Advances in diagnosis, classification, and management of pain in Parkinson's disease

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With over 10 million people affected worldwide, Parkinson's disease is the fastest-growing neurological disorder. More than two-thirds of people with Parkinson's disease live with chronic pain, which can manifest in various stages of the disease, substantially affecting daily activities and quality of life. The Parkinson's disease Pain Classification System overcomes the limitations of previous classification systems by distinguishing between pain related to Parkinson's disease and unrelated pain, while also incorporating clinical and pathophysiological (mechanistic) descriptors such as nociceptive, neuropathic, and nociplastic pain. This system provides a framework for accurate diagnosis and mechanism-based therapy. Alongside the appropriate classification of pain, consideration of treatment approaches that include non-invasive (pharmacological and non-pharmacological) and invasive strategies tailored to specific types of pain will refine and inform research trials and clinical practice when it comes to treating pain in Parkinson's disease.

Introduction

Parkinson's disease is the fastest-growing neurological disorder globally.[1] Now understood as a systemic neurodegenerative disease involving interconnected nervous system networks, Parkinson's disease manifests as a unique and evolving set of motor and non-motor symptoms.[2,3] Chronic pain, a non-motor symptom affecting more than two-thirds of people with Parkinson's disease, impairs activities of daily living and diminishes health-related quality of life.[4,5] Concomitant motor impairment (ie, axial postural abnormalities and gait impairment) and common non-motor symptoms (eg, anxiety, depression, and sleep disturbance) can all aggravate pain in Parkinson's disease.[6–10] Despite its prevalence and burden on activities of daily living, chronic pain in patients with Parkinson's disease is often under-reported and improperly assessed, resulting in suboptimal management.[11,12]

New insights into the multifaceted nature of Parkinson's disease-related chronic pain[4] have revealed the likely involvement of a range of pathophysiological mechanisms, from peripheral nervous system dysfunction to alterations in central dopaminergic and non-dopaminergic pain-processing neurotransmitter pathways.[13,14] The Parkinson's disease Pain Classification System (PD-PCS) was published in 2021 by a panel of pain specialists (including doctors, nurses, physiotherapists, and psychologists) and movement disorders experts, and it was validated through an international, cross-sectional multicentre study with a retest validation step.[5] The PD-PCS addresses the limitations of previous pain assessment tools by distinguishing between Parkinson's disease-related chronic pain—which is aggravated by or begins with Parkinson's disease symptoms—and unrelated chronic pain, on the basis of the association of pain with Parkinson's disease occurrence and manifestations.[5,15] This classification incorporates clinical and pathophysiological descriptors of pain (neuropathic, nociceptive, and nociplastic) in accordance with the International Association for the Study of Pain (IASP) classification, to simplify the diagnosis and management of pain in Parkinson's disease.[16]

Our Review addresses three main challenges: the under-reporting and subsequent underassessment of chronic pain resulting from a lack of standardised approaches specifically designed to classify chronic pain in Parkinson's disease; the underutilisation of positive diagnostic criteria to differentiate between chronic pain directly related to Parkinson's disease and pain arising from other conditions; and the presence of numerous non-motor symptoms, such as anxiety, depression, or sleep disturbances, in patients with Parkinson's disease, which can bidirectionally worsen the pain experience in patients with Parkinson's disease.

Clinical features of pain in Parkinson's disease

Parkinson's disease is not associated with a unique pain syndrome. The classification of pain in Parkinson's disease reflects our general knowledge of pain mechanisms underlying various types of chronic pain according to the IASP classification.[16,17] The PD-PCS first differentiates between pain related to Parkinson's disease and unrelated pain, and then distinguishes three clinical and pathophysiological (mechanistic) pain descriptors: nociceptive, neuropathic, and nociplastic (panel 1).[5] Finally, the pain intensity (from 0 to 10), frequency (1=rare, 2=intermediate, or 3=frequent) and effect on daily living (1=low, 2=moderate, or 3=severe) can be rated. A final score (from 0 to 90) can be obtained by multiplying these scores for each category of pain. Higher scores indicate a greater burden of pain. The criteria used to develop this new classification system were established by an international panel of experts in pain and movement disorders through an international, cross-sectional multicentre study with a retest validation step.[5] This rigorous methodology ensured to address the limitations of previous systems by adapting and refining them for the specific context of Parkinson's disease.[5]

Lancet Neurol 2025; 24: 331–47

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Panel 1: **Clinical and pathophysiological descriptors of chronic Parkinson's disease-related pain**

Nociceptive pain

- Pain is associated with damage or inflammation to non-neural body tissues, leading to the repetitive activation of nociceptors and the subsequent development and persistence of chronic pain.
- Nociceptors are high-threshold sensory receptors of the peripheral somatosensory nervous system capable of transducing and encoding noxious stimuli. Most instances of nociceptive pain are musculoskeletal disorders. An example would be a patient with Parkinson's disease who has shoulder pain due to concurrent tendinitis and limb rigidity.
- Classification and body locations: mainly classified as musculoskeletal pain perceived in joints, bones, muscles or tendons, occurring as regional pain or with a somatic referred distribution such as the myofascial pain syndrome. Typically localised in the lower limbs, lower back, or the shoulder and the upper limbs, the pain could be an early sign of the onset of motor symptoms in 25% of patients.

Neuropathic pain

- Pain in a body region shows signs of sensory deficit (or allodynia in some cases) due to a dysfunction or lesion in the somatosensory system.
- Most reported cases of neuropathic pain in patients with Parkinson's disease are peripheral. De novo central pain due to Parkinson's disease can be possible or probable since no discrete lesion of the somatosensory system accounting for the pain can be detected. When pain of neuropathic characteristics is clinically present but a dysfunction or lesion to the somatosensory system cannot be confirmed by paraclinical exams (eg, MRI or nerve conduction studies), the neuropathic pain is said to be probable.
- Classification and body locations: neuropathic descriptors include burning, painful cold, electric shock-like, tingling, pins and needles, numbness, and itching. Pain arises in a body region where sensory abnormalities are present, usually sensory loss and occasionally allodynia.

Nociplastic pain

- Abnormal gain in nociceptive processing is the primary driver of nociplastic pain. There are no lesions or diseases to the somatosensory system or somatic tissues that can account for the pain.
- Classification and body locations: unlike neuropathic pain (which is localised to a specific body area with a sensory deficit), and unlike musculoskeletal pain (which is often regional), nociplastic pain in Parkinson's disease is often poorly localised, periabdominal, or even diffuse, and can shift in location over time. Neuropathic pain often occurs in the context of dopamine agonist withdrawal syndrome or dopamine dysregulation syndrome, in which pain coexists with intense dysphoria, motor restlessness or choreiform dyskinesia, anxiety, and autonomic activation. Non-motor off-state and leg motor restlessness are also assocated with nociplastic pain when the neuropathic component is not predominant.
- Cases previously reported as central pain in patients with Parkinson's disease fit this mechanistic descriptor. The term central pain is often used to describe a type of pain in Parkinson's disease that is diffuse and periabdominal; it can arise without a clear structural abnormality and falls within the nociplastic pain category. Such pain often has a diffuse distribution and is accompanied by neuropsychiatric symptoms related to non-motor fluctuations and dopamine-related neurobehavioural events. The term is often confused with central neuropathic pain, which is a completely different, well defined, and validated syndrome. In our expert opinion, to avoid confusion, the term central pain should not be used in patients with Parkinson's disease, but rather these instances of pain should be classified as nociplastic pain.

Mixed pain

- Although not an officially recognised pain mechanism, mixed pain is often used in clinical practice to describe instances in which patients present with more than one pain mechanism in the same body location. The pain could be associated with a single health condition; for example, nociceptive and neuropathic pain in lower back pain associated with acute compressive radiculopathy and neuropathic pain.

Earlier classifications had substantial drawbacks related to the absence of a clinical and pathophysiological framework, the exclusion of pain unrelated to Parkinson's disease and of nociplastic pain, and finally the lack of validation in some cases. The new classification has shown its potential to guide therapeutic approaches, as evidence suggests that different types of Parkinson's disease-related pain could have different responses to treatments.[5] For example, repetitive transcranial magnetic stimulation (TMS) of the posterior–superior insula showed an analgesic effect only in patients with Parkinson's disease-related nociceptive chronic pain.[18] As a result, accurately characterising Parkinson's disease-related pain in both research trials and clinical practice could substantially enhance treatment outcomes for individuals with Parkinson's disease.

