Curr Neurol Neurosci Rep (2016) 16:28
DOI 10.1007/s11910-016-0628-7

Integrated Approach for Pain Management in Parkinson Disease

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Abstract Pain, one of the most frequent nonmotor symptoms of Parkinson disease (PD), is recognized as an important component of the illness that adversely affects patient quality of life. The aims of this review are to summarize the current knowledge on the clinical assessment and to provide a detailed overview of the evidence-based pharmacologic and nonpharmacologic approaches to treating pain. Results of a literature search include studies investigating pain/sensory abnormalities in PD. The effects of levodopa administration, deep brain stimulation (DBS), pallidotomy, spinal cord stimulation, rehabilitation, and complementary/alternative medicine are reviewed critically. PD patients have altered pain and sensory thresholds; levodopa and DBS improve pain and change sensory abnormalities toward normal levels through antinociceptive and/or modulatory effects that remain unknown. A wide range of nonpharmacologic approaches require further investigation. A multidisciplinary approach is fundamental in managing pain syndromes in PD.

Keywords Nonmotor symptoms · Pain · Sensory thresholds · Pain management

This article is part of the Topical Collection on *Movement Disorders*

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Introduction

Pain, one of the most frequent nonmotor symptoms in Parkinson disease (PD), is recognized as an important component of the illness that adversely affects patient quality of life (QOL) [1–3]. First described by James Parkinson in 1817 [4], pain in PD was underestimated for a long time. In recent years, however, new attention has been focused on pain symptoms because of their role in increasing disability and their effects on patients' QOL [3, 5, 6].

The average prevalence of PD pain symptoms is 67.6 %, with up to 85 % of PD patients experiencing pain [7, 8••, 9]. Pain affects the lower limbs most frequently, and very interestingly, only 52.4 % of PD patients with pain use pain relief drugs, most often nonopioids [9].

Because of the significantly high prevalence of PD pain, it is crucial for neurologists and other health care providers to have a better understanding of these pain syndromes; unfortunately, however, literature on clinical predictors in PD is

Published online: 15 February 2016

scant. Patients who have PD with motor complications appear to have a greater risk of developing pain [3], and pain seems to increase as parkinsonian symptoms worsen [10, 11]. Female gender, depression, comorbid symptoms, and concomitant medical conditions (e.g., diabetes, osteoporosis, rheumatic disease, arthritis) may be associated with pain symptoms. [10–16] Also, genetic contributions have been suggested as possible risk factors for pain in PD. Variants within the *SCN9A* and *FAAH* genes [17] and polymorphisms in the *COMT* gene are associated with an increased risk of pain in patients with PD. [18] Nevertheless, this topic remains complex because pain in PD is a strongly heterogeneous symptom with regard to both quality and body distribution [10]. Moreover, because pain might have different origins, distinctive therapeutic approaches may be recommended.

The International Association for the Study of Pain (IASP) Subcommittee on Taxonomy defines *pain* as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." In other words, other domains, such as emotion and cognition, may be involved in the origin and maintenance of pain, as well as in its management.

The aim of this review is to provide readers with a complete update of evidence-based evaluations and pharmacologic and nonpharmacologic treatments for pain management in PD patients.

Pain Classification

The classification and pathophysiology of pain in PD are both complex and closely related. The wide variety of pain types patients with PD may experience makes it difficult to understand the pathophysiology of PD pain.

With regard to PD, Ford [19] proposed the currently used classification that divides pain into the following categories: musculoskeletal, radicular, central, and dystonic pain, and akathisia. The last disorder recently was excluded from most studies evaluating pain, because patients usually do not report akathisia as a type of pain. The other pain types are significantly different from one another and may be experienced singularly or coexist in the same patient.

Of the aforementioned pain types, musculoskeletal pain is reported most frequently [20]. *Musculoskeletal pain* refers to the aching, cramping, joint pains reported in different locations by patients with PD. It appears to be associated with rigidity and severe bradykinesia, but also may result from decreased mobility in affected limbs and joints, as well as abnormal postures, and tends to be worse during the "off" periods of PD. [21–25]

The second most frequent type of PD pain is dystonic pain, which is associated with the sustained, forceful twisting movements that lead to abnormal postures and deformities. Dystonic pain may be paroxysmal, spontaneous, or triggered by movement or activity, and its duration, intensity, and response to treatment also may vary. Lim et al. [26] reported that after levodopa administration, only PD patients with dyskinetic pain have an increase in cold pain threshold and tolerance. These effects may reflect a process of sensitization to the analgesic and motivational effects of levodopa.

The other types of pain occur less frequently and may be considered as belonging to the neuropathic pain syndromes. *Radicular pain* refers to the achiness and discomfort localized around a nerve or nerve root. Finally, central pain in PD is presumed to be a direct consequence of the disease and not the result of dystonia, rigidity, or a musculoskeletal cause. Bizarre, unexplained sensations of stabbing, burning, scalding, or formication (a sort of paresthesia in which there is a sensation of tiny insects crawling over the skin) with no clear radicular origin usually are classified in this category [2, 6, 19–21].

Understanding which type of pain a patient is experiencing is essential in providing tailored, symptomatic treatment. Although the aforementioned classification system may be very helpful, it cannot be applied easily in all situations, because clear objective measures are lacking, and our understanding of pain syndrome mechanisms is poor. Although clinically, PD pain related to motor symptoms can be distinguished from that unrelated to motor symptoms [22], this distinction also may be difficult. Non-PD pain stems from sources other than PD. PD-related pain is caused or aggravated by PD and may be subclassified as PD-pain direct if it cannot be associated with other health problems or PD-pain indirect if comorbidities are present and PD is aggravating the intensity of the pain [11].

Independent of the pain's type and underlying pathophysiology, a clear reduction in QOL is associated with pain in PD. Treatment of PD symptoms does not always relieve pain, and pain-directed treatments are not usually administered in clinical practice.

Pathophysiology of Pain

Various mechanisms have been associated with the occurrence of pain in PD; they generally may be categorized as either central or peripheral. Central pain mechanisms have been described since the role of the basal ganglia in nociception was investigated extensively in animal models and human studies [27]. In PD patients with pain, several studies reported abnormalities in pain threshold and pain tolerance. Compared with healthy controls, PD patients with and without pain (muscular, dystonic, and peripheral neuropathic) showed lower pain thresholds to electrical stimuli [12, 28–30]. No differences were found between PD patients with pain and those without it.

Reduced pain threshold to cold water was reported in PD patients without and with pain (primary central pain)

compared with healthy controls; however, no clear differences were observed when PD patients with pain were compared with those without it [31, 32]. Pain threshold to a heated thermode appeared to be reduced in PD patients with primary central pain compared with PD patients without pain. A decrease in pain threshold to thermode application also was found when comparing PD patients without and with pain (primary central and musculoskeletal) versus healthy subjects [33, 34].

