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PAIN IN PARKINSON´S DISEASE: MECHANISTIC SUBSTRATES, MAIN CLASSIFICATION SYSTEMS, AND HOW TO MAKE SENSE OUT OF THEM.

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Abstract

Parkinson´s disease (PD) affects up to 2% of the general population older than 65 years and is a major cause of functional loss. Chronic pain is a common non-motor symptom that affects up to 80% of patients with (Pw) PD both in prodromal phases and during the subsequent stages of the disease, negatively impacting patient's quality of life and function. Pain in PwPD is rather heterogeneous and may occur due to different mechanisms. Targeting motor symptoms by dopamine replacement or with neuromodulatory approaches may only partially control PD-related pain. Pain in general has been classified in PwPD according to the motor signs, to pain dimensions or to pain subtypes. Recently, a new classification framework focusing on chronic pain was introduced to group different types of PD-pains according to mechanistic descriptors: nociceptive, neuropathic, or neither nociceptive nor neuropathic. This is also in line with the International Classification of Disease-11, which acknowledges the possibility of chronic secondary musculoskeletal/nociceptive pain due to disease of the CNS. In this narrative review and opinion article, a group of basic and clinical scientists revise the mechanism of pain in PD and the challenges faced when classifying it as a steppingstone to discuss an integrative view of the current classification approaches and how clinical practice can be influenced by them. Knowledge gaps to be tackled by coming classification and therapeutic efforts are presented, as well as a potential framework to address them in a patient-oriented manner.

Keywords: Parkinson disease, rigidity, chronic pain, neuropathic pain, musculoskeletal pain, secondary pain, dopamine, deep brain stimulation.

INTRODUCTION

Recent advances in the classification of pain disorders

From a medical and pragmatic perspective, classification of mechanisms, syndromes, phenotypes, or diseases serves to group individuals in terms of similar prognostic or treatment response profiles. By doing so, the expected natural history and progression of a person's medical condition may be delineated, enabling more assertive and direct management. In the last years several new important steps have been made to improve the classification of chronic pain disorders (i.e., pain present for most days for more than 3 months) [111,137]. On one hand, an enormous taxonomy effort was undertaken by the International Association for the Study of Pain (IASP) and the International Classification of Diseases-11 (ICD-11) working groups to provide a framework to classify pain disorders into primary and secondary categories, with subsequent subclassifications introducing the concept of primary pain syndromes [76,100,105,128]. It also acknowledged the possibility of non-neuropathic pains caused by neurological diseases (e.g., chronic secondary musculoskeletal pain due to disease of the CNS – MG30.32). Additionally, the ICD-11 introduced the option to individualize pain assessment based on the use of extension codes covering pain intensity, pain-related distress, interference, and presence of different psychosocial factors such as catastrophizing, fear, anger, avoidance, and negative interferences of pain on work and interpersonal relationships.

On the other hand, the classification of pain into mechanistic descriptors was updated, by adding a third mechanistic descriptor to the traditional nociceptive and neuropathic pain subtypes [42,65]: the term nociplastic pain was suggested to replace “idiopathic pain” for instances where pain was neither nociceptive nor neuropathic, and a grading system for nociplastic pain has also been proposed [63]. It is therefore currently possible to categorize a patient’s pain according to the ICD-11 framework for classification purposes, while also acknowledging its putative mechanisms. However, the improvement in classification and communication of pain disorders brought about by the new taxonomy frameworks remains challenging. This is especially true in instances where pain and sensory symptoms can worsen over time due to neurodegeneration, or be markedly influenced by treatment, such as in the case of Parkinson´s disease (PD) [92]. As also seen in dystonia, and lateral amyotrophic sclerosis, for example, a disease of the motor system can cause pains that are not simply of musculoskeletal mechanisms, because diseases process leading to motor impairment may also affect pain integration or pain modulatory networks.[73,78] This is also valid for systemic disease, which may affect motor and somatosensory systems in different proportions leading to different types of pain syndromes[5,67,87,89,112,130] .