Diagnostic criteria for pain in Parkinson's disease

Chronic pain, defined as pain lasting more than 3 months and present most of the time, affects 17–20% of the general population.[19] Chronic pain in Parkinson's disease might be unrelated to (ie, present before disease onset and not affected by Parkinson's disease) or associated with (ie, aggravated by or starting with Parkinson's disease symptoms) the disease. Parkinson's

disease-related pain is a key non-motor symptom of the disease, present from premotor to advanced stages, and is prevalent in 70–83% of patients.[15] Chronic pain related to Parkinson's disease should be diagnosed when at least one of five criteria is met: pain onset coincident with Parkinson's disease onset; pain worsening with Parkinson's disease onset; presence of pain during the off-state (ie, low dopaminergic stimulation); pain responsiveness to dopaminergic treatment; and pain during states of relative dopaminergic overstimulation (choreiform dyskinesia, dystonic dyskinesia, or both; figure 1).[5] The PD-PCS questionnaire, which is based on earlier classifications, addresses these criteria in the diagnosis of Parkinson's disease-related pain.[5,20] The PD-PCS also provides a score that covers pain intensity, effect, and frequency.

The presence of Parkinson's disease-related pain for at least 1 month can also be assessed with the King's Parkinson's disease Pain Scale (KPPS), which is primarily tailored to assess pain specific to Parkinson's disease, with a focus on the frequency and intensity of pain across seven distinct domains—musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discolouration or oedema and swelling, and radicular pain.[21] However, the utility of the KPPS for assessing chronic pain is limited as it does not comprehensively address the diverse clinical and pathophysiological mechanisms that underpin chronic pain conditions in Parkinson's disease. By contrast, the PD-PCS serves as a diagnostic framework, categorising pain into six primary types on the basis of association or not with Parkinson's disease (ie, related or unrelated) and on clinical and pathophysiological pain descriptors (ie, neuropathic, nociceptive, and nociplastic). Incorporating concepts from the KPPS, the PD-PCS can help to not only obtain an intensity and frequency scoring of different types of pain in Parkinson's disease but also relate them to specific pathological (mechanistic) processes, with the potential to guide researchers and clinicians towards a better definition and treatment of the various pain syndromes in Parkinson's disease.

Classification of Parkinson's disease-related pain

The clinical and pathophysiological (mechanistic) description of pain provides a framework for a general classification of chronic pain according to the IASP, which, by extension, is also applicable to chronic pain in Parkinson's disease, irrespective of whether the pain is primary or secondary to another disease (figure 1, panel 1).[5,16] Nociceptive, neuropathic, and nociplastic pain are the three main categories of pain according to clinical and pathophysiological pain descriptors identified in Parkinson's disease-related chronic pain. Each of these categories accounts for a number of pain syndromes,

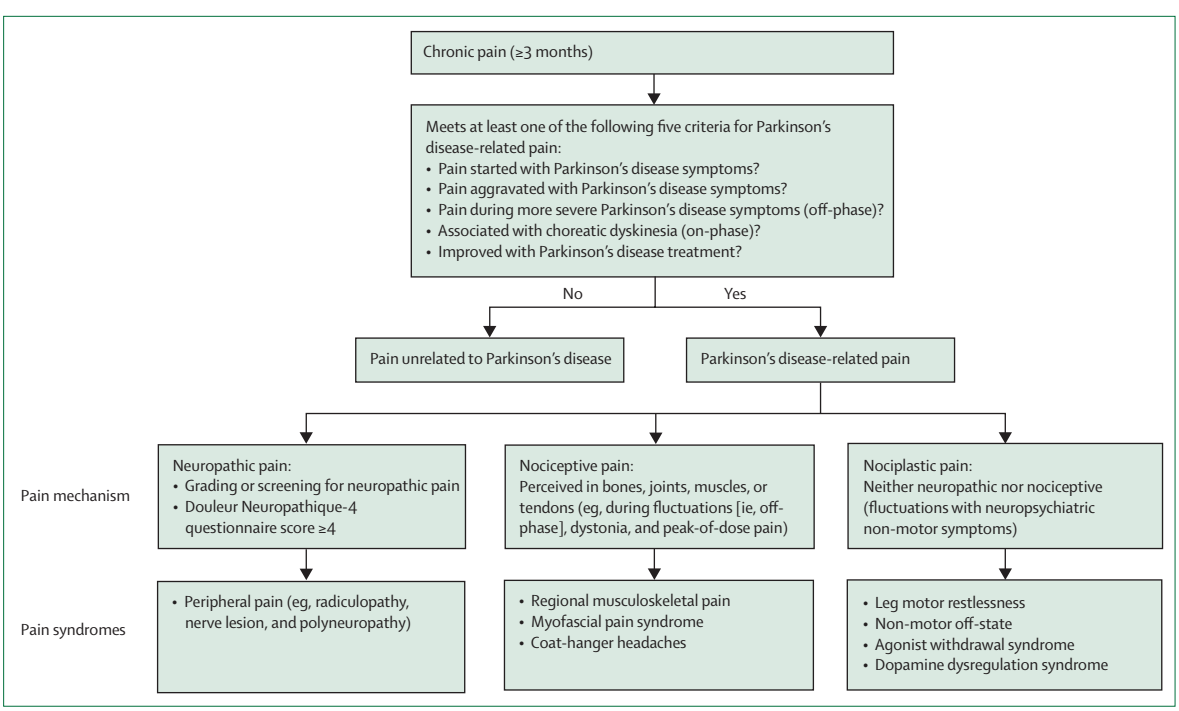

Figure 1: **Diagnostic approach according to the Parkinson's disease Pain Classification System**
This figure illustrates the classification of chronic pain (≥3 months in duration) in patients with Parkinson's disease on the basis of clinical and pathophysiological pain descriptors (mechanistic) and syndromes. Chronic pain is categorised first as either related to Parkinson's disease or unrelated, with Parkinson's disease-related pain meeting at least one of five criteria. Then, according to clinical and pathophysiological pain descriptors, Parkinson's disease-related pain is divided into three main categories (neuropathic, nociceptive, and nociplastic). Each of these categories accounts for a number of pain syndromes, defined in the figure as the diagnostic category of pain on the basis of clinical manifestations.

here defined as the diagnostic category of pain on the basis of clinical manifestations.

Nociceptive pain (present in 55% of patients with Parkinson's disease) originates in the peripheral nervous system and can be maintained by abnormal processing via plastic changes in nociceptive pathways.[5] This pain type can occur chronically during motor and non-motor off-states and tends to respond to levodopa supplementation.[22] The International Classification of Disease-11 classification of chronic secondary musculoskeletal pain now includes pain in Parkinson's disease.[23] Nociceptive pain includes syndromes such as regional musculoskeletal pain, myofascial pain syndrome with tender trigger points, and coat-hanger headaches caused by neck and shoulder muscle strain associated with orthostatic hypotension.

Neuropathic pain (present in 16% of patients with Parkinson's disease) refers to pain that occurs secondary to an identifiable dysfunction (or lesion) affecting the somatosensory system.[5,24] A grading system further classifies neuropathic pain into possible, probable, and definite.[25] Screening questionnaires, such as the Douleur Neuropathique-4 (DN4) questionnaire, help to identify pain descriptors for diagnosing cases as possible or probable.[26] Neuropathic pain includes syndromes such as radiculopathy, nerve lesions, or polyneuropathy.

Nociplastic pain (present in 22% of patients with Parkinson's disease) refers to instances in which chronic pain occurs in the absence of a clear somatic or somatosensory lesion or disease;[5,27] central maladaptive neuroplastic changes due to abnormal somatosensory processing are probably the main drivers of this pain type.[28] The majority of cases previously diagnosed before the IASP classification as central pain in patients with Parkinson's disease would currently be classified as nociplastic and not as central neuropathic pain (panel 1).[16] Nociplastic pain includes syndromes such as leg motor restlessness, non-motor off-state pain, dopamine agonist withdrawal syndrome, and dopamine dysregulation syndrome.

This clinical–pathophysiological classification might also apply to other Parkinson's disease-related pain types, such as visceral and nocturnal pain.[21,29] Visceral pain, often abdominal, is usually nociceptive but can be nociplastic when linked to non-motor fluctuations or dopamine-related symptoms. Nocturnal pain, mostly nociceptive or nociplastic, can stem from leg restlessness, akinesia, or dystonia, all worsened by reduced night-time dopaminergic supply.[29] Both types of pain require evaluation based on characteristics, timing, and comorbidities to guide treatment.

