Clinical Parkinsonism & Related Disorders 2 (2020) 1–8

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.elsevier.com/locate/prdoa

An overview of pain in Parkinson's disease

Yi-Cheng Tai [a], Chin-Hsien Lin [b,*]

[a] Department of Neurology, E-DA Hospital, Kaohsiung, Taiwan
[b] Department of Neurology, National Taiwan University, College of Medicine, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 29 June 2019
Received in revised form 20 October 2019
Accepted 25 November 2019
Available online 28 November 2019

Keywords:
Pain
Parkinson's disease
Review

ABSTRACT

Pain is a common non-motor symptom of Parkinson's disease (PD) and the prevalence of pain among PD patients varies because of the disease stage, co-morbidities, and evaluating tools. Risk factors for pain in PD include an early age of onset, long disease duration, motor complications, concomitant depressive symptoms, female gender, and associated medical conditions. In patients with PD, pain can be classified as musculoskeletal pain, chronic body pain (central or visceral), fluctuation-related pain, nocturnal pain, orofacial pain, pain with discolouration/oedema/