Tinazzi et al. [35–37] found a lower pain threshold to laser CO_2 in pain-free PD patients compared with healthy subjects. A lower threshold also was found in PD patients with central pain compared with pain-free patients and healthy subjects [34]. In addition, a decrease in N2/P2 amplitudes of laser-evoked potentials was observed in patients with muscular pain compared with pain-free patients and healthy subjects [37] as well as in pain-free PD patients compared with healthy subjects [35, 36]. Pain tolerance to electrical stimuli was reduced in PD patients without and with pain (musculoskeletal and neuropathic) compared with healthy subjects; however, no differences were observed between PD patients with pain and those without it [12]. Studies based on the nociceptive withdrawal reflex (NWR) to electrical stimuli (pain processing in the spinal cord) also showed a reduced NWR threshold in patients with PD with musculoskeletal pain [38]. A reduced threshold also was found in pain-free PD patients compared with healthy subjects [28, 29].

In summary, central pain mechanisms seem to be impaired in PD patients regardless of whether they have pain. The abnormalities in nociceptive processing described in PD may be associated with reduced basal ganglia dopamine levels, although some studies suggest that other neurotransmitters (e.g., acetylcholine) [39] also may contribute to abnormal pain processing [18].

In another line of research, new evidence suggests that the peripheral nervous system also may be involved in PD pain [39]. The findings in PD patients of nociceptor neurodegeneration [40], cutaneous denervation in skin biopsies [41], and reduced unmyelinated nerve fiber density [42] support the hypothesis that the peripheral nervous system may at least contribute to the presence of some types of pain in PD.

Pain Assessment

Clinical assessment of pain generally focuses on pain diagnosis and/or the assessment of specific clinical features (e.g., pain intensity, quality, and disability) to plan specific treatments. Clinical assessments play an important role in both the research setting and clinical practice; however, no standardized, specific clinical assessments have been developed yet for the evaluation of pain in PD patients. Many clinical and instrumental measures were used in several observational/interventional studies involving patients with different types and qualities of pain both on and off medication. Various body parts, such as the head, neck, trunk, back, and upper and lower extremities, were investigated. A list of clinical and instrumental measures is presented in Table 1.

With regard to diagnosis, negative and positive signs of neuropathic pain have been proposed as simple bedside tests. Quantitative sensory testing provides objective data regarding mechanical sensitivity and vibratory and thermal sensation.

To evaluate pain processing from the peripheral to the central nervous systems further, several analytic tools have been used, including skin biopsy, thermal stimulators (e.g., Peltier-based contact temperature stimulators), handheld pressure algometers, and electrical stimulation (Table 1). Transcutaneous electrical stimulators are particularly interesting because they enable one to assess the thresholds of three types of afferent fibers (Aβ, Aδ, and C) via different sinusoidal frequencies (2000, 250, and 5 Hz) and electrical intensities (ranging from 0.01 to 9.9 mA) [49].

When combined with electromyography, the electrical stimulator enables the assessment of the nociceptive flexion reflex (RIII) that characterizes pain processing at the spinal cord level. The Medoc VSA-3000 and TSA-2001 (Minneapolis, MN), devices that can generate and document responses to repeatable thermal and vibratory stimuli, also have been used [24].

$H^{15}O_2$ positron emission tomography (PET) has been used to investigate cerebral activations in the nociceptive network, including the thalamic nuclei, insula, and somatosensory and prefrontal cortices [43]. CO_2 laser-evoked potentials have been used to explore noninvasively the functional status of cerebral structures responding to nociceptive inputs [35–37]. With regard to clinical scales, both unidimensional and multidimensional measures were used in previous investigations. Among unidimensional measures, the visual analog and numerical rating scales are used most frequently to evaluate pain intensity (Table 1). The Pain Catastrophizing Scale is a reliable and valid measure for evaluating the emotional component of pain by quantifying a patient's thoughts and feelings about the pain he or she is experiencing.

The other scales listed in the table may be considered multidimensional and/or "nonspecific" measures. The latter do not focus specifically on pain evaluation but assess other aspects of PD (e.g., severity) and include subitems for pain. Among the multidimensional scales, those commonly used in clinical practice are the PainDETECT and Douleur Neuropathique 4 questionnaires, the Neuropathic Pain Symptom Inventory, and the Leeds Assessment of Neuropathic Symptoms and Signs. Basically, all these instruments are used to investigate whether neuropathic symptoms and signs are present (Table 1). In contrast, the McGill Pain Questionnaire (as well as its short form), the Brief Pain Inventory, and the Gracely Box scale evaluate different

Table 1 Objective and subjective measures of pain and sensory thresholds in PD

Clinical assessment[a]	Reference(s)	Usefulness[b]
Bedside tests for negative and positive signs—quantitative sensory testing		
Von Frey filaments/Semmes-Weinstein nylon monofilaments	[23–25, 33, 41]	MSK, RN, D, CP
Rydel-Seiffert tuning fork	[23]	MSK, RN
Cold/warm water	[25, 26, 31–33]	MSK, RN, CP, D
Instrumental evaluations		
Thermal stimulator	[23–25, 30, 33, 38, 41, 43–48]	MSK, RN, CP, D
Electromyography with electrical stimulation	[28–30, 38, 43]	MSK, RN, CP, D
Electrical stimulation	[12, 30, 38, 49]	MSK, RN, CP, D
VSA-3000/TSA-2001, vibratory device	[24]	MSK, RN, D
$H^{15}O_2$ PET	[31, 32, 43, 46]	RN, CP
Pressure algometer	[47, 48, 50]	n.a.
CO_2 laser-evoked potentials	[35–37]	MSK
Skin biopsy	[41]	n.a.
Unidimensional scales		
VAS / ordinal Scale	[3, 10–12, 24, 28, 30–33, 37, 38, 41, 44, 46, 49, 51–57, 58•]	MSK, RN, CP, D
Numerical rating scale	[29, 36, 59, 60•, 61–63]	MSK, RN, CP, D
Pain catastrophizing Scale	[57]	MSK, RN, CP, D
Multidimensional and pain-specific scales		
PainDETECT	[23]	MSK, RN
Douleur Neuropathique 4	[24, 57]	RN
Neuropathic pain symptom inventory	[46, 57]	RN
McGill Pain Questionnaire	[24, 26, 32]	MSK, RN, D
The Short Form of McGill Pain Questionnaire	[11, 57, 64]	MSK, RN, CP, D
Brief Pain Inventory	[11, 20, 24, 49, 51, 57]	MSK, RN, CP, D
Gracely Box scales	[26]	MSK, D
Leeds Assessment of Neuropathic Symptoms and Signs	[65]	RN
Nonspecific pain scales		
Palliative care assessment	[51]	MSK, RN, CP, D
Medical Outcomes Study 36-Item Short Form	[20]	MSK, RN, CP, D
Nottingham Health Profile subitem related to pain	[66]	MSK, RN, CP, D
Unified Parkinson Disease Rating subitem related to pain	[64, 67]	MSK, RN, CP, D

D dystonic, *CP* central or primary, *MSK* musculoskeletal, *n.a.*, pain type not available or not classified, i.e., studies in which the sensory thresholds were evaluated in pain-free PD patients, *RN* radicular/neuropathic

[a] For all outcome measures, including instrumental evaluations, validity studies in people in PD are not available

[b] Usefulness indicates in which type of pain the measures were used in the listed studies

qualities of pain, including the sensorial and emotional experience. Among the "nonspecific" measures, palliative care assessment, the Medical Outcomes Study 36-Item Short Form, the Nottingham Health Profile, and the Unified Parkinson's Disease Rating Scale, are the most widely used clinical rating scales to characterize PD severity [68].