Parkinson's disease-related chronic pain syndromes (figure 1) are more frequent during motor and non-motor fluctuations, probably due to periods of low dopaminergic stimulation (ie, wearing-off, early morning-off, nocturnal-off, and limb dystonia).[5] Pain present only during periods of high dopaminergic stimulation (ie, peak-on dyskinesia) occurs rarely.[5,30]

Given the prevalence of pain in the general population, chronic pain pre-dating Parkinson's disease and not aggravated by Parkinson's disease should be considered unrelated to Parkinson's disease. Regarding the prevalence of back and shoulder pain among patients with Parkinson's disease, a reciprocal influence has been shown between musculoskeletal causes and Parkinson's disease-related pain.[31,32] In this context, osteoporosis should be considered as a potential risk factor for pain and properly treated to reduce the pain component associated with it.[33] Nociceptive pain syndromes of the lower back frequently manifest concurrently with radicular or pseudoradicular neuropathic pain, particularly in patients with Parkinson's disease who have axial postural abnormalities.[8,34,35] Polyneuropathy, which is more prevalent in Parkinson's disease due to α-synuclein peripheral pathology or cobalamin deficiency (possibly associated with high-dose levodopa treatment), might manifest with neuropathic pain.[36,37]

Factors influencing pain in Parkinson's disease

Pain in Parkinson's disease is associated with female sex, younger age, affective and autonomic symptoms, and with the severity of motor symptoms and levodopa-induced fluctuations.[38] Cardiovascular symptoms, sleep, depression, and anxiety are all associated with pain.[9,10] A noradrenergic deficiency subtype of Parkinson's disease, predominantly associated with rapid eye movement sleep behaviour disorder, pain, anxiety, and cardiovascular and urinary dysautonomia, has recently been described.[39]A retrospective study in the UK reported that White people with Parkinson's disease received significantly more pain relief, in particular for opioid analgesics, compared with Black and Asian people, despite a similar pain burden.[40] Therefore, ethnic disparities should be considered in the holistic approach to pain management in patients with Parkinson's disease.

Moreover, genetic stratification comes into play since genetics can have a role in pain processing, as shown in animal models and clinical studies.[41] The human transient receptor potential cation channel, subfamily M, member 8 (TRPM8), transmits cooling and noxious cold perception and is expressed in approximately 15% of small-diameter sensory neurons. Following a genome-wide association study of susceptibility for pain in Parkinson's disease, two single-nucleotide polymorphisms were identified at the gene encoding TRPM8.[42] A study involving 229 patients with Parkinson's disease identified specific single-nucleotide polymorphisms, including rs6746030 in the *SCN9A* gene and rs324419 and rs2295633 in the *FAAH* gene, as potential factors contributing to increased pain susceptibility in Parkinson's disease.[41] These findings underscore the need for further investigation of the pain experience among patients with different forms of monogenic Parkinson's disease.[43]

Multidisciplinary management

The management of chronic pain in Parkinson's disease is often neglected because it is not seen as a typical Parkinson's disease symptom. As with other conditions causing chronic pain, a biopsychosocial model that takes into account biological, sociocultural, and psychological factors should integrate distinctive pain mechanisms for which treatment should include self-management with pharmacological and non-pharmacological therapy.[3] The most recent advances building on recommendations for a mechanism-based treatment approach to patients with Parkinson's disease-related chronic pain are summarised in the following sections.[5,15,44,45] Pharmacological treatments are presented first, followed by non-invasive, non-pharmacological approaches (eg, brain neuromodulation and exercise), and finally, invasive neuromodulation techniques.

Pharmacological treatment of Parkinson's disease-related chronic pain

First, chronic pain must be established as related to or unrelated to Parkinson's disease before defining the main pain mechanisms (figure 1). For Parkinson's disease-related chronic pain, the initial step in pharmacological therapy is to optimise dopaminergic treatment (eg, based on a diary assessing motor fluctuations and dyskinesia), as in many pain syndromes the dopaminergic deficiency can be a key contributor to pain (figure 2). This approach can include optimising the dopaminergic schedule, managing dopaminergic fluctuations by adding catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase-B (MAOB) inhibitors, and using extended-release formulations for nocturnal or early morning off-states. Advanced approaches (eg, deep brain stimulation [DBS], levodopa–carbidopa intestinal gel or subcutaneous infusion, and continuous apomorphine infusion) might be necessary when fluctuations cannot be properly managed, and can be useful also for pain relief.[58] If this approach is unsuccessful, other causes of pain should be investigated. Although increasing levodopa is a key option for Parkinson's disease-related pain, chronic high-dose exposure requires caution due to hyperdopaminergic effects such as dyskinesia, orthostatic hypotension, and neurobehavioural symptoms, and the risk of peripheral neuropathy possibly sustained or increased by cobolamin deficiency.[37] Several large randomised clinical trials (RCTs) in Parkinson's disease have assessed pain as a primary outcome. Although evidence is still sparse, new treatment approaches have been explored in several studies.[15] Published trials are listed by pain mechanism, drug class, and quality of evidence in the table. The

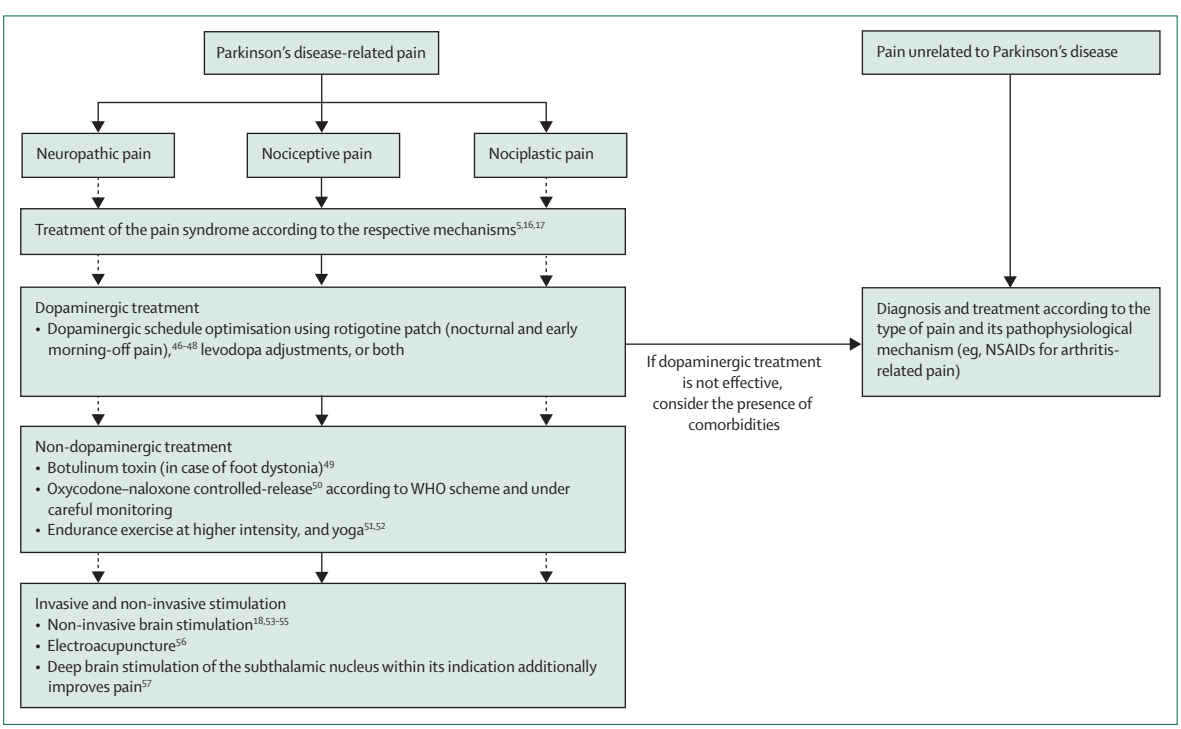

Figure 2: **Algorithm for pain therapy in Parkinson's disease**
This figure illustrates a possible algorithm for pain treatment in Parkinson's disease. The evidence base for clinically relevant treatment is focused on nociceptive pain. No studies to date have been conducted on neuropathic or nociplastic pain. For these mechanisms, the same therapeutic strategies as for nociceptive pain could be attempted despite the absence of scientific evidence, as indicated by the arrows with dotted lines. Adjustment of the dopaminergic schedule should be the first step in the treatment of Parkinson's disease-related chronic pain. If the treatment is partly or not effective, the presence of comorbidities possibly contributing to pain syndrome should be considered. In case no other comorbidities are identified to justify the pain, further therapeutic options should be attempted, including non-dopaminergic treatment and non-invasive or invasive stimulation. NSAIDs=non-steroidal anti-inflammatory drugs.

quality of studies was rated using the American Academy of Neurology Classification of Evidence criteria for interventional studies.