Pain as a non-motor symptom of Parkinson´s disease

Motor parkinsonism (also known as akinetic-rigid syndrome) is defined by the presence of bradykinesia (i.e., the slowness and decrement in amplitude or speed of movement) in combination with rigidity (i.e., the increased muscle tonus upon slow passive movement of major joints), rest tremor (i.e., 4 to 6 Hz tremor in the fully resting limb, which is frequently suppressed during movement initiation), or both. There are several causes of parkinsonism, such as drug-related, traumatic brain injury, neuro-infection, and neurodegeneration, among others. The most prevalent cause of parkinsonism is neurodegeneration, headed by Parkinson´s disease (PD) among its several aetiologies. Motor symptoms in PD are asymmetric and usually very responsive to dopamine replacement therapy, at least initially.

Despite being recognised by James Parkinson and others [49,51,70,107,119,138], non-motor symptoms (NMS) in PD received less attention than motor ones for many decades. Initially thought to be synonymous with non-dopaminergic symptoms and considered to be present only in initial phases of the disease, it soon became clear that non motor symptoms were prevalent during all stages of PD and may have dopaminergic or non-dopaminergic mechanisms. NMSs are acknowledged to pose a heavy burden on patient's quality of life and include chronic pain, sleep and impulse control disorders, mood symptoms, cognitive dysexecutive complaints, olfactory loss, constipation, and urinary urge-incontinence, among others. Importantly, non-motor symptoms occur due to disease affecting multiple organs and systems and are not all dependent on dopaminergic modulation [15,29,30,34,86,120,142,144,145].

The general premise is that a single disease (PD) may cause different types of symptoms because it may disrupt different types of physiological functions or networks in different patients, according to individual susceptibility profiles [9,33,55,88]. For instance, some PD patients may present with tremor-predominant disease, while about one third will not present with incapacitating rest tremor [2,88,108] during disease evolution. The “disease” is the same in both instances, but its interaction with the individual leads to different neuronal networks or functions to be affected in a unique manner, with different mechanistic abnormalities giving rise to diverse clinical manifestations. The same occurs with NMS such as pain [114]. PD may cause pain via different mechanisms in different patients, and these mechanisms may or may not be related to a) altered motor control (e.g., rigidity) and b) altered dopaminergic signalling. Proper diagnostic classification of these multiple different types of pain in PD may seem like an academic exercise, but it will become highly relevant when clinical assessment and auxiliary exams can identify the pain type such that specific management may proceed.

It has been shown that pain in PD may on one hand be musculoskeletal (i.e., nociceptive), on the other hand may have characteristics of central neuropathic pain or may have to be labelled “other chronic pain” (“unspecified in ICD-11, “nociplastic” characteristics according to the IASP’s mechanistic descriptors). Such differentiations may be strategic in determining prognosis and treatment options [42,43,57,97,110]. In parallel to all these possibilities, pain can also be classified according to the motor state of patients and the effect of dopamine-replacement therapy at the moment pain is assessed [110]or according to “PD-pain domains” [16]. All the above possibilities and different combinations of pain occurrence and mechanistic backgrounds may combine to give rise to several varieties of motor and pain presentations seen in clinical practice [4,24,80,81]. Currently, different questionnaires, scales, classification frameworks and systems have been proposed to cover each of these different approaches. The present text aims to critically review and to propose an integrative approach of the current classification schemes for pain in patients with Parkinson´s disease (PwPD). This consolidative view may help basic scientist and clinicians to make the best out of the current evidence and improve research design and patient care.

METHODS

The search strategy included the databases MEDLINE (through PubMed), Web of Science, and EMBASE, which were screened since inception until March 2023. Conference proceedings were not included. Historically relevant books and reports were included and reference list from major research papers and reviews were screened and used when necessary. The International Classification of Diseases (ICD) -11 website and the International Association for the Study of Pain (IASP) definitions list and classification frameworks were also consulted and searched for. Search strings blended Parkinson (´s) disease and pain, and related terms such as parkinsonism, nociception, treatment, analgesia, chronic pain, questionnaire, and scale. Original studies, reviews and white papers were included if they provided relevant information related to chronic pain definition, mechanisms of specific chronic pain etiologies such as musculoskeletal pain, mechanistic information about chronic pain mechanistic descriptors. Studies reporting somatosensory, intraepidermal nerve fiber density counting, or pain thresholds in chronic pain in patients with Parkinson´s disease were included. Studies assessing the effects of motor treatment based on dopamine replacement (e.g., levodopa, apomorphine) and deep brain stimulation in