The existing measures, however, have many limitations. For example, in studies assessing sensory/pain thresholds in PD, cognitive function deficits may influence a patient's performance [69]. In addition, rigidity, tremor, and akinesia promote continuous sensory stimuli, making it difficult for the patient to concentrate during superimposed sensory stimuli, such as a mechanical liminal stimulus or thermal probe [69]. Moreover, according to the definition proposed by the IASP, pain should be considered a multidimensional experience and cannot be summarized into a unidimensional rating [70].

In conclusion, the assessment should involve multidimensional aspects of pain (e.g., sensory and emotional); therefore, multidimensional scales, along with instrumental assessments, are recommended. The mechanisms underlying pain in PD must be understood better than they are currently, because pain has a multifactorial etiology [19] and is a dynamic process that cannot be encapsulated at one time point but must be monitored over time.

Treatment Procedures

In a cross-sectional survey of the prevalence of pain in PD, Beiske et al. [20] found that 50 % of patients with pain received no treatment, either with pharmacotherapy or physiotherapy. The lack of treatment procedures aimed at pain relief is a common finding, suggesting at least two weak points in PD pain management: the lack of specific diagnostic/assessment procedures and the lack of specific multidisciplinary clinical pathways for pain in PD.

To date, most treatment options have focused on pharmacologic approaches. Based on the literature, few attempts have been made to manage painful conditions with nonpharmacologic approaches, the most common of which is deep brain stimulation (DBS) of the subthalamic nucleus (STN). Therefore, we propose an evidence-based algorithm describing the various steps in managing pain in people with PD (Fig. 1).

Pharmacologic Approaches

Evidence-based recommendations for pharmacologic treatment of pain in PD are scarce [71]. The possibility of performing double-blind placebo-controlled studies in this group of patients is reduced by the subjective evaluation of pain and the coexistence of pain with other symptoms of the disease.

Dopaminergic Agents

Because the properties of PD-related pain and certain other types of pain are more common during off periods, a trial optimizing treatment with levodopa and other antiparkinsonian medications should be performed as a first step [69]. A survey by Stacy [72] showed that 45 % of patients reported less pain while in the on-state than the off-state. Similarly, Nebe and Ebersbach [73] reported from their open-label uncrossed study that jejunal infusion of levodopa reduced pain during the on-state.

Although case studies reported analgesic effects of pramipexole, no significant differences in visual analog scale (VAS) pain scores were found between the pramipexole and placebo groups in a double-blind, placebo-controlled trial evaluating the antidepressant effect of this drug [74]. A case report and case series reported that apomorphine was beneficial in treating pelvic and dystonic pain [75, 76]. Finally, the results from the post hoc analysis of the RECOVER (Randomized Evaluation of the 24-h Coverage: Efficacy of Rotigotine) study suggested that pain improved in PD patients who received rotigotine therapy [77]. However, prospective studies are needed to determine whether this effect is secondary to the improvement in motor symptoms.

The effect of levodopa and dopamine agonists on pain might be explained by the potential involvement of the basal ganglia in networks related to pain processing. This hypothesis is supported by the observation that pain tends to occur more frequently during "off" periods [78] and that levodopa normalizes pain perception abnormalities in nigrostriatal degeneration [28, 34].

Analgesics with Systemic Effects

There is no evidence to support the use of any specific analgesic medication in PD. Based on the experience of patients with other advanced diseases, acetaminophen usually is recommended [71]. The use of oxycodone and tramadol is an alternative in patients who do not respond to first-line analgesic treatment. Morphine and codeine might be used, but with caution because of their psychotropic effects [79]. Pregabalin and gabapentin may have a benefit in patients with radicular pain; however, no studies have been performed specifically in patients with PD. Duloxetine was evaluated for the treatment of several types of painful symptoms in PD. Although 65 % of the patients in the study showed varying degrees of benefit, the results need to be analyzed in the context of an uncontrolled open-label trial [80].

Local Treatments

The use of localized treatment for some types of pain in PD may be a reasonable option, especially in patients with musculoskeletal pain. This approach is particularly relevant in patients who have not responded to dopaminergic treatment adjustments or have had no response, poor tolerance, or adverse effects with the use of systemic analgesics. Botulinum toxin (BTX) injections were evaluated for the treatment of dystonic clenched fist in patients with PD and showed moderate benefit [81]. The use of BTX also was described for lateral axial dystonia, in which it decreased pain by improving posture [82, 83•]. It is noteworthy that BTX has demonstrated an analgesic effect not only by reducing muscular hyperactivity (musculoskeletal origin). Recent studies suggest that this neurotoxin might have direct analgesic mechanisms apart from its neuromuscular actions [84]. A double-blind placebo-controlled crossover pilot study is under way to evaluate the utility of BTX type A for treating pain in advanced PD (ClinicalTrials.gov Identifier: NCT02472210).

Nonpharmacologic Approaches

Deep Brain Stimulation

Functional stereotactic surgery is performed mainly to treat motor symptoms, especially in the advanced stages of PD. However, several studies have demonstrated its effects on pain