Nociceptive pain: dopaminergic drugs

To our knowledge, no RCT to date has evaluated the effect of levodopa on chronic pain in Parkinson's disease. A 2022 cohort study in China, which used the dopaminergic effect on musculoskeletal pain as an inclusion criterion, reported at least a 30% reduction in pain measured by the Numerical Rating Scale (NRS) in 83% of 452 participants.[55] In a cohort in France of 310 patients with Parkinson's disease who had motor and non-motor fluctuations, analysis of responses to a non-motor fluctuation questionnaire disclosed a 63% reduction in pain following acute administration comparing the off-state (after an overnight discontinuation of all dopaminergic treatments for a minimum of 12 h) with the on-state (1 h after administering a dose equal to 150% of the first-morning levodopa equivalent dose).[70]

Rotigotine is the most extensively studied dopamine agonist in RCTs for Parkinson's disease (table). The phase 3b RECOVER RCT in 287 patients with Parkinson's disease who had unsatisfactory early-morning motor symptom control reported improvement in motor function, sleep, and pain as measured with a Lickert pain scale.[60] Post-hoc analyses showed a greater effect in patients with improved motor function and sleep.[71] The only study we identified with pain as a primary endpoint showed no notable changes between the rotigotine or placebo group in the 7-day average pain intensity evaluated by the 11-point Lickert pain scale, whereas two-fold numerical improvement on the KPPS fluctuation-related pain domain was measured in the rotigotine versus placebo group as a secondary endpoint.[46] A large RCT in 750 patients on entacapone, a COMT inhibitor, showed marked improvement in health-related quality of life but not in pain as measured with the 36-item short form survey pain domain.[59] Opicapone, another COMT inhibitor, is being investigated for its analgesic effect in 140 people with Parkinson's disease with end-of-dose motor fluctuations and associated pain in a phase 4 trial using domain 3 of the KPPS (fluctuation-related pain) as the primary outcome measure (NCT04986982; table).

Safinamide, an MAOB inhibitor with both dopaminergic and glutamatergic properties, reduced analgesic use, time with no or non-troublesome dyskinesia, and bodily discomfort measured by the Parkinson's disease Questionnaire (PDQ)-39 subscales as secondary outcomes in a phase 3 trial of 669 patients with mid-to-late stage Parkinson's disease who had motor fluctuations.[61] In contrast, a phase 4 RCT on the analgesic effect of safinamide in patients with Parkinson's disease who had motor fluctuations and chronic pain did not show superiority in reducing pain intensity as measured with the NRS (NCT03841604; table).

Nociceptive pain: non-dopaminergic conventional analgesics

To our knowledge, no studies have evaluated the analgesic effect of non-steroidal anti-inflammatory drugs in Parkinson's disease, although they are the most frequently used drugs for pain in the disease.[72] The PANDA trial, in 202 people with Parkinson's disease and severe pain, found no significant effect on the primary pain outcome with oxycodone–naloxone compared with placebo, as measured by a reduction in the 24 h average pain NRS score. However, the trial did show considerable pain reduction at later timepoints and in specific pain-related symptoms (eg, musculoskeletal and nocturnal pain) as measured with the KPPS, which might suggest a beneficial effect on nociceptive pain.[47]

Two recent surveys of cannabis users among patients with Parkinson's disease reported that 37–40% had improvement.[51,52] However, an RCT involving patients with Parkinson's disease using cannabis did not show a major effect on pain.[5,45] Additionally, a recent RCT in 61 people with Parkinson's disease who had baseline Movement Disorder Society Unified Parkinson's Disease Rating Scale motor scores of 20 or more, evaluated the 2-week efficacy of high cannabidiol with low dronabinol on motor symptoms in patients with low baseline scores. This trial also showed no reduction in pain intensity, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity 3a Short Form, and interference, as measured by the PROMIS Pain Interference 4a Short Form.[63]

As reported in a previous RCT,[48] a recent open-label study[56] involving 25 patients with Parkinson's disease found considerable improvement in foot dystonia-associated pain as measured by dystonia severity (subjective scale) and the associated Visual Analogue Scale (VAS) for pain after focal botulinum toxin type A injection at various doses and locations.

Nociplastic pain

The OXYDOPA RCT compared the analgesic effect versus placebo of increasing daily levodopa versus adding prolonged-release oxycodone for parkinsonian central pain in 66 patients.[64] High doses of levodopa showed no improvement in parkinsonian central pain as measured by VAS and were less effective than placebo, and prolonged-release oxycodone proved neither superior nor well tolerated.

An open-label study involving 20 patients with highly intense parkinsonian central pain (measured by VAS with scores higher than 7 out of 10) reported marked improvement in clinical pain scales after 6 weeks' administration of 60 mg duloxetine, a serotonin and norepinephrine reuptake inhibitor.[73] However, an RCT using lower doses of duloxetine (up to 40 mg) over 10 weeks did not confirm these findings in 46 patients with low intensity Parkinson's disease-related pain (without specified pain type) as measured by VAS.[62]

	Design	Participants	Treatment	Outcomes	Outcome assessment time	Results	Classification of evidence*
Dopaminergic medication							
Olanow et al, 2004[59]	Prospective, randomised, multicentre, double-blind, placebo-controlled, parallel-group trial	Patients with Parkinson's disease who have stable response to levodopa, without motor complications	Oral administration: entacapone (200 mg) added to each levodopa dose (n=373) or placebo (n=377)	Primary: change in UPDRS part 3; secondary: change in PDQ-39, SF-36 pain domain	26 weeks	No marked difference between groups in UPDRS part 3 (p=0·8) and SF-36 pain domain (p=0·1); significant difference in PDQ-39 in the group receiving entacapone (p<0·001)	II
Trenkwalder et al, 2011[60]	Phase 3b, randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease who have unsatisfactory early morning motor symptom control	Transdermal patch: rotigotine 2–16 mg/24 h (n=190) or placebo (n=97)	Coprimary: changes in UPDRS part 3 and in Parkinson's disease Sleep Scale-2; secondary: Likert pain scale	4 weeks	Marked differences between groups in UPDRS part 3 (p<0·001), Parkinson's disease Sleep Scale-2 (p<0·0001), and Likert pain scale (p<0·001)	II
Borgohain et al, 2014[61]	Phase 3, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease at mid-to-late-stage, with motor fluctuations	Oral administration: safinamide 100 mg/day (n=224) or safinamide 50 mg/day (n=223), or placebo (n=222)	Primary: change in time with no or non-troublesome dyskinesia; secondary: change in PDQ-39 subscales scores	24 weeks	Marked differences between groups (safinamide 50 mg and 100 mg versus placebo) in time with no or non-troublesome dyskinesia (both p=0·02) and in PDQ-39 bodily discomfort (safinamide 100 mg, p=0·01)	II
Rascol et al, 2016[46]	Multicentre, randomised, double-blind, placebo-controlled, pilot trial	Patients with Parkinson's disease who have at least moderate Parkinson's disease-associated chronic pain	Transdermal patch: rotigotine (4–16 mg/24 h (n=35) or placebo (n=33)	Primary: change in 7-day average pain intensity (11-point Likert pain scale); secondary: percentage of responders (2-point Likert pain scale reduction), KPPS domains	12 weeks	No notable difference between groups (Likert pain scale, p=0·17); proportion of responders per group was 18 of 30 (60%) for rotigotine *vs* 14 of 30 (47%) for placebo; two-fold numerical improvement in domain 3 (fluctuation-related pain) on KPPS observed in rotigotine *vs* placebo	I
NCT04986982	Phase 4, international, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease who have end-of-dose motor fluctuations and associated pain	Oral administration: opicapone 50 mg (n=70) or placebo (n=70)	Primary: change over baseline in domain 3 (fluctuation-related pain) on the KPPS	24 weeks	Not available	Not available
NCT03841604	Phase 4, international, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease who have motor fluctuations and chronic Parkinson's disease-related pain	Oral administration: safinamide 100 mg (n=46) once daily or placebo (n=25)	Primary: change in scores on NRS; secondary: number of subjects with reduction of ≥2 points in pain severity	16 weeks	No marked difference in pain severity between groups (p=0·16) nor in number of subjects with pain reduction (p=0·07)	I
Non-dopaminergic medication							
Trenkwalder et al, 2015[47]	Phase 2, international, randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease (Hoehn and Yahr Stage II–IV) who have severe pain (average 24-h pain score of at least 6 on an 11-point rating scale)	Oral administration: oxycodone–naloxone (n=93) *vs* placebo (n=109)	Primary: average 24-h pain score (11-point NRS) in 7 days preceding week 16; secondary: percentage of responders (≥30% pain reduction over baseline); exploratory: changes in Parkinson's disease pain subtypes (KPPS)	4, 8, 12, and 16 weeks	No marked difference in reduction in primary endpoint of average 24-h pain score at 16 weeks between oxycodone and placebo groups (p=0·058); marked differences at other points for oxycodone group; higher percentage of responders in oxycodone than in placebo group (48% and 34%, respectively; p=0·021); greater improvement in musculoskeletal and nocturnal pain (KPPS domains 1 and 4) in oxycodone group (p=0·02 and p=0·01, respectively)	I
Rieu et al, 2018[48]	Randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease who have painful foot dystonia	Intramuscular injection: incobotulinumtoxin A 100 UI in the flexor digitorum longus (n=16) or brevis muscle (n=13), or placebo (n=16)	Primary: change in Clinical Global Impression of change measured at 6 and 18 weeks after injection; secondary: dystonia severity (subjective scale) and associated pain (VAS)	18 weeks	Botulinum toxin injections improved mean Clinical Global Impression of change compared with placebo (p=0·039) and reduced pain and dystonia severity over baseline scores (p<0·01)	II
Iwaki et al, 2020[62]	Single-centre randomised, double-blind, placebo-controlled trial	Patients with Parkinson's disease who have Parkinson's disease-related pain	Oral administration: duloxetine 40 mg/day (n=23) or placebo (n=23)	Primary: change in pain intensity measured on VAS; secondary: change in MPQ-SF scores	10 weeks	No marked difference between groups in pain intensity measured on VAS, or in McGill pain questionnaire scores	I