pain and sensory thresholds in patients with Parkinson´s disease (PwPD) were included, along with efforts to assess and validate general pain assessment tools in PwPD, and effort to create new pain classification, scales and questionnaires in PD. Relevant information related to the interplay of the somatosensory system and the basal ganglia, as well as the relationship between the basal ganglia and nociception and pain processing were included when relevant. When available, official sources of data and definitions such as the IASP, the Movement Disorders Society and the ICD-related publications were privileged. Literature review was initially conducted by DCA and VM, and all co-authors contributed to it with subsequent updates or additions. The manuscript has the first draft made by VM and DCA and several online and written electronic exchanges were performed with all authors for discussion and development of the final version of the manuscript.

RESULTS

Pioneering classification attempts of pain in PD

Detailed attempts have been made to classify pain in PD and provided an invaluable framework and important insights into PD physiology. Quinn et al. [110], were among the first to provide a comprehensive classification scheme of pains in PD according to the motor status of patients. They described four scenarios in a clinical case-based format and were among the first to acknowledge a very important aspect of pain in PD: levodopa intake would at least partially improve pain associated with non-motor off symptoms such as anxiety or depressive spells, irrespective of the motor state patients were in. This supported the currently evolving concept that motor and the different dopamine-responsive non-motor symptoms may present different levodopa levels thresholds for their control. Therefore, patients with pain fluctuations may benefit from levodopa adjustments even when control of motor symptoms is already optimised [58,120,139–141]. Several arguments support that dopamine replacement therapy adjustments should be the first attempt when caring for PD patients with non-motor symptoms. While this strategy is not backed up by strong clinical evidence, it is supported by long-term clinical experience and experimental data [6,7,12,15,21,28,47,136].

Later, Ford [44,45] proposed a classification of pain in PwPD into five categories: i. musculoskeletal pain, ii. radicular/neuropathic pain, iii., dystonia, iv., central or primary pain, v. akathisia pain. This approach can be challenging for non-specialists in pain and movement disorders because it includes pains classified according to diseases/aetiologies (primary pain, MSK pain, radiculopathy), with pains

based on syndromes (neuropathic pain), and also pains based on motor findings (dystonia, akathisia). Moreover, the use of “central” as a synonym for “primary” is misleading: central should refer to CNS diseases, while in primary pain there is no underlying disease and chronic pain itself is the disease[101]. It is known today that these instances of pain are not mutually exclusive and that different aetiologies of pain may share the same mechanistic background. Furthermore, this framework concerns present pain, and no information is provided about pain recurrence or chronicity. However, Ford clearly acknowledged that if musculoskeletal (MSK) pain has no apparent cause, PD dopamine-based treatment adjustments should be tried, in line with views that pain is a non-motor symptom that may fluctuate independently of motor ones, and that dopamine acts as a potential modulator of nociceptive processing in PD patients. He also proposed that PD patients may have neuropathic pain, which he called “radicular and neuritic” pains. While not all radiculopathies are associated with pain, and while other aetiologies of neuropathic pain may exist in PD apart from nerve root abnormalities, detecting neuropathic pain in PD has therapeutic implications.

Following Souques, who described instances of diffuse, unexplained migrating pain in PD patients as affecting areas not commonly affected by MSK or dystonic pain such as the abdomen or genitalia [119], Ford proposed that PD patients could have “central or primary pains”. He acknowledged that these patients would often experience pains in episodes of restlessness, obsessional, and distressing spells, associated with autonomic changes and visceral sensations, that would commonly overshadow their classic motor complaints. He reported that these pains may not respond to levodopa increases, and that their therapeutic control was challenging. Whether this pain should be called “primary” is questionable, since they are associated to PD. It is acknowledged that the majority of PwPD have musculoskeletal pain, but there are also non-musculoskeletal pains possibly associated with dopamine dysregulation syndrome. These have received different labels, often alluding to some “central” mechanisms[25].

Not all pains due to central diseases are central neuropathic pain.

