et al.[23]	117	Oupatient	40	17	R	R	NR	NR
2004 Quittenbaum et al.[21]	57	Outpatient	68.4	18	NR	R	NR	NR

[a]In percentages.
NR, no quantitative data; R, quantitative data reported in article.

and 11.8% (SD = 1.3) of patients used coanalgesics, mainly antidepressant or anticonvulsive drugs.

Discussion

Prevalence

There is a wide variability in prevalence of pain in PD, ranging from 40% to 85%.[7,23] Possible explanations are methodological disparities, differences in the definition of (chronic) pain, a lack of distinction between pain-related and unrelated pain to PD, and recruitment bias in specialized tertiary centers. Thereby, pain is also a prevalent symptom in the general population and increases with age.[31] Community-based studies suggest that the prevalence of pain in elderly is around 70%,[32–34] with back and lower limbs as the most common sites of mostly arthritic pain.[35,36] Only a few studies[12,14,19,21] compared PD patients with an elderly population with or without chronic disorders. Most of them found a significantly higher intensity and prevalence of pain in the PD population.[12,14,19] This, in combination with the fact that 57.6% of PD patients with pain think their pain is PD-related, supports the hypothesis of different pain origin in PD compared to elderly persons with or without non-PD disorders. In addition, Djaldetti et al.[37] and Tinazzi et al.[38] found that PD patients both with and without pain may have a low heat pain threshold and abnormal pain-evoked responses, which suggests that PD patients may be predisposed to developing pain.

Distribution and Type of Pain

The observation that most pain is located in the lower limbs is in line with Boushassira et al.[39] who found that chronic pain with neuropathic characteristics was mainly located in the lower limbs. However, it is difficult to compare our data with studies in non-parkinsonian patients due to their heterogeneity. In the general population, back pain is reported as the most frequent pain location,[40,41] so possibly there is a tendency for PD patients to report more pain in the lower limbs compared to non-parkinsonian patients. This could also give insight into the difference in pain origin in PD patients and non PD-patients.

To assess pain type and segregate PD related from non-PD related pain, a good classification system is warranted. Quinn et al.[42] believed pain was caused by motor fluctuations or dopaminergic treatment and made a system according to that hypothesis. Several years later, Ford[28,29] designed a classification not based on disease influences but instead used patients' descriptions to categorize pain into 5 groups (musculoskeletal, radicular-neuropathic, dystonic, central neuropathic, or akathisia). Recently, Chaudhuri and Schapira[43] nicely combined features of both classifications, categorizing pain types into PD-related pain (motor fluctuation, dyskinesia-related pain, and central pain) and secondary forms of pain not directly related to PD (eg, musculoskeletal pain or limb pain). However, the possible overlap in both categories illustrates the difficulty in designing a good classification system, but evaluating different pain types may help to segregate influences of PD from other factors; eg, the contribution of age.

Medication

Only one-half of PD patients with pain use some kind of analgesic, while PD patients seem to benefit from analgesic treatment.[13,14,22] One possible explanation for low analgesic use is the lack of distinction between intermittent and chronic pain in most studies, but even in chronic pain many patients used no analgesics.[7] A large study by Brefel-Courbon et al.[13] studied intermittent and chronic drug prescriptions in PD patients and found analgesic prescriptions in 82% of PD patients, including chronic analgesic use in 33%. However, drug prescriptions do not always mean that patients take the medication, and they included analgesics that may be used for other indications than pain. Another explanation for low analgesic use might be found in the suggested different origin of pain in PD compared to other disorders.[37,38] Patients could have tried pain treatment, but discontinued it due to its ineffectiveness. This is in line with the finding of Negres-Pages et al.,[19] in which patients with PD-related pain reported fewer analgesic consumption compared to non-PD pain and other disorders than PD exhibiting chronic pain, despite greater indices of pain intensity in PD-related pain. Due to the poor understanding of pain origin in PD, other types of pain management such as dopaminergic drug adjustment or physiotherapy could have been the preferred choice before embarking on regular conventional analgesics. Further investigation and assessment of the effect of analgesic drugs in PD and its consequences, eg, on quality of life, are required.

Conclusions and Future Directions

This is the first systematic review on the prevalence of pain in PD, by using the modified QUADAS tool. Pain is present in 67.6% of PD patients, most frequently located in the lower limbs, and musculoskeletal origin in almost one-half of patients. Of the PD patients reporting pain, only one-half of them used some kind of analgesic medication. PD patients seem to be predisposed to developing pain, and physicians should be aware of pain as a common feature of PD. Clarifying the origin of PD pain in combination with establishment of the beneficial effects of analgesic use should be future research goals. Prospective studies with usage of clear pain classifications distinguishing chronic from intermittent pain and PD-related from

PD-unrelated pain will help to develop better treatment strategies. Currently, as many as one-half of PD patients with pain may be missing out on a potentially useful treatment, and proper treatment could result in an increase in quality of life in PD patients.

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