(Table continues on next page)

	Design	Participants	Treatment	Outcomes	Outcome assessment time	Results	Classification of evidence*
(Continued from previous page)							
Liu et al, 2024[63]	Phase 2, single site, randomised, double-blind, parallel-group, placebo-controlled trial	Patients with Parkinson's disease who have a score ≥20 on the motor part of the MDS-UPDRS; type of pain not stated	Oral administration: high cannabidiol–dronabinol (n=31) or placebo (n=30)	Primary: change on MDS-UPDRS part 3 (motor examination) scores; secondary: change in PROMIS-pain intensity 3a short form, and change in PROMIS-pain interference 4a short form	2 weeks	No marked difference between groups on motor scale (p=0·5) nor on pain intensity and interference scales (p=0·5 and p=0·4, respectively)	II
Brefel-Courbon et al, 2024[64]	Randomised, double-blind, double-dummy, placebo-controlled, multicentre, three-arm, parallel-group trial	Patients with Parkinson's disease who have parkinsonian central pain	Oral administration: levodopa–benserazide treatment optimisation (n=20) or opioid with prolonged-release oxycodone (n=23) *vs* placebo (n=23)	Primary: change in VAS score; secondary: percentage of responders (30% and 50% pain relief)	8 weeks	No differences between prolonged-release oxycodone or levodopa/benserazide *vs* placebo groups (p=0·8 and p=0·2, respectively); responder analysis showed no differences between groups	I
Non-invasive stimulation							
Li et al, 2020[59]	Randomised controlled double-blind trial	Patients with Parkinson's disease who have musculoskeletal pain (n=52)	High-frequency repetitive TMS or sham stimulation over M1 (one session/day, for 5 days at 20 Hz)	Primary: pain intensity (NRS); secondary: motor symptoms, depression, anxiety, autonomic symptoms, sleep quality, and overall severity of Parkinson's disease	At 5 days, then at 2 and 4 weeks	Marked improvement in NRS scores and secondary outcomes for the repetitive TMS group, but not the sham stimulation group	II
Lapa et al, 2023[65]	Pilot, double-blind, randomised, controlled, parallel-group trial	Patients with Parkinson's disease who have musculoskeletal pain (n=26)	bTsMS (n=13) or sham stimulation (n=13), five daily sessions, then twice a week for 7 weeks	Primary: number of responders (≥50% reduction in average pain intensity on NRS; secondary: mood, quality of life, global impression of change, and adverse events	8 weeks	bTsMS group: more responders, greater reduction in depression symptom scores, and more positive global impression of change compared with the sham stimulation group	I
González-Zamorano et al, 2024[66]	Randomised, controlled, triple-blind trial	Patients with Parkinson's disease (n=22)	Transcranial DCS or sham stimulation over M1 (20 min per session, ten sessions; anode electrode C3 or C4, cathode Fp2 or Fp1; 2 mA intensity stimulation contralateral M1 to pain)	Primary: KPPS; secondary: BPI, widespread mechanical hyperalgesia, temporal summation of pain, and conditioned pain modulation	2 and 15 days	Marked reduction in KPPS scores and positive changes in conditioned pain modulation for transcranial DCS group	I
Barboza et al, 2024[18]	Double-blinded, randomised sham-controlled trial	Patients with Parkinson's disease who have chronic Parkinson's disease-related pain (n=25)	PSI-repetitive TMS or sham stimulation (five daily sessions for 1 week, then once weekly maintenance stimulations for 7 weeks; repetitive TMS delivered at 10 Hz and 80% of resting motor threshold	Primary: ≥30% pain intensity reduction at 8 weeks over baseline; secondary: NRS, BPI and MPQ-SF, Hospital Anxiety and Depression Scale, Mini-Mental State Examination, PD-PCS, UPDRS part 3, Neuropathic Pain Symptom Inventory, NMSS, PDQ-8, and quantitative sensory testing	8 weeks	No notable difference in pain reduction response rates between active (42·7%) and sham groups (14·6%, p=0·26); post-hoc analysis showed greater pain relief in patients with Parkinson's disease with nociceptive pain after active (85·7%) compared with sham PSI-repetitive TMS (25%, p=0·032)	I

(Table continues on next page)

	Design	Participants	Treatment	Outcomes	Outcome assessment time	Results	Classification of evidence*
(Continued from previous page)							
Exercise							
Reuter et al, 2011[67]	Three-arm randomised controlled trial; assessors blinded to the intervention	Three groups of 30 patients with Parkinson's disease, Hoehn and Yahr stages II–III each	Walking or Nordic walking *vs* flexibility and relaxation programme, three times weekly for 70 min	Walking parameters on UPDRS, UPDRS part 3, PDQ-39, and frequency of pain in body regions, pain ratings (VAS) for different regions	6 months	73·3% of the Nordic walking group reported pain at baseline *vs* 40% post-intervention; marked reduction of pain intensity in all body regions noted across all three groups; greatest improvements in back pain, and pain in hands and legs in walking and Nordic walking groups	III
Myers et al, 2021[49]	Two-arm, single-blinded randomised, controlled trial; assessors blinded to the intervention	Patients with Parkinson's disease who have low back pain	Yoga intervention (n=13 [twice-weekly, for 12 weeks, yoga incorporating breathing, meditation, and physical postures, with focus on postural transitions]) *vs* controls (n=13, usual routine)	Balance Evaluation Systems Test, Beck Anxiety Inventory, and ROSW	12 weeks	Low back pain improved after yoga intervention (ROSW decreased by 2·1 points, p=0·03) but not in controls	III
Complementary and alternative therapies							
Shaosong et al, 2024[68]	Randomised, single-blind, controlled trial	Two groups of 30 patients with Parkinson's disease who have musculoskeletal pain	Electroacupuncture group and sham acupuncture (five sessions per week, for 4 weeks)	Primary: KPPS; secondary: VAS, real-time shear wave elastography, modified Ashworth score, MDS-UPDRS; Hamilton Depression Scale	4 weeks	Marked improvement in primary and secondary outcomes after active electroacupuncture	I
Invasive stimulation							
Dellapina et al, 2012[69]	Short-term, randomised, double-blind, controlled, cross-over	Patients with Parkinson's disease treated who have STN-DBS (n=16, 8 with central pain)	STN-DBS on *vs* STN-DBS off	Primary: subjective heat pain threshold; secondary: pain-induced cerebral activity	3 h after intervention	STN-DBS increased subjective heat pain threshold (p=0·03) and reduced pain-induced cerebral activity in the somatosensory cortex	II
Ghilardi et al, 2024[53]	Randomised, open-label	Patients with Parkinson's disease with motor fluctuations (n=27)	STN-DBS *vs* GPi-DBS	Primary: NMSS, UPDRS part 3, PDQ-39; pain specific: NMSS item 27 (pain not accounted for by other known conditions), UPDRS part 3 item 17 (sensory complaints), PDQ-39 bodily discomfort item	6 months	STN-DBS group: item 27 decreased by 66%, item 17 by 55%, and bodily discomfort by 71%; GPi-DBS group: item 27 decreased by 27%, item 17 by 29%, and bodily discomfort by 40%	III

BPI=Brief Pain Inventory. bTsMS=lower-cervical burst trans-spinal magnetic stimulation. DBS=deep brain stimulation. DCS=direct current stimulation. GPi=globus pallidus internus. KPPS=King's Parkinson's Pain Scale. M1=primary motor cortex. MDS=Movement Disorder Society. MPQ-SF=short-form McGill Pain Questionnaire. NMSS=Non-Motor Symptoms Scale. NRS=numeric rating scale. PD-PCS=Parkinson's disease Pain Classification System. PDQ-8=8-item Parkinson's disease Questionnaire. PDQ-39=Parkinson's disease 39-item Questionnaire. PROMIS=Patient-Reported Outcomes Measurement Information System. PSI=posterior–superior insula. ROSW=Revised Oswestry Disability Index. SF-36=36-item short form survey. STN=subthalamic nucleus. TMS=transcranial magnetic stimulation. UPDRS=Unified Parkinson's disease Rating Scale. VAS=visual analogue scale. *According to the American Academy of Neurology Classification of Evidence criteria[54] to assess the quality of the randomised controlled trials: class I represents randomised controlled trials comparing two or more intervention groups simultaneously, with masked or objective, clearly defined outcome assessment, conducted in a clearly defined representative population, in which relevant baseline characteristics are substantially equivalent among treatment groups, with <20% of drop-outs; class II randomised controlled trials lack one or two class I criteria; class III is all other controlled trials (including well defined natural history controls or patients serving as own controls) in a representative population where the outcome is independently and objectively assessed.