There is little doubt that “central” alterations in nociceptive processing tend to occur to some extent in all people with acute or chronic pain[123,124]. Thus “central” plastic changes do not discriminate between different types of pain [24,27]. However, there is a clear definition of what constitutes central neuropathic pain. IASP and WHO have defined neuropathic pain as pain due to lesion or disease of the somatosensory nervous system, and for central neuropathic pain such lesions or diseases affect the somatosensory system components in spinal cord, brainstem, thalamus, or cortex. Although the striatum and *globus pallidus* are part of the extrapyramidal motor system, there is evidence that some of their functional loops subserve non-motor functions, including nociceptive signal processing in the putamen

in experimental animal and human studies [10,17–19,59,74,134].Thus, PwPD may be considered to suffer from central neuropathic pain. According to the grading system [40,77,126], the next question is if pain distribution is consistent with the receptive fields of the somatosensory system structure. Like for cortical stroke, this question is difficult to answer for basal ganglia; in principle, hemibody or quadrant pain would be consistent with “possible neuropathic pain”. To reach the level “probable neuropathic pain, some sensory signs must be present in the painful region. Lesions to the basal ganglia do not easily correlate with abnormalities in the sensory clinical exam, as they do not clearly lead to sensory deficits. Also, data from dystonic patients show that deep brain stimulation to these structures do not influence sensory thresholds [74,75]. This means that the clinical picture of lesions or disease to these structures may not lead to a pain type that clinically has sensory findings like other neuropathic pain. Thus, whether “central” in Ford’s classification may imply “central neuropathic pain” is still questionable and challenged. One would probably need to (re)define what constitutes a sensory sign in PD; possibly analogous to the redefinition of triggered attacks as sensory signs of trigeminal neuralgia that has traditionally been thought to be neuropathic although most patients have neither sensory deficits nor gains [5,27]. In “central PD pain”, while pain may have descriptors such as tingling or burning character [39,41,61], the sensory examination does not provide signs that would confirm the location of the lesion to the somatosensory system (i.e., basal ganglia). In fact, pain in PD was reported to occur more commonly axially, in the lower back, shoulders and neck, and its relief not to correlate with motor or somatosensory changes after treatment [20,24].

In Ford´s classification, central pain patients had complex neuropsychiatric manifestations, and frequently complained of pain in a context of what would be classified today as either dopamine dysregulation syndrome, dopamine agonist withdrawal syndrome or non-motor offs, so that pain in this situation is just one of the several symptoms dominating the clinical picture. Thus, the term “central” in Ford’s classification may be interpreted to refer to the concepts of “central sensitization like pain” [102]or “nociplastic pain” [66]. Although central sensitization is usually referred to spinal signal processing, sensitization at cortical levels would explain the comorbidity of chronic pain with anxiety and depression [124]. Further supporting the idea that Ford´s “central pain is not central neuropathic pain”, Marques et al. [80,82] suggested these pains would fulfil the definition of “nociplastic” pain in the sense of being non-nociceptive and non-neuropathic.

Validated assessment tools for pain in PwPD.

In the first systematic review evaluating the use of general pain scales and questionnaires in PD patients, Perez-Lloret et al., 2016 [109] found several studies reporting on the use of classic pain

questionnaires such as the douleur neuropathique-4, the brief pain inventory, and McGill pain questionnaire (short-form) [37] to characterise pain in PwPD. At that point, these tools had not yet been fully validated for use in PD, thus leading to the Movement Disorders Society Committee on Rating Scales to recommend for their use with caution. In the following years, most of these tools were eventually specifically tested in PD patients and their clinometric properties were granted for these patients. Lately, a specific pain assessment tool was developed to characterise pain occurring within the previous month without any clear cause and judged to be caused by PD by the clinician. The Kings Parkinson's disease Pain Scale [16] (KPPS) proposed the subdivision of PD-related pains into 7 “domains”. These 7 pain domains consist of musculoskeletal, central, fluctuation-related, nocturnal, orofacial, burning pain in the limbs with oedema and swelling and radicular pain. It remains to be determined whether the KPPS seven domains represent specific clinical entities or markers of specific pain mechanisms. Active research is being performed to create treatment strategies specifically designed to these domains which would provide new personalized strategies to treat specific subdomains of pain in PD [68]. Quinn´s, and Ford´s classifications concerned any pain event in PwPD, not necessarily chronic pain, while the King´s scale concerns pain directly related to PD (no explainable cause other than PD) lasting for more than 1 month. Up to 60% of PwPD will present pain most of the days and lasting for more than 3 months (ie, chronic pain), which may impact quality of life as much as motor symptoms and is a major unmet need in the management PwPD.