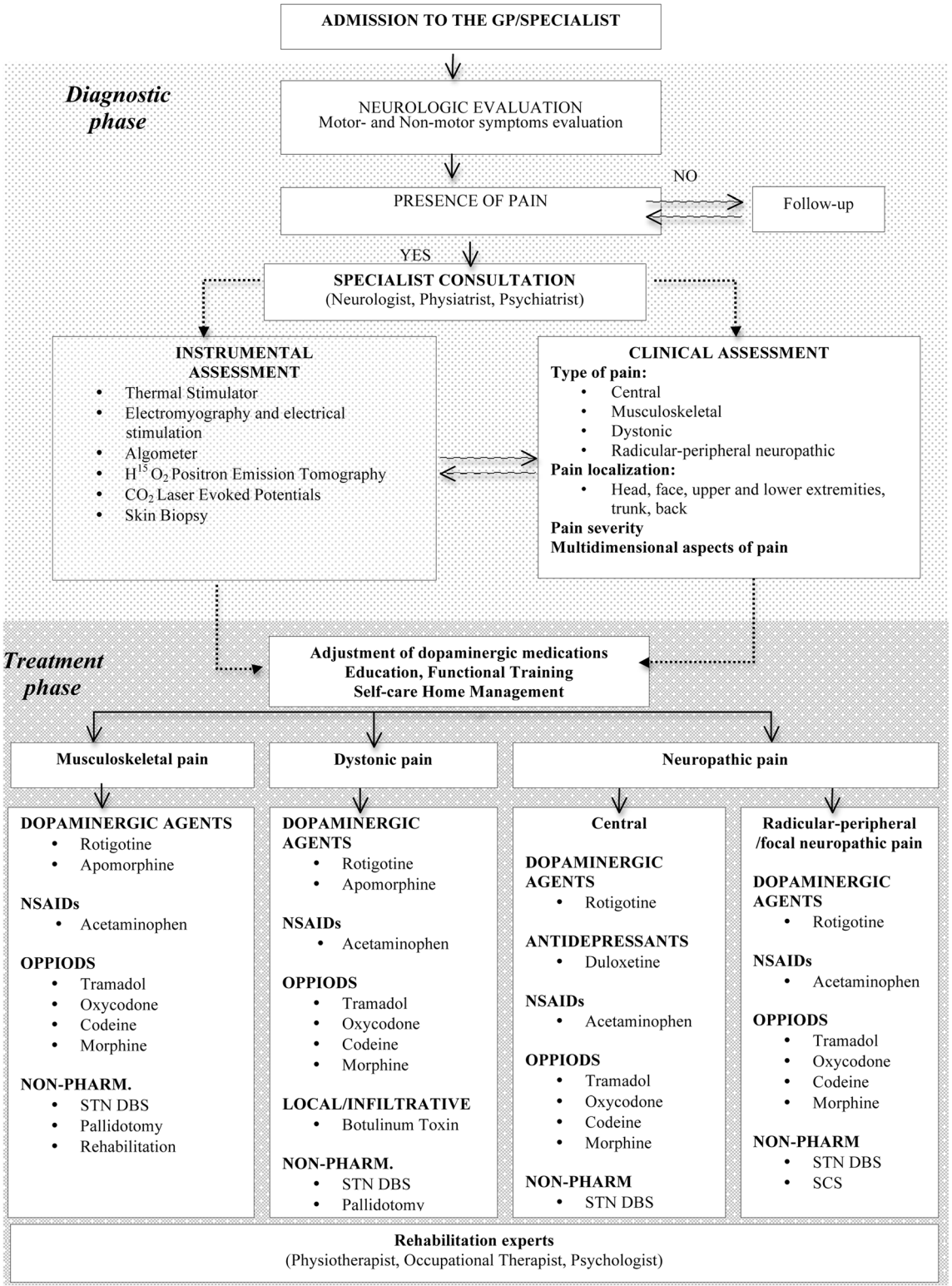

Fig. 1 Evidence-based algorithm describing the various steps in managing pain in PD. *GP* General Practitioner; *Non-pharm* Nonpharmacological Approaches; *STN DBS* Subthalamic Deep Brain Stimulation; *SCS* Spinal Cord Stimulation; *NSAIDs* Nonsteroidal anti-inflammatory drugs

and sensory thresholds. The globus pallidus internus (GPi) [85] or STN is usually the target selected through unilateral or bilateral stimulation in patients in the advanced stages of the disease [86].

STN-DBS may reduce pain in 87 % [63] of patients with PD [57, 59], especially in the off periods [87]. Several types of pain syndromes may be treated with STN-DBS, with dystonic pain being the most responsive at an improvement rate of

100 %. Central pain, neuritic/radicular pain, and musculoskeletal pain were reported to be responsive in 92, 63, and 61 % of patients, respectively. Low back pain was responsive in 14 % of patients [63].

STN-DBS increases the subjective heat pain threshold and reduces pain-induced cerebral activity in the somatosensory cortex. In contrast, PD patients without pain reported no effects [46]. STN-DBS increases the mechanical pain threshold and mechanical pain tolerance [48] and modulates the small fiber-dependent sensory threshold, but has no effect on the vibration detection threshold [24]. It improves the cold and warm detection threshold and thermal sensory limen [23, 88]; however, Spielberger et al. [45] found no statistically significant change in cold and warm detection threshold or cold and heat pain threshold with ON-stim. Studies on the effects of DBS on pain and sensory thresholds are reported in Table 2.

Several studies also reported long-term effects of STN-DBS on pain improvement. Oshima et al. [55] showed a significant reduction in VAS pain score—by 69 % at 6 months and 80 % at 12 months after surgery—in a sample of PD patients with mostly musculoskeletal pain. Pellaprat et al. [64] reported a decrease in pain symptoms 12 months after surgery. Kim and colleagues [60•, 61] reported further improvement at 24 months and 8 years, even if new musculoskeletal and central pain symptoms were measured at follow-up.

Despite the short- and long-term effects of STN-DBS in improving pain, however, a direct correlation between pain relief and motor control was not found [48, 56], suggesting that not all pain syndromes are the result of increased muscle tone or reduced mobility. The peculiar effect of STN-DBS might be on nonmotor pathways, considering its modulatory role in sensory thresholds [23, 24, 46, 88].

With regard to STN-DBS-induced pain relief in PD, three possible mechanisms exist. First, pain relief may decrease the muscle tone induced by musculoskeletal or dystonic pain, in turn leading to further pain reduction [82, 83•]. This mechanism also represents a valid explanation for the effects of dopaminergic medication and pallidotomy.

Second, STN-DBS may decrease pain perception and/or increase pain tolerance. *Pain perception* refers to a sensory-discriminative component of pain, whereas *pain tolerance* pertains to psychological aspects of pain, a complex interaction between affective and cognitive functions [88]. The modulatory effect induced by STN-DBS on the sensory-discriminatory component of pain is hypothesized to be a result of the interaction between the STN and the descending pain inhibitory system [48]. The sensory-discriminative aspect of pain then is integrated at the level of the somatosensory cortices, whereas the related affective aspects are correlated with activity in the insular cortex, anterior cingulate gyrus, and nucleus accumbens [69, 89]. Using a PET study, Dellapina et al. [46] showed that STN-DBS reduces the abnormal somatosensory cortex activation in PD patients with central parkinsonian pain.

Third, improvement in mobility as a result of better motor function might reduce pain in PD. This theory proposes that pain is associated with an adaptation in motor behavior that involves redistribution of activity within and between muscles, as well as changes in mechanical behavior. These mechanisms lead to "protection" from further pain or injury, which involves changes at multiple levels of the motor system. These changes may be complementary, additive, or competitive, with positive short-term benefits but potential long-term consequences due to factors such as increased load, decreased movement, and decreased variability [90].