Table: **Randomised controlled trials of pharmacological and non-pharmacological treatments for pain in patients with Parkinson's disease**

Non-pharmacological treatment

Non-invasive neuromodulation

High-frequency repetitive TMS applied to the primary motor cortex on the side opposite the symptoms has been shown to reduce Parkinson's disease-related musculoskeletal pain in 52 people with Parkinson's disease and musculoskeletal pain as measured by NRS (table).[50] In a recent RCT in 25 patients with Parkinson's disease-related chronic pain according to the PD-PCS, repetitive TMS of the posterior–superior insula had an analgesic effect only in patients with Parkinson's disease-related nociceptive chronic pain, as measured by a pain intensity reduction of 30% or more at 8 weeks compared with baseline.[18] Lower-cervical burst trans-spinal magnetic stimulation was safe and showed response in a phase 2 double-blind, sham-controlled trial in 26 patients for Parkinson's disease-associated nociceptive pain.[65] Transcranial direct current stimulation over the contralateral primary motor cortex reduced Parkinson's disease-related pain in an RCT involving 22 patients; the trial showed significant improvements, particularly in fluctuation-related and nocturnal pain, as measured by the KPPS.[66] Overall, these findings indicate the potential of non-invasive brain stimulation for the treatment of Parkinson's disease-related pain. Further studies to identify the proper target and types of stimulation according to the different categories of Parkinson's disease-related pain are needed.

Exercise and complementary approaches

The effectiveness of multimodal non-pharmacological interventions for pain in Parkinson's disease has been shown, with physical activity proving particularly beneficial.[74] In an RCT in 90 patients participating in a 6-month programme (three exercise sessions per week), walking or Nordic walking improved pain, especially in the back, hands, and legs, probably due to exercise-induced hypoalgesia, compared with flexibility and relaxation programmes.[67,74] Yoga also alleviated lower back pain after 12 weeks, as measured by a validated tool for assessing disability and functional impairment due to low back pain (the Revised Oswestry Disability Index), in 26 patients with Parkinson's disease who had postural instability, lower back pain, and anxiety, as part of a large intervention study.[49] Two studies on passive treatments, such as massage and acupuncture, suggested potential benefits for nociceptive pain, with skin stroking specifically reported to alleviate musculoskeletal pain.[68,75]

Invasive neuromodulation

The effects of subthalamic nucleus DBS (STN-DBS) on pain have been assessed in several non-randomised studies.[76] Most published studies report positive effects for more than 6 months, with one study showing effects lasting for up to 8 years.[77] One study, involving 41 patients with Parkinson's disease who had refractory motor symptoms, showed positive effects of STN-DBS on dystonic and musculoskeletal pain but not on central or neuropathic pain as measured by changes in pain prevalence and intensity 1 year after surgery.[78] However, improvement with this treatment seemed unrelated to motor improvement and mood changes.[57] Improvement in scores on the Oswestry Low Back Pain Disability Index, which evaluates the degree of disability and functional impairment caused by lower back pain, remained for at least 1 year after bilateral STN-DBS in 16 patients with lower back pain.[79] An open-label RCT comparing the efficacy of globus pallidus internus DBS with that of STN-DBS reported greater improvement in pain-related outcomes after STN-DBS in 27 patients, as measured by the Non-Motor Symptoms Scale subitem sensory complaint (table).[53] A short-term, randomised, double-blind, controlled crossover study comparing the effects of STN-DBS in the on-state versus the off-state in 16 patients with Parkinson's disease with or without neuropathic pain reported that the on-state increased subjective heat pain thresholds, as assessed using a Peltier-based contact temperature stimulation device, and reduced pain-induced cerebral activity in the somatosensory cortex, as measured by $H_2{}^{15}O$ PET.[69]

Effects of epidural spinal cord stimulation on motor and non-motor outcomes in patients with Parkinson's disease are controversial, as studies have reported mixed results. A 2023 systematic review examined five non-randomised studies involving 56 patients with Parkinson's disease who had lower back or leg pain; most studies reported benefits, with a mean reduction of 59% in pain intensity.[80]

Pathophysiology of pain in Parkinson's disease

Mounting evidence suggests that Parkinson's disease is associated with dysfunctional nociceptive pathways at multiple levels of the nervous system. The basal ganglia—through dopaminergic transmission—integrate pain perception in key regions of the pain neuraxis in patients with Parkinson's disease.[12] Other pathophysiological mechanisms involve non-dopaminergic (eg, noradrenergic, serotonergic, γ-aminobutyric acid, and glutamatergic) pathways, which play a role in integrating and modulating nociceptive information.[12] Animal models have been used to investigate the pathophysiological mechanisms of pain in Parkinson's disease (panel 2).

Psychophysical and neurophysiological studies

Psychophysical measures of pain detection and pain tolerance thresholds to stimuli and neurophysiological measures of the nociceptive withdrawal reflex, conditioned pain modulation, and laser-evoked potentials have been applied to assess pain in patients with Parkinson's disease (panel 3).[12]

Pain detection and tolerance thresholds are noted to be lower in patients with Parkinson's disease who are in the off-state (drug-naive or dopaminergic withdrawal) than in healthy controls, regardless of whether pain is present;

pain thresholds can be partly ameliorated in the on-state with dopaminergic therapy.[89] Most studies have found no significant difference in experimental pain sensitivity between patients with Parkinson's disease who have diverse types of pain (ie, musculoskeletal, neuropathic peripheral, or central pain) and patients with Parkinson's disease who are pain-free.[90] Some studies, however, have reported a moderate-sized effect (Cohen's effect sizes for the standardised mean difference 0·4–0·7) of hyperalgesia in those patients with pain. The incomplete normalisation of pain hypersensitivity in the on-state suggests a role for other neurotransmitters in the pathophysiology of Parkinson's disease-related pain (ie, serotonin, noradrenaline, and glutamate); this hypothesis is supported by studies in animal models and by imaging studies on patients with Parkinson's disease (panel 2).[91,92] The application of the nociceptive withdrawal reflex has revealed a probable alteration in spinal neuronal activity already at an early stage of the disease, which has been found to change further in conjunction with motor symptoms.[89,90] It has been shown that this proposed altered activity can be reversed by levodopa and DBS.[89,90] However, the precise nature of the somatosensory pathways that contribute to this effect is unclear.

Descending inhibitory control can be explored with a conditioned pain modulation protocol, which consists of delivering a painful conditioning stimulus alongside another experimentally induced painful test stimulus. According to the principle of pain-inhibits-pain, a physiological reduction of the perceived test stimulus is usually observed. Conditioned pain modulation was shown to be unimpaired and unchanged by levodopa in Parkinson's disease with or without pain.[89,90]

Studies using laser-evoked potentials have reported an altered N2/P2 complex in patients with Parkinson's disease who are pain-free and in those with musculoskeletal pain (panel 3).[93] An absence of change in the N1/P1 component that precedes N2/P2 suggests that altered nociception might rely on central rather than peripheral processes.[93,94]

A 2017 study that evaluated the effects of laser-evoked potentials on motor cortex by TMS in patients with Parkinson's disease with or without pain showed an abnormal pain-motor integration, regardless of therapeutic status (off-state or on-state).[94]

In addition to proposed central pathogenic mechanisms, evidence for common subclinical peripheral neuropathy in patients with Parkinson's disease, underpinned by pathological accumulation of phosphorylated α-synuclein correlating with length-dependent small fibre loss,[36] highlights that peripheral nervous system abnormalities probably play a role in chronic pain in Parkinson's disease. More studies should focus on the differential (or synergistic) role of peripheral and CNS mechanisms of pain correlating with Parkinson's disease to enhance understanding of basic pathophysiological mechanisms and improve personalised treatment strategies.