To fill in this gap, several groups have proposed to classify chronic pain directly related to PD according to the IASP mechanistic descriptors of pain. It was argued that such classification system could be used along with other motor status or domain-based classifications systems, and also to disease-oriented classification systems such as the ICD-11. PwPD presenting with chronic pain had their pains classified as nociceptive, neuropathic or nociplastic. In nociceptive pain, nociceptors are activated by mechanical, thermal, or inflammatory stimuli related to actual or potential lesions of non-neural tissue. This pain type includes the musculoskeletal (MSK) pain syndromes, such as osteoarthritis, and other chronic conditions where tissue lesions and/or inflammation predominates. Neuropathic pain is defined as being directly due to a lesion or disease of the peripheral or central somatosensory system [127]. In the neuropathic pain grading system, history and physical examination allow for the diagnosis of “possible neuropathic pain”, while “probable” and “definite” neuropathic pain require evidence for location (neurologically plausible sensory signs) and nature of the lesion [41]. “Nociplastic” pain mechanistic descriptor comprise instances where the nociceptive system is overactive without any evidence of somatosensory system lesion or peripheral activation of nociceptors [65]. Although not yet applied to

PD, a recent grading system proposed an algorithm to propose positive evidence for an overactive nociceptive system in potentially nociplastic pains [63].

The IASP mechanistic classification system was tested in PwPD recently [97]. PD-related pain was proposed as present if: i. pain started or became more severe after the initiation of motor symptoms of PD, ii., pain was aggravated by motor slowness or rigidity, iii., pain was associated with excessive involuntary movements; iv., pain was improved by dopaminergic drugs [93,135]. Seventy-seven percent of patients with PD and chronic pain had PD-related pain (either aggravated by PD or directly associated with PD) [93,135]. Once PD related pain was determined, patients filled in the Douleur Neuropathique-4 (DN-4) questionnaire [92], including items on patient examination. Patients with a positive DN4 were considered as being positively screened for neuropathic pain, which was present in 16% of PD pain patients. If it was negative, signs of off-period pain, dystonia pain, or peak-of-dose pains, with muscle soreness and regional or localised pain upon palpation of tendons or fascia, could be classified as nociceptive pain. This was the most common pain mechanism affecting 55% of the sample. Those not fulfilling DN-4 positivity or nociceptive criteria were considered as having “nociplastic” pain (in the sense of being non-nociceptive and non-neuropathic) and in these cases dysautonomia features, anxiety and dysphoria, non-motor off fluctuations and behavioural mood oscillation predominated. Such “nociplastic” pain occurred in 22% of the sample. After this publication, an effort to provide a grading system for nociplastic MSK pain was proposed and awaits validation[64]. Using this system most patients would not reach the level “possible nociplastic pain” because this requires the presence of documented positive sensory signs.

Pain phenotypes in Parkinson´s disease

Although not based on the grading system for neuropathic or nociplastic pains a simple mechanistic classification using previously proposed definitions was able to segregate patients with different clinical profiles. For example, “nociplastic” pain was associated with widespread pain, affecting on average 10 body locations (which is actually a criterion from the grading system for nociplastic pain), in contrast with nociceptive pain, which was more localised, more fluently affecting the trunk[71], and being present in average on 4.8 body locations [97]. Pains with possible neuropathic pain according to screening had more intense pain compared to the other two mechanisms, while “nociplastic” pain was associated with more sensory and affective descriptors of pain and had less levodopa-induced dyskinesia. Additionally, a principal component analysis confirmed that the three different pain mechanisms had a distinct distribution within the factors.