Ablative Procedures

Pallidotomy is a surgical procedure used to manage dystonia and pain. Laitinen et al. [91] observed a decrease in the percentage of patients reporting dystonia and/or pain—from 63 to 32 %—after this surgery. The long-term effects of pallidotomy on reducing pain were shown in 21 patients with PD-related pain at 6 weeks and 1 year after surgery [62].

Spinal Cord Stimulation

Emerging data suggest that spinal cord stimulation (SCS) of the dorsal column might be an important therapeutic option for treating neuropathic chronic pain conditions in PD. [54, 92] Its pain relief properties may be explained, at least in part, by the gate control theory [93], although evidence shows that the effects of SCS are mediated by a complex interaction among many structures at several levels of the nervous system [92]. The effects of SCS appear to be greatest in patients with chronic pain, especially sympathetic-mediated and neuropathic pain. Clinical experience shows that SCS has no detectable detrimental effect on the nervous system and no side effects at the recommended stimulation levels [92].

Rehabilitation

Two studies evaluated the effects of physical exercise in patients with PD, although pain evaluation was not the primary outcome measure of the research. A single-group, uncontrolled study showed the effects of 12 weeks of exercise on several outcome domains, including pain, in 20 patients with PD. A slight nonsignificant improvement in pain symptoms (8 %) was reported after treatment [66].

A randomized controlled trial included 90 PD patients who were assigned to one of three treatment groups: flexibility and relaxation exercises, walking, or Nordic walking. After 6 months of treatment, the number of patients reporting neck, hip, and iliosacral joint pain decreased. In addition, the walking and Nordic walking groups reported a reduction in pain intensity in the back, hands, and legs compared with the relaxation and flexibility group [52].

Table 2 Summary of evidence for nonpharmacologic procedures for pain management in PD

Author	Type of pain	Body distribution	Treatment	Main findings
Loher et al. 2002 [85]	n.a.	Neck, trunk, upper and lower extremities	GPi-DBS (unilateral, bilateral)	Pain and dysesthesia improved after 3–5 days after surgery and sustained at 1 year of FU
Witjas et al. 2007 [87]	n.a.	n.a.	STN-DBS (bilateral)	Improvement of pain symptoms after 12 months
Kim et al. 2008 [63]	Dystonic, central, neuritic/radicular, musculoskeletal	Head, neck, upper and lower extremities, trunk	STN-DBS (unilateral, bilateral)	Improvement of pain symptoms after 3 months
Gierthmühlen et al. 2010 [23]	Neuropathic, nociceptive	Hands, back, upper and lower extremities, neck	SNT-DBS (bilateral) and levodopa	Improvement of pain symptoms and intensity, and changes in CDT, WDT, and TSL with ON-stim. No influences of SNT-DBS on pain threshold.
Maruo et al. 2011 [88]	–	–	STN-DBS (bilateral)	CDT and WDT were lower with On-Stim. No differences in CPT or HPT.
Spielberger et al. 2011 [45]	n.a.	n.a.	STN-DBS (bilateral) and levodopa	No significant changes in CDT, WDT, CPT, or HPT with ON-stim
Ciampi de Andrade et al. 2012 [24]	Dystonic, musculoskeletal	n.a.	STN-DBS (bilateral)	No changes in MDT, VDT with ON-stim; increased MPT, HPT but CPT decreased with ON-stim; WDT decreased and CDT increased. VAS score in SuH and InC was reduced with ON-stim.
Oshima et al. 2012 [55]	Musculoskeletal, dystonic, somatic PD related, central, neuritic/radicular	Face, neck, upper and lower limb, abdomen, back	STN-DBS (bilateral)	Improvement in pain intensity after 2 weeks post surgery (VAS scale decreased by 75 %), 6 months (by 69 %), and 12 months (by 80 %) with ON-stim
Kim et al. 2012 [61]	Dystonic, musculoskeletal, neuritic/radicular, and central	Head, neck, upper and lower extremities	STN-DBS (unilateral, bilateral)	Improvement in pain symptoms after 3 and 24 months
Wolz et al. 2012 [56]	n.a.	n.a	STN-DBS (bilateral)	No changes in pain with ON-stim
Sürücü et al. 2013 [59]	Dystonic, musculoskeletal, neuritic/radicular, and central	Neck, abdomenl/viscera, arm, leg, lumber spine, multifocal	STN-DBS vs. levodopa	Eight patients with ON-levodopa showed improvement in pain. Greater improvements were observed with ON-stim, with long-lasting effects (41 months).
Dellapina et al. 2012 [46]	Neuropathic, nociceptive	Upper and lower limb, trunk	STN-DBS (bilateral)	Significantly increased HPT, reduced pain and pain-induced cerebral activity in the somatosensory cortex and cerebellum in patients with pain with ON-stim. Stim had no effect in pain-free patients.
Marques et al. 2013 [48]	Central	Upper limb, hand	STN-DBS (bilateral)	MPT and MPTo increased with ON-stim and ON-levodopa, compared with OFF state, condition
Pellaprat et al. 2014 [64]	n.a.	Head, neck, trunk, upper and lower limb	STN-DBS (bilateral)	ON-stim decreased pain symptoms after 12 months (19 patients were pain-free)
Cury et al. 2014 [57]	Musculoskeletal, dystonic, radicular/neuropathic, central	Head, neck, back, upper and lower limb	STN-DBS	Decrease in pain intensity with ON-stim. The highest response was in dystonic pain, followed by musculoskeletal. Central pain and neuropathic pain were not influenced by treatment.
Jung et al. 2015 [60•]	Dystonic, musculoskeletal, neuritic/radicular, central	Head, neck, trunk, upper and lower extremities	STN-DBS (unilateral, bilateral)	Improvement in pain symptoms in 83 % of patients, with long-term effects at 8 years
Honey et al. 1999 [62]	Somatic exacerbated by the PD, musculoskeletal, dystonic, dysesthetic	Upper and lower limbs	Unilateral pallidotomy	Significant reduction in overall pain scores at 6 weeks and 1 year following pallidotomy
Fénelon et al. 2012 [54]	Neuropathic	Lower limb	SCS (T9–T10 level)	Improvement in pain symptoms with ON-stim
Shulman et al. 2002 [67]	n.a.	n.a.	Acupuncture	Improvement in pain symptoms after completing the acupuncture protocol
Rodrigues de Paula et al. 2006 [66]	n.a.	n.a.	Exercise programs	Improvement in pain symptoms after 12-week training program (tendency toward significant values)
Donoyama and Ohkoshi 2012 [53]	Musculoskeletal	Whole body	Traditional Japanese massage	Improvement in pain symptoms after a single massage session (30 min)
Reuter et al. 2011 [52]	n.a.	Neck, arms, hands, back, iliosacral joint, hip, knees, feet, toes	Nordic walking, walking, flexibility exercises	Improvement in pain symptoms after a 6-month training program

CDT cold detection threshold, *CP* chronic pain, *CPT* cold pain threshold, *DBS* deep brain stimulation, *FU* follow-up, *GPi* globus pallidus internus, *HPT* heat pain threshold, *InC* infrathreshold cold stimulation, *MPT* mechanical pain threshold, *MPTo* mechanical pain tolerance, *n.a.* not available, *OFF-levodopa* PD patient in "off" period, *OFF-stim* DBS turned off, *ON-levodopa* PD patient in "on" period, *ON-stim* DBS turned on, *SCS* spinal cord stimulation, *stim* DBS stimulation, *STN* subthalamic nucleus, *SuH* suprathreshold heat stimulation, *TSL* thermal sensory limen, *VDT* vibration detection threshold, *WDT* warm detection threshold

Exercise may influence two primary physiologic processes: pain modulation through dopaminergic and nondopaminergic pain inhibitory pathways and promotion of neuroplasticity and neurorestoration [94]. In addition,

increased mobility may reduce pain by alleviating mechanical contributions to the recurrence and persistence of pain, as previously discussed [90].