***Panel 2:* Insights from animal models on pain mechanisms in Parkinson's disease**

Animal models have been used to investigate the pathophysiological mechanisms of pain in Parkinson's disease. Tonic dopamine release on phasic signals in the nucleus accumbens has resulted in noxious stimulus-dependent activation of a mesolimbic circuit and decreased dopaminergic tone when the noxious stimulus was ongoing.[81] In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) murine model of Parkinson's disease, the model-associated behavioural phenotype of mechanical allodynia and thermal hyperalgesia, along with MPTP-induced astrocyte activation and inflammatory mediator expression, was reduced by dexmedetomidine, an α2 adrenoceptor agonist, suggesting a role for the noradrenergic system in neuroinflammatory response and dopaminergic neuron protection and analgesia.[82] The neuropharmacological effect of noradrenaline on sensory function was investigated in a 6-hydroxydopamine medial forebrain lesion model of Parkinson's disease, where concurrent ablation of cerulean noradrenergic transmission correlated behaviourally with changes in animal nociceptive thresholds.[83]

Serotonin, which is intrinsic to pain regulatory circuits, activates 5-HT3 receptors in the dorsal horn of the spinal cord where it induces neuronal excitability. In rats with 6-hydroxydopamine lesions, 5-HT3 receptor antagonism inhibited spinal neuronal responses and increased serotonergic transmission in the raphe nuclei and hyperalgesia.[84,85] This finding is consistent with evidence for abnormal functional connectivity of the raphe nuclei with key nodes in the pain matrix in patients with Parkinson's disease who have persistent pain.[86]

Peripheral nervous system abnormalities have been implied in chronic pain. Peripheral nervous system excitability in Parkinson's disease has also been studied in MPTP murine models, in which hyperalgesia associated with the behavioural phenotype was correlated with dorsal root ganglia neuronal hyperexcitability in a manner modulated by safinamide, a reversible monoamine oxidase-B inhibitor that also blocks sodium voltage-sensitive channels and modulates the stimulated release of glutamate.[87] Pathophysiological manifestations of disease in peripheral and CNS circuitry were also found following peripheral inoculation of mouse α-synuclein in a Parkinson's disease transgenic model.[88]

Brain imaging studies

Functional imaging using $H_2{}^{15}O$ PET in patients with Parkinson's disease who were pain-free and in the off-state showed hyperactivity in several brain areas associated with pain processing, including the insula, the secondary somatosensory cortex, the anterior cingulate cortex, and the prefrontal cortex. Of note, levodopa reduced the pain activation profiles in these patients.[95] PET studies of pain-induced activity of brain areas in the off-state in patients with Parkinson's disease who had pain showed that pain-induced activation in the right prefrontal cortex and the posterior insula was lower, and pain-induced activation in the right anterior cingulate cortex was higher, than in patients without pain, indicating preferential recruitment of the medial affective system in patients who have pain.[22]

Consistent with these results, functional MRI (fMRI) studies have identified correlations between pain intensity and connectivity of the nucleus accumbens with the primary motor cortex, sensory areas, and hippocampus in patients with Parkinson's disease, and levels of connectivity between the nucleus accumbens and the brainstem in patients reporting greater pain intensity, which could reflect impaired descending pain modulation, amongst other mechanisms.[96] These cerebral functional

Panel 3: Psychophysical, neurophysiological, and neuroimaging pain assessment and nociceptive pathways

Psychophysical or behavioural

Pain thresholds for different kinds of stimuli (ie, mechanical, thermal, and electrical)

- The intensity of stimulation at which a change in sensation from painless to faintly painful is reported in exploring the sensory-discriminative pain component of the lateral spinothalamic pathway (ie, thalamus, posterior insula, and secondary somatosensory cortex [also known as S2]).

Pain tolerance to different kinds of stimuli (ie, mechanical, thermal, laser, electrical)

- The intensity of stimulation at which an intolerable painful sensation is reported in exploring the affective-cognitive pain component of the medial spinoreticulothalamic pathway projecting to the insula, the anterior cingulate cortex, and the periaqueductal grey.

Conditioned pain modulation

- Experimental paradigm to assess pain modulatory processes by examining the effect of a conditioning stimulus on pain perception when applied concurrently to a heterotopically applied test stimulus. The effect of the conditioning stimulus on the test stimulus (ie, modulated perception as compared with test stimulus alone) is mainly mediated by noradrenergic mechanisms with some influence of opioidergic, serotonergic, and propriospinal mechanisms. Conditioned pain modulation represents the human behavioural correlate of diffuse noxious inhibitory control, initially described in rats.

Neurophysiological

Laser evoked potentials

- Generated by brief pulses of peripherally applied laser that penetrate the skin and selectively activate nociceptors. Nociceptive signals dependent on A-delta fibres (thinly myelinated) are conducted via the spinothalamic tract and recorded via scalp EEG electrodes as a nociceptive evoked potential. Potentials include an N1 component and the N2–P2 complex at the vertex. The N1 component is believed to originate from the operculoinsular region; it modulates initial cortical processing of nociceptive input and might involve discriminatory aspects of the stimulus. The N2–P2 complex originates from the anterior cingulate cortex and the anterior insula, two cortical areas involved in the affective-motivational aspects of pain.

Nociceptive withdrawl reflex

- A nociceptive reflex for which appearance is tightly related to an individual´s pain threshold. It is dependent on A-delta fibres and a segmental spinal integration. The muscular response is commonly recorded at the biceps femoris (80–150 ms, RIII component; the RIII component, which appears within this latency range, is mediated by high-threshold A-delta cutaneous cutaneous afferent fibres and represents a polysynaptic withdrawal reflex associated with pain processing) as an electromyography response.

Neuroimaging

PET scan $H_2{}^{15}O$

- Measures regional cerebral blood flow changes during experimental nociceptive stimulation and shows pain-induced activation of cortical areas.

Functional MRI

- Explores functional (correlational) connectivity between cerebral areas involved in central pain integration.

Dopamine transporter imaging with single-photon emission CT

- Assesses striatal dopaminergic uptake.

Nociceptive pathways

Lateral spinothalamic pathway

- A fast-conducting system projecting to the thalamus and the posterior insula and S2 areas; it subserves sensory-discriminatory pain components.

Medial spinoreticulothalamic pathway

- A slow-conducting system projecting to several subcortical and cortical areas—the medullary core, the mesencephalon, the periaqueductal grey, the hypothalamus, the insula, and the anterior cingulate cortex. This pathway subserves affective and cognitive pain components.

Somatosensory system

- A broad definition that includes activity in afferents from all somatosensory modalities (eg, proprioceptive, interoceptive, nociceptive, mechanical touch, vibration) and from sensory modulatory systems (eg, descending and propriospinal). In the clinic, this system is often conceptualised as the sensory system, and includes all sensory modalities amenable to examination. The special senses (sight, smell, hearing, taste) are not included in this system.

Descending inhibitory pain pathway

- Originating in higher brain centres and upper and lower brainstem, this pathway modulates dorsal horn spinal neuronal activity, and involves brainstem structures (ie, periacqueductal grey and rostral ventral medulla).

changes are not necessarily due to chronic dopaminergic treatment, since an fMRI study during experimental nociceptive stimulation showed abnormal central pain processing with an increase in metabolic activity of the somatosensory cortex, the cerebellum, and the inferior pons in patients with Parkinson's disease who were drug-naive compared with healthy controls.[97] These findings suggest that central abnormalities could be present at onset of the disease, and might even precede the development of pain detection abnormalities.[98] Further evidence for the involvement of neurotransmitter systems dependent on pain type has been obtained from dopamine transporter single-photon emission CT imaging, which showed that pain perception abnormalities in patients

with Parkinson's disease who had central pain could be linked to extrastriatal monoaminergic systems, whereas musculoskeletal pain could more likely be associated with the severity of striatal dopamine deficiency.[91,92]

To summarise, abnormal somatosensory processing in Parkinson's disease is common. The partial efficacy of levodopa in improving quantifiable measures associated with Parkinson's disease-related pain suggests a complex pathophysiology involving dopaminergic and non-dopaminergic networks. The finding of similar pain processing alterations in patients with Parkinson's disease who are pain-free and those who are pain-affected suggests that neurodegeneration-associated mechanisms in Parkinson's disease could predispose individuals to pain, but are not solely determinative. Additional Parkinson's disease-related factors (eg, motor complications and dystonia) and other common medical conditions associated with painful symptoms (eg, peripheral neuropathy, arthritis, anxiety, depression), are probably necessary for pain to manifest (figure 3).

Conclusions and future directions

This Review highlights the importance of identifying pain related to Parkinson's disease and unrelated pain, and specific clinical and pathophysiological pain descriptors (neuropathic, nociceptive, and nociplastic), as the foundation for understanding various pain syndromes according to the validated PD-PCS questionnaire published in 2021.[5] Recognising the underlying mechanism enables clinicians to tailor treatment strategies more effectively to address the specific type of pain that individuals with Parkinson's disease have.[5]

Pain in patients with Parkinson's disease was originally thought to be due to muscle rigidity and motor abnormalities; however, it is now recognised that nigrostriatal dopamine depletion can increase pain sensitivity and alter non-painful sensory discriminatory capacity. Other mechanisms, neurotransmitters, and central and peripheral pathways are also involved. On the basis of pathophysiology, an approach that addresses Parkinson's disease symptoms and fluctuations is the initial step in diagnosis and treatment, followed by either a mechanism-related or a symptom-related approach, as appropriate.