In these classification systems an operational definition of pain with neuropathic pain descriptors was based on the positivity of a screening questionnaire, which only allow for the diagnosis of “possible” neuropathic pain in PD. One of the few studies using in-person validated criteria for neuropathic pain found that 6.9% of PD patients had definite neuropathic pain [24,41], which is close to the prevalence in the general population. Moreover, neuropathic pain was markedly unresponsive to deep brain stimulation, and all patients with neuropathic pain had a disease to the somatosensory system other than PD [24,41].

Like the IASP/ICD-11 pain classification, the mechanistic classification of pain in PD can be performed in parallel to other aetiology, situational, or domain-based classifications, such as those reported by the King's Parkinson’s disease pain questionnaire [16], Ford's [44] or Quinn's [110] pain classification systems (Figure 1).

One developing perspective to non-motor symptom classification in PD is endophenotyping. While motor subtype classification of PD has been shown to be unstable over time, recent work focussing on non-motor endophenotyping seem promising. Initial descriptions included PD pain as a specific subtype which included unexplained lower limb pain syndromes commonly seen in moderately advanced PD [48,83,113,133]. Further work suggests that PD pain segregates into a noradrenergic subtype of PD which could also carry implications on personalised medicine and subtype specific treatment strategies for pain in PD [84].

DISCUSSION

PD somatosensory “gain” and its impact in pain classification

Experimental studies have demonstrated that dopamine D_2 receptors participate in the modulation of nociceptive signals centrally both at the striatum, and at the spinal cord via hypothalamic A11 descending projections to the spinal cord. It has also been shown that motor neuromodulatory interventions depend on these receptors to provide pain relief in models of neuropathic pain [1,56,132]. In healthy humans, low density of D2 receptors is associated with cold pain thresholds increase and defective descending pain modulatory activity [85,122]. Initial reports using quantitative sensory testing have suggested that PwPD had lower [99,104] and higher [20,104] pain thresholds compared to age-matched healthy individuals. These contradictory results could be due to the fact that using reaction time-based approaches to determine thresholds in a disease with asymmetric motor signs could be a source of bias. Additionally, one marked peculiarity of PD is that several somatosensory channels are

influenced by the treatment status on the time of data collection, be it pharmacological (levodopa, dopamine agonists) or neuromodulatory (DBS), which requires standardization and report on whether patients were in the On or Off treatment condition when assessments were made. Later studies with larger sample sizes, in which medication intake was controlled for, and using reaction time-independent quantitative sensory testing methodologies have suggested that mechanical, cold and heat pain are in fact lower than the expected for age [12,20,26,53,54,72,117,131] in PwPD. So, it is believed that irrespective of the presence of chronic pain, PwPD have lower pain thresholds both during the Off and On medication states (i.e., when the effect of dopamine replacement therapy medication wears off, or when it is adequate, respectively) when compared to healthy age- and sex-matched controls [11,20,26,27,92,94]. It has also been shown that sensory detection abnormalities may exist in patients with idiopathic rapid eye movement sleep disorder, considered to be potentially prodromal of PD [62,121] in a significant proportion of cases, as well as in patients in early stages of PD, before levodopa was started and additionally suggested to progress as disease advances [60,92]. *De novo* pain in PD has been reported as being partially influenced by levodopa administration, which generally does not affect pains unrelated to PD [28,110]. Additionally, PD-related pains are more common during off episodes (i.e., when patients stop medication or neuromodulatory treatment). Like other non-motor symptoms, PD-related pain may be aggravated/appear when patients experience non-motor Offs, commonly leading to accompanying mood and behavioural abnormalities [50].

MSK pain in PwPD has historically thought to be due to muscle rigidity. Indeed, the musculogenic theory initially proposed that pain in PD was mainly due to the presence of increased motor tonus [118], which would lead to muscle contractures and pain. This theory as the sole explanation for pain in PD was challenged by the finding that chronic pain is common in early disease stages [35] when motor symptoms are still incipient, and that although pain improvement may occur after levodopa therapy or deep brain stimulation, their subsequent analgesic effects are not correlated with motor improvement [24,79]. It was also shown that even pain-free patients would present quantitative sensory test signs of “gain” in sensory processing [143]. Furthermore, pain may also occur along with excessive movements, as is the case of choreiform dyskinesias, when levodopa levels are thought to be high [23,110]. Together, these data suggest that pain in PwPD may not exclusively be due to peripheral generators of pain such as motor rigidity but would also be influenced by an intrinsic state of allodynia and hyperalgesia potentially maintained by dysfunctional somatosensory processing, possibly at the basal ganglia[14,27].