Complementary and Alternative Medicine: Traditional Japanese Massage and Acupuncture

Vitamins and herbs, massage therapy, and acupuncture are the most commonly used complementary and alternative therapies in PD. [95] Although no evidence has been reported that vitamins and herbs relieve pain, some data exist regarding massage therapy and acupuncture that suggest their possible complementary role. Donoyama and Ohkoshi [53] showed the effects of traditional Japanese massage therapy on PD symptoms in 10 patients under their care, who reported a significant improvement in pain symptoms after massage. Acupuncture is a procedure in which different anatomic locations on the skin are stimulated by the insertion of small, thin needles that are then manipulated manually or electrically. Although no statistically significant improvement has been observed with this technique, Shulman et al. [67] reported that after acupuncture, 85 % of their patients reported a subjective improvement in PD symptoms, including pain.

Conclusions

This review highlights the many procedures that have been implemented to improve pain diagnosis and assessment in PD patients. In contrast, few studies have focused on specific treatments, particularly with regard to the integration of pharmacologic with nonpharmacologic approaches. These limitations might be overcome by implementing a multidisciplinary approach involving medical specialists from different disciplines (e.g., neurologists, physiatrists, psychiatrists) and rehabilitation experts (e.g., physical and occupational therapists, psychologists). This perspective might allow a comprehensive strategy to address pain in PD, beginning with the diagnosis and continuing to treatment based on the biopsychosocial model of pain [96]. Furthermore, as recommended by an IASP task force, an interdisciplinary approach should be implemented in the same facility, allowing greater coordination among professionals.

Compliance with Ethical Standards

Conflict of Interest Christian Geroin, Marialuisa Gandolfi, Nicola Smania, and Michele Tinazzi declare that they have no conflict of interest.

Veronica Bruno has received an Allergan-sponsored clinical research fellowship (co-investigator study for the use of botulinum toxin for pain in advanced PD).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. Parkinsonism Relat Disord. 2004;10:129–36.
2. Mao CJ, Chen JP, Zhang XY, Liu CF, et al. Parkinson's disease patients with pain suffer from more severe non-motor symptoms. Neurol Sci. 2015;36:263–8.
3. Tinazzi M, Del Vesco C, Fincati E, et al. Pain and motor complications in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77:822–5.
4. Parkinson J. An essay on the shaking palsy. London: Whittingham and Rowland; 1817.
5. Ford B. Pain in Parkinson disease: the hidden epidemic visual rating of atrophy aids diagnostic accuracy. Nat Rev Neurol. 2009;5:242–3.
6. Ha AD, Jankovic J. Pain in Parkinson's disease. Mov Disord. 2012;27:485–91.
7. Toda K, Harada T. Prevalence, classification, and etiology of pain in Parkinson's disease: association between Parkinson's disease and fibromyalgia or chronic widespread pain. Tohoku J Exp Med. 2010;222:1–5.
8. •• Defazio G, Gigante A, Mancino P, Tinazzi M. The epidemiology of pain in Parkinson's disease. J Neural Transm. 2013;120:583–6. **Defazio et al. reviewed the literature on pain epidemiology in PD patients. They showed that pain affects a large population of patients and should be considered a nonmotor symptom. This study shows that different qualities of pain may be present in PD and that there is a variable relationship between pain and motor signs and the response to dopaminergic medications**.
9. Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. Mov Disord. 2012;27:480–4.
10. Defazio G, Berardelli A, Fabbrini G, et al. Pain as a nonmotor symptom of Parkinson disease: evidence from a case-control study. Arch Neurol. 2008;65:1191–4.
11. Nègre-Pagès L, Regragui W, Bouhassira D, Grandjean H, Rascol O, DoPaMiP Study Group. Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. Mov Disord. 2008;23:1361–9.
12. Zambito Marsala S, Tinazzi M, Vitaliani R, et al. Spontaneous pain, pain threshold, and pain tolerance in Parkinson's disease. J Neurol. 2011;258:627–33.
13. Broetz D, Eichner M, Gasser T, Weller M, Steinbach JP. Radicular and nonradicular back pain in Parkinson's disease: a controlled study. Mov Disord. 2007;22:853–6.
14. Vela L, Facca A, Lyons KE, Lieberman AN. Pain and Parkinson's disease. Mov Disord. 2002;17:S154–5.
15. Goetz CG, Tanner CM, Lewy M, et al. Pain in Parkinson's disease. Mov Disord. 1986;1:45–9.
16. McNamara P, Stavitsky K, Harris E, et al. Mood, side of motor symptom onset and pain complaints in Parkinson's disease. Int J Geriatr Psychiatry. 2010;25:519–24.
17. Greenbaum L, Tegeder I, Barhum Y, et al. Contribution of genetic variants to pain susceptibility in Parkinson disease. Eur J Pain. 2012;9:1243–50.
18. Li W, Chen Y, Yin B, Zhang L. Pain in Parkinson's disease associated with COMT gene polymorphisms. Behav Neurol. 2014;2014:304203.