Several relevant issues remain open. More data on experimental pain sensitivity could elucidate the role of non-dopaminergic transmitters, as dopamine reverses only part of the increase in pain sensitivity at different disease stages. Furthermore, brain imaging studies could identify additional factors that potentially contribute to chronic pain. An area of focus for future clinical trials is to devise a mechanism-based approach that incorporates the course of disease according to Parkinson's disease subtyping based on motor and non-motor symptoms, such as the recently developed data-driven classification of patients with Parkinson's disease in benign-motor, intermediate, and diffuse-malignant categories.[99] This approach will further enable the characterisation of pain

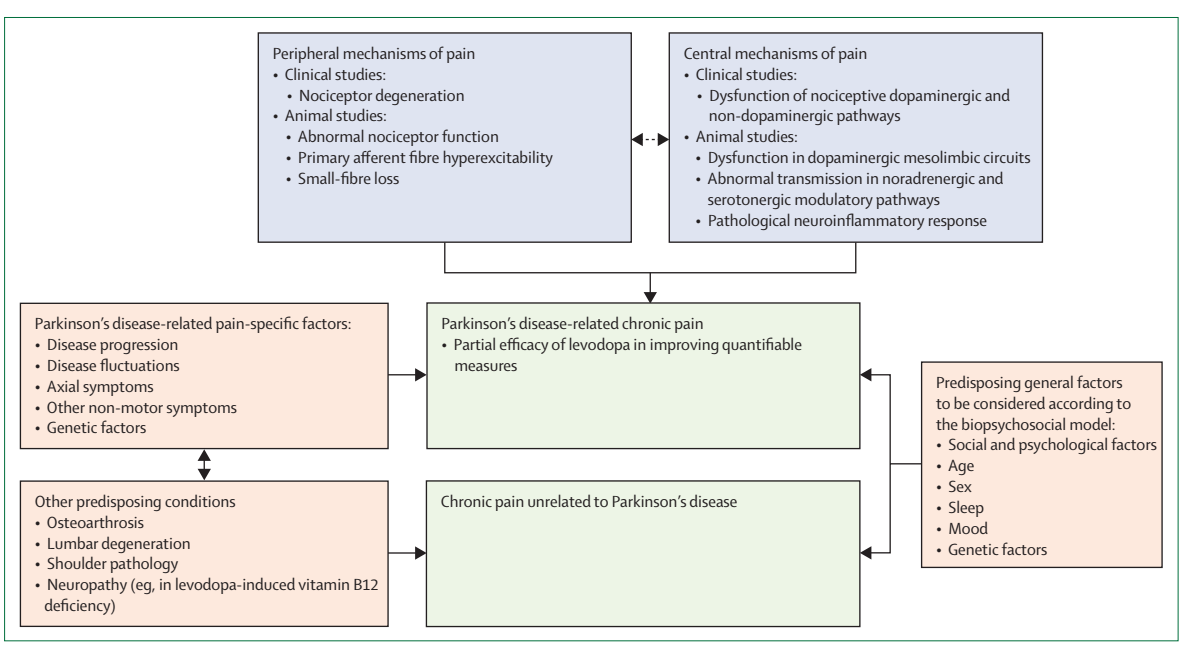

Figure 3: **Factors and mechanisms underlying pain development in Parkinson's disease**
Peripheral and central factors (blue boxes) contribute to the pathophysiology of chronic pain in patients with Parkinson's disease. These factors might act independently, influence each other, or both, and mechanistically they might cause certain aspects of Parkinson's disease-related chronic pain. Parkinson's disease-related and unrelated chronic pain (green boxes) might be influenced by Parkinson's disease-specific factors and other pathologies (orange boxes). Factors within the biopsychosocial model of chronic pain might also influence the manifestation of pain. This model considers biological, sociocultural, and psychological aspects to understand pain as a multifaceted process, and emphasises the complex interplay of these dimensions in shaping an individual's pain experience, integrating distinct pain mechanisms to guide treatment strategies. These strategies should include both self-management and a combination of pharmacological and non-pharmacological therapies.

categories and facilitate investigation of treatment approaches.

Overall, there is little evidence for pain treatment with pharmacological and non-pharmacological therapies in Parkinson's disease. Furthermore, trial data on pain as the primary outcome are scarce. Both invasive and non-invasive brain stimulation have shown an effect on chronic pain in patients with Parkinson's disease. Nevertheless, a mechanism-based approach has been found to be effective only for nociceptive pain upon insular stimulation in one repetitive TMS study to date.[18] STN-DBS can modify sensory thresholds and improve chronic pain in patients with Parkinson's disease, with a further positive effect on quality of life unrelated to the post-surgical improvement of motor functions.[78] DBS studies have shown that the optimum stimulation site for the treatment of chronic pain differs slightly from that for motor function.[100] However, the exact and optimum pathways to be stimulated remain unclear.

In conclusion, well designed RCTs targeting pain in Parkinson's disease are urgently needed, as most trials to date have faced limitations or yielded negative results. Future RCTs should focus on specific pain types to define the study sample, and follow the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, addressing pain intensity, physical function, quality of life, emotional health, patient perspectives, and safety. Additionally, translating clinical disease presentations into Parkinson's disease animal models remains essential to identify novel therapeutic targets to be tested in valid animal models.

For more on the **Initiative on Methods, Measurement and Pain Assessment in Clinical Trials** see https://www.immpact.org/

Search strategy and selection criteria

We searched PubMed and Web of Science for articles published between July 1, 2019, and July 1, 2024, with no language restrictions. The search string to query PubMed was ("Parkinson Disease"[Mesh]) AND "Pain"[Mesh] AND (2019:2024[pdat]); the string to query Web of Science was "Parkinson disease" AND "pain" (last 5 years). The articles were screened in two stages: abstract screening and then full-text screening by six assessors (MG, KB, CB-C, SP-L, KR, and CAA) who selected original research articles and review articles on epidemiology, pathophysiology, diagnosis, classification, and treatment. The selection criteria were: study originality, evidence level, and relevance for the scope of this review, as established by consensus among the review authors. Excluded were case reports, case series, and small cohort studies, which experts deem non-relevant. Pertinent systematic reviews were retained for reference verification, whereas narrative reviews that experts deem non-relevant were excluded. The Rayyan tool for reviews was used to enhance screening transparency and accuracy. We used the American Academy of Neurology Classification of Evidence criteria for rating interventional studies and to assess the quality of randomised controlled trials on pain in Parkinson's disease.

Contributors

MT and VM conceptualised the manuscript. MG, CAA, KR, KB, SP-L and CB-C searched and selected the references. All authors wrote the first draft, which was subsequently reviewed and refined by MT, MG, DCdA, CAA and VM. VM and KB edited the figures. All authors contributed and revised the draft for critical content and approved the final version of the manuscript.

Declaration of interests

VM declares grants from Parkinson Switzerland, the Dr Wilhelm Hurka Foundation, BIAL, and Zambon; honoraria from Abbvie and BIAL for presentations; travel compensation from Zambon. VM consulted for BIAL; is a member of the scientific board of Parkinson Switzerland; and is a member of the editorial board of the *European Journal of Pain*. SP-L declares grants from the Agencia de Promoción Científica, Fundación Bunge y Born, Fundación Esteban Bullrich, and Instituto Universitario Barceló. SP-L owns stocks from TeleNeuro Solutions. DCA is vice chair for the research committee of the European Federation of International Association for the Study of Pain chapters; is section editor for the *European Journal of Pain*; is on the advisory board of *Pain Reports*; is an employee of Aalborg University, Denmark; is a non-remunerated collaborator professor of University of Sao Paulo, Brazil; declares institutional investigator-initiated research grants from Cristalia, Mundipharma, St Jude Medical–Abbott Medical, Medtronic, Magventure, and Grunenthal; received remuneration for lectures for Mundipharma, GreenCare, and Magventure; received conference travel support from the Pain Center at University of Sao Paulo, Brazil, and Megventure; declares research grants from FAPESP (Fundacao de Amparo à Pesquisa do Estado de Sao Paulo), Brazil, Novo Nordisk Foundation, Neuroscience Academy Denmark (Lundbeck Foundation), Horizon Europe (Fresco4NoPain European consortium), and the European Research Council. CAA received speaker honoraria from Abbvie, Bial, Zambon, Lusofarmaco, and Ralpharma. CB-C received consultancy fees from Merz, Bial, NHC Care, and Orkyn; declares grants from the French Ministry of Health (programme hospitalier de recherche clinique), the French Ministry of Research (ANR), France Parkinson, Fondation AXA, Everpharma, Elivie, NHC Care, and Orkyn; has received honoraria for speeches from Orkyn, Novartis, and AJR Medical; and received support for attending meetings or travel from Orkyn, AJR, Abbvie, NHC Care, and Adelia. KB received research funding from Parkinson's UK. Outside of the submitted work, MT has received research funding from the Italian Ministry of Health, University of Verona, and the Verona Brain Research Foundation, and personal fees from Abbvie, Bial, Chiesi Farmaceutici, Zambon, and the Movement Disorders Society. MG has received research funding from the Italian Multiple Sclerosis Foundation and the Verona Brain Research Foundation. KB has received research funding from Parkinson's UK. All other authors declare no competing interests.

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