PD patients in moderate or advanced phases of the disease have marked nigrostriatal degeneration, which leads to a lower storage capacity of dopamine in axonal terminations from the substantia nigra

reaching the striatum [52]. When dopamine replacement therapy is initiated, dopamine storage fluctuates according to blood levels of medication, leading to oscillations in motor control, which can rise from a low (rigidity, slowness of movement) to an excessive dopaminergic synaptic availability (hyperkinetic choreiform dyskinetic movements) in minutes. These motor oscillations are a hallmark of moderate/advanced disease, and their treatment, when refractory, requires specific medication or neuromodulatory interventions. It was reported that non-motor symptoms that are partially dependent on dopamine such as mood and pain would also oscillate according to dopamine storage in the striatum. The subsequent non-motor On's and Off's do not necessarily correlate with motor oscillations. This means that patients on a relatively stable and controlled motor symptoms, may experience non-motor symptom oscillations due to different needs and sensitivities to dopamine level oscillations in non-motor cortico-striato-thalamo-cortical loops. Indirect evidence suggests that PD-related pain would also present oscillations due to non-motor Offs. This is supported by clinical experience and by studies showing that motor control after pharmacological or neuromodulatory treatment is dissociated from pain relief. Sensory oscillations can be captured by non-motor symptom questionnaires in clinical and research settings [15]. Reports suggest that patients with pain should request adjustments in their dopamine replacement therapy slightly above the dosage necessary to relieve motor symptoms [36,88,120,141]. This concept is further supported by the occurrence of dopamine agonist withdrawal syndrome, which refers to the emergence of fatigue, cognitive complaints, and diffuse widespread pain in patients who have good motor control, and in whom a decrease in dosage of dopamine agonists is attempted [103,110]. Patients tolerate dosage reduction from the motor perspective but cannot bear the new onset of symptoms associated with dopaminergic medication tapering.

Practical issues when assessing and managing pain in PwPD.

The examination of patients with PD and rigidity with pain frequently reveals tender joints, sensitive fascia and enthesis and muscle pain upon gentle palpation that would not otherwise hurt [24]. These points would argue that pain associated with rigidity has nociceptive characteristics and that soft tissue injuries are clearly driving pain [71,90,91,97]. It was later acknowledged that patients at an early stage of the disease would present intense pain, despite having low levels of rigidity [35]. Also, interventions known to ameliorate motor symptoms, rigidity included, may also improve pain, but in these instances pain improvement is not necessarily correlated to rigidity control [24,34,145]. It means that in instances of rigidity and pain, it is usually not possible to ascertain that pain is specifically caused by rigidity, and not by another peripheral nociceptive driving factor that is centrally augmented. So, in a pragmatic approach, the finding of rigidity and pain could classify pains as nociceptive, thus acknowledging that

MSK system is to some degree contributing to the occurrence of pain as a peripheral pain generator being centrally over-amplified [71,125].