19. Ford B. Pain in Parkinson's disease. Mov Disord. 2010;25:S98–S103.
20. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. Pain. 2009;141:173–7.
21. Ford B. Pain in Parkinson's disease. Clin Neurosci. 1998;5:63–72.
22. Sage JI. Pain in Parkinson's disease. Curr Treat Options Neurol. 2004;6:191–200.
23. Gierthmühlen J, Arning P, Binder A, et al. Influence of deep brain stimulation and levodopa on sensory signs in Parkinson's disease. Mov Disord. 2010;25:1195–202.
24. de Ciampi AD, Lefaucheur JP, Galhardoni R, et al. Subthalamic deep brain stimulation modulates small fiber-dependent sensory thresholds in Parkinson's disease. Pain. 2012;153:1107–13.
25. Granovsky Y, Schlesinger I, Fadel S, Erikh I, Sprecher E, Yarnitsky D. Asymmetric pain processing in Parkinson's disease. Eur J Neurol. 2013;20:1375–82.
26. Lim SY, Farrell MJ, Gibson SJ, Helme RD, Lang AE, Evans AH. Do dyskinesia and pain share common pathophysiological mechanisms in Parkinson's disease? Mov Disord. 2008;23:1689–95.
27. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain. 1995;60:3–38.
28. Gerdelat-Mas A, Simonetta-Moreau M, Thalamas C, et al. Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study. J Neurol Neurosurg Psychiatry. 2007;78:1140–2.
29. Perrotta A, Sandrini G, Serrao M, et al. Facilitated temporal summation of pain at spinal level in Parkinson's disease. Mov Disord. 2011;26:442–8.
30. Mylius V, Engau I, Teepker M, et al. Pain sensitivity and descending inhibition of pain in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2009;80:24–8.
31. Brefel-Courbon C, Payoux P, Thalama C, et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. Mov Disord. 2005;20:1557–63.
32. Brefel-Courbon C, Ory-Magne F, Thalamas C, Payoux P, Rascol O. Nociceptive brain activation in patients with neuropathic pain related to Parkinson's disease. Parkinsonism Relat Disord. 2013;19:548–52.
33. Djaldetti R, Shifrin A, Rogowski Z, Sprecher E, Melamed E, Yarnitsky D. Quantitative measurement of pain sensation in patients with Parkinson disease. Neurology. 2004;62:2171–5.
34. Schestatsky P, Kumru H, Valls-Sole J, et al. Neurophysiologic study of central pain in patients with Parkinson disease. Neurology. 2007;69:2162–9.
35. Tinazzi M, Del Vesco C, Defazio G, et al. Abnormal processing of the nociceptive input in Parkinson's disease: a study with CO2 laser evoked potentials. Pain. 2008;136:117–24.
36. Tinazzi M, Recchia S, Simonetto S, et al. Hyperalgesia and laser evoked potentials alterations in hemiparkinson: evidence for an abnormal nociceptive processing. J Neurol Sci. 2009;276:153–8.
37. Tinazzi M, Recchia S, Simonetto S, et al. Muscular pain in Parkinson's disease and nociceptive processing assessed with CO2 laser-evoked potentials. Mov Disord. 2010;25:213–20.
38. Mylius V, Brebbermann J, Dohmann H, Engau I, Oertel WH, Möller JC. Pain sensitivity and clinical progression in Parkinson's disease. Mov Disord. 2011;26:2220–5.
39. Conte A, Khan N, Defazio G, Rothwell JC, Berardelli A. Pathophysiology of somatosensory abnormalities in Parkinson disease. Nat Rev Neurol. 2013;9:687–97.
40. Reichling DB, Levine JD. Pain and death: neurodegenerative disease mechanisms in the nociceptor. Ann Neurol. 2011;69:13–21.
41. Nolano M, Provitera V, Estraneo A, et al. Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. Brain. 2008;131:1903–11.
42. Kanda T, Tsukagoshi H, Oda M, Miyamoto K, Tanabe H. Changes of unmyelinated nerve fibers in sural nerve in amyotrophic lateral sclerosis, Parkinson's disease and multiple system atrophy. Acta Neuropathol. 1996;91:145–54.
43. Dellapina E, Gerdelat-Mas A, Ory-Magne F, et al. Apomorphine effect on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. Mov Disord. 2011;26:153–7.
44. Nandhagopal R, Troiano AR, Mak E, Schulzer M, Bushnell MC, Stoessl AJ. Response to heat pain stimulation in idiopathic Parkinson's disease. Pain Med. 2010;11:834–40.
45. Spielberger S, Wolf E, Kress M, Seppi K, Poewe W. The influence of deep brain stimulation on pain perception in Parkinson's disease. Mov Disord. 2011;26:1367–8.
46. Dellapina E, Ory-Magne F, Regragui W, et al. Effect of subthalamic deep brain stimulation on pain in Parkinson's disease. Pain. 2012;153:2267–73.
47. Vela L, Cano-de-la-Cuerda R, Fil A, Muñoz-Hellín E, Ortíz-Gutiérrez R, Macías-Macías Y, et al. Thermal and mechanical pain thresholds in patients with fluctuating Parkinson's disease. Parkinsonism Relat Disord. 2012;18:953–7.
48. Marques A, Chassin O, Morand D, et al. Central pain modulation after subthalamic nucleus stimulation: a crossover randomized trial. Neurology. 2013;81:633–40.
49. Chen Y, Mao CJ, Li SJ, et al. Quantitative and fiber-selective evaluation of pain and sensory dysfunction in patients with Parkinson's disease. Parkinsonism Relat Disord. 2015;21:361–5.
50. Vela L, Lyons KE, Singer C, Lieberman AN. Pain-pressure threshold in patients with Parkinson's disease with and without dyskinesia. Parkinsonism Relat Disord. 2007;13:189–92.
51. Lee MA, Walker RW, Hildreth TJ, Prentice WM. A survey of pain in idiopathic Parkinson's disease. J Pain Symptom Manag. 2006;32:462–9.
52. Reuter I, Mehnert S, Leone P, Kaps M, Oechsner M, Engelhardt M. Effects of a flexibility and relaxation programme, walking, and nordic walking on Parkinson's disease. J Aging Res. 2011;2011, 232473.
53. Donoyama N, Ohkoshi N. Effects of traditional Japanese massage therapy on various symptoms in patients with Parkinson's disease: a case-series study. J Altern Complement Med. 2012;18:294–9.
54. Fénelon G, Goujon C, Gurruchaga JM, et al. Spinal cord stimulation for chronic pain improved motor function in a patient with Parkinson's disease. Parkinsonism Relat Disord. 2012;18:213–4.
55. Oshima H, Katayama Y, Morishita T, et al. Subthalamic nucleus stimulation for attenuation of pain related to Parkinson disease. J Neurosurg. 2012;116:99–106.
56. Wolz M, Hauschild J, Koy J, et al. Immediate effects of deep brain stimulation of the subthalamic nucleus on nonmotor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2012;18:994–7.
57. Cury RG, Galhardoni R, Fonoff ET, et al. Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. Neurology. 2014;83:1403–9.
58.• Kim YE, Lee WW, Yun JY, Yang HJ, Kim HJ, Jeon BS. Musculoskeletal problems in Parkinson's disease: neglected issues. Parkinsonism Relat Disord. 2013;19:666–9. **Kim et al. identified the prevalence and clinical features of musculoskeletal problems in patients with PD in their study enrolling 400 PD patients and 138 age- and sex-matched controls. They found a significantly greater prevalence of musculoskeletal problems in the PD group than in the control group (66.3% vs. 45.7%). The body parts commonly involved were the low back, knees, and shoulders. This study highlights the importance of evaluating musculoskeletal problems in people with PD**.
59. Sürücü O, Baumann-Vogel H, Uhl M, Imbach LL, Baumann CR. Subthalamic deep brain stimulation versus best medical therapy for L-dopa responsive pain in Parkinson's disease. Pain. 2013;154:1477–9.
60.• Jung YJ, Kim HJ, Jeon BS, Park H, Lee WW, Paek SH. An 8-year follow-up on the effect of subthalamic nucleus deep brain stimulation on pain in Parkinson disease. JAMA Neurol. 2015;72:504–10. **Jung et al. evaluated the long-term effects of STN-DBS in patients with PD**

and pain. This study demonstrated that STN-DBS can improve pain and that the effects persist after 8 years of follow-up.

61. Kim HJ, Jeon BS, Lee JY, Paek SH, Kim DG. The benefit of subthalamic deep brain stimulation for pain in Parkinson disease: a 2-year follow-up study. Neurosurgery. 2012;70:18–23.
62. Honey CR, Stoessl AJ, Tsui JK, Schulzer M, Calne DB. Unilateral Pallidotomy for reduction of parkinsonian pain. J Neurosurg. 1999;91:198–201.
63. Kim HJ, Paek SH, Kim JY, et al. Chronic subthalamic deep brain stimulation improves pain in Parkinson disease. J Neurol. 2008;255:1889–94.
64. Pellaprat J, Ory-Magne F, Canivet C, et al. Deep brain stimulation of the subthalamic nucleus improves pain in Parkinson's disease. Parkinsonism Relat Disord. 2014;20:662–4.
65. Hanagasi HA, Akat S, Gurvit H, Yazici J, Emre M. Pain is common in Parkinson's disease. Clin Neurol Neurosurg. 2011;113:11–3.
66. de Rodrigues PF, Teixeira-Salmela LF, de Coelho MFCD, de Rocha BP, Cardoso F. Impact of an exercise program on physical, emotional, and social aspects of quality of life of individuals with Parkinson's disease. Mov Disord. 2006;21:1073–7.
67. Shulman LM, Wen X, Weiner WJ, et al. Acupuncture therapy for the symptoms of Parkinson's disease. Mov Disord. 2002;17:799–802.
68. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society UPDRS Revision Task force. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129–70.
69. Cury RG, Galhardoni R, Fonoff ET, et al. Sensory abnormalities and pain in Parkinson disease and its modulation by treatment of motor symptoms. Eur J Pain. 2015.
70. Clark WC, Yang JC, Tsui SL, Ng KF, Bennett CS. Unidimensional pain rating scales: a multidimensional affect and pain survey (MAPS) analysis of what they really measure. Pain. 2002;98:241–7.
71. Perez-Lloret S, Rey MV, Dellapina E, Pellaprat J, Brefel-Courbon C, Rascol O. Emerging analgesic drugs for Parkinson's disease. Expert Opin Emerg Drugs. 2012;17:157–71.
72. Stacy M. The wearing-off phenomenon and the use of questionnaires to facilitate its recognition in Parkinson's disease. J Neural Transm. 2010;117:837–46.
73. Nebe A, Ebersbach G. Pain intensity on and off levodopa in patients with Parkinson's disease. Mov Disord. 2009;24:1233–7.
74. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010;9:573–80.
75. Factor SA, Brown DL, Molho ES. Subcutaneous apomorphine injections as a treatment for intractable pain in Parkinson's disease. Mov Disord. 2000;15:167–9.
76. Frankel JP, Lees AJ, Kempster PA, et al. Subcutaneous apomorphine in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1990;53:96–101.
77. Kassubek J, Chaudhuri KR, Zesiewicz T, et al. Rotigotine transdermal system and evaluation of pain inpatients with Parkinson's disease: a post hoc analysis of the RECOVER study. BMC Neurol. 2014;14–42.
78. Juri C, Rodriguez-Oroz M, Obeso JA. The pathophysiological basis of sensory disturbances in Parkinson's disease. J Neurol Sci. 2010;289:60–5.
79. Ghoche R. The conceptual framework of palliative care applied to advanced Parkinson's disease. Parkinsonism Relat Disord. 2012;18:S2–5.
80. Djaldetti R, Yust-Katz S, Kolianov V, Melamed E, Dabby R. The effect of duloxetine on primary pain symptoms in Parkinson disease. Clin Neuropharmacol. 2007;30:201–5.
81. Cordivari C, Misra VP, Catania S, Lees AJ. Treatment of dystonic clenched fist with botulinum toxin. Mov Disord. 2001;16:907–13.
82. Bonanni L, Thomas A, Varanese S, Scorrano V, Onofrj M. Botulinum toxin treatment of lateral axial dystonia in Parkinsonism. Mov Disord. 2007;22:2097–103.
83.• Tassorelli C, De Icco R, Alfonsi E, et al. Botulinum toxin type A potentiates the effect of neuromotor rehabilitation of Pisa syndrome in Parkinson disease: a placebo controlled study. Parkinsonism Relat Disord. 2014;20:1140–4. **Tassorelli et al. evaluated the effects of BTX type A in reducing hyperactive trunk muscles and enhancing the rehabilitation intervention. Their preliminary data suggest that BTX type A in conjunction with a rehabilitation program may improve axial posture and trunk mobility, as well as pain symptoms. This study highlights the importance of an integrated approach to managing motor and nonmotor symptoms in PD patients**.
84. Sim WS. Application of botulinum toxin in pain management. Korean J Pain. 2011;24:1–6.
85. Loher TJ, Burgunder JM, Weber S, Sommerhalder R, Krauss JK. Effect of chronic pallidal deep brain stimulation on off period dystonia and sensory symptoms in advanced Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002;73:395–9.
86. Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med. 2001;345:956–63.
87. Witjas T, Kaphan E, Régis J, et al. Effects of chronic subthalamic stimulation on nonmotor fluctuations in Parkinson's disease. Mov Disord. 2007;22:1729–34.
88. Maruo T, Saitoh Y, Hosomi K, et al. Deep brain stimulation of the subthalamic nucleus improves temperature sensation in patients with Parkinson's disease. Pain. 2011;152:860–5.
89. Ogino Y, Nemoto H, Inui K, Saito S, Kakigi R, Goto F. Inner experience of pain: imagination of pain while viewing images showing painful events forms subjective pain representation in human brain. Cereb Cortex. 2007;17:1139–46.
90. Hodges PW. Pain and motor control: from the laboratory to rehabilitation. J Electromyogr Kinesiol. 2011;21:220–8.
91. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg. 1992;76:53–61.
92. Oakley JC, Prager JP. Spinal cord stimulation: mechanisms of action. Spine (Phila Pa 1976). 2002;27:2574–83.
93. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
94. Allen NE, Moloney N, van Vliet V, Canning CG. The rationale for exercise in the management of pain in Parkinson's disease. J Parkinsons Dis. 2015.
95. Rajendran PR, Thompson RE, Reich SG. The use of alternative therapies by patients with Parkinson's disease. Neurology. 2001;57:790–4.
96. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. Am Psychol. 2014;69:119–30.