As mentioned above, a common challenge is the determination of lesion to the somatosensory system in PD when attempting to diagnose neuropathic pain in PwPD. Studies assessing intraepidermal nerve fiber density by PGP9.5 staining showed that PD leads to major small fibre denervation [31,104]. It was additionally later described that extranigral, extra-cephalic Lewy body neuronal deposition[32,104] could also be detected in sensory afferents in the skin. However, small-fibre intra-epidermal decrease, also called small fiber pathology, is also found in a long list of other neurological diseases, and their functional meaning is debatable. To date, it has never been shown in PwPD that these changes occur on body areas where pain is present. Furthermore, sensory gain and loss of function in PD may be significantly impacted by intake of levodopa or deep brain stimulation, suggesting that changes are rather dynamic. Changes in somatosensory gain are likely to be influenced by functional oscillatory activity at a network level, rather than solely relying on hard-wired structural neurodegeneration [3,27,38,106]. This creates a situation when neuropathic pain would only be diagnosed as “definite” according to the revised grading systems if clear sensory sings could be identified and characterized, similar to triggered attacks in trigeminal neuralgia [22,129]. On the other hand, in the absence of a clear pain distribution compatible with lesion to classic somatosensory structures, a neuropathic pain directly related to PD, if it is proven to exist, could only reach the “possible” degree of diagnostic certainty. Some have chosen to use positivity of screening tools for neuropathic pain such as the Douleur Neuropathic-4 for identifying PwPD with neuropathic pain components [46]. These strategies have revealed that around 1/5 of chronic pain PwPD have positivity in screening tools. While these patients should not be called “definite” neuropathic pain patients, they do fulfil the diagnosis of possible neuropathic pain. The screening questionnaire-based classification has been shown to allow for the classification of PwPD and pain with clinically different profiles and characteristics, which are likely to be related to different mechanisms of disease and respond differently to treatment [97]. Attempts to comprehensively characterize the extent of the somatosensory system and what comprises a neuroanatomically plausible sensory sign in future may help shed light to these instances.

Implications of the current knowledge to the care of PwPD with pain

Pain in general is ominous in PwPD. It can be classified according to motor status as proposed by Quinn, according to Ford´s framework or according to pain subtypes, by using the KPPS (Figure 1). Chronic pain, in particular, is also very prevalent in PwPD and may not respond to treatments aimed at motor control. Chronic pain may be unaffected and unrelated to the disease (i.e., PD-unrelated pain) or

affected by/related to it (i.e., PD-related pain). Although the distinction between nociplastic and neuropathic pains could not made according to the grading systems, the tentative mechanistic classification allowed for the segmentation of patients with different pain characteristics and associated symptoms and were able to select responders to specific treatment approaches[69,71]. To date, solid evidence-based treatment for chronic pain in PD is lacking [95,115,116] or poor. When clinically possible and safe, there is a general agreement to try small increases in dopamine-replacement therapy as a therapeutic test in instances of pain directly related to PD, even when motor control is optimized. Recent studies are to incorporate patients' selection based on different pain types or discrete endophenotypes in clinical trials to treat chronic pain in PwPD and are promising [68]. The advances in classification presented here are likely to improve treatment towards distinct types of pain in PD in the future, but they also reveal some general classification and mechanistic gaps that need to be refined in coming translational multidisciplinary efforts.

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Figures titles and legends

Fig 1. Summary of the main current classification and scoring systems for pain in patients with Parkinson´s disease.

PD (Parkinson´s disease) related pain includes new pain and previous pain aggravated by PD. Since pain may precede motor symptoms by several years, determining if a pain is emerging *de novo* as motor symptoms appear, or if it is a previous pain that was aggravated by PD can be challenging clinically. So, a pragmatic approach is to merge these two instances under PD-related pain. Such strategy has been validated [98](Mylius 2021) and showed to provide classification of pain based on mechanistic descriptors. To be considered PD-related pain, chronic pain had to fulfil at least one of the following prerequisites: i. Pain started or became more severe after other PD symptoms started, ii. Pain is aggravated when rigidity, tremors or slowness of movements are more intense, iii. Pain is associated with excessive, abnormal movements (choreiform dyskinesia), iv. Pain is somehow improved when PD medications are taken (based on Quinn 1986 [95], Wasner & Deuschl 2012 [114], Mylius 2015 [83]

* Data refer to the prevalence of chronic pain in PD in general (up to 80%) [8,13], and to the prevalence of PD-related pain within the chronic pain sample [97].

** footnotes on subtypes: in the ICD-11 framework - 1. MG30.32 – chronic secondary musculoskeletal pain due to disease of the nervous system, or 2. MG30.50: chronic central neuropathic pain, or 3. MG30.Z “chronic pain, unspecified”. In the mechanistic descriptor framework, 1. is nociceptive, 2. is neuropathic, and 3. “other”, as it concerns those who did not fulfill nociceptive or neuropathic criteria according to (Mylius et al., 2021 [96,98]. In the original publication it was termed “nociplastic” as a synonym for non-nociceptive/non-neuropathic, as the published grading system [64] is not suitable to identify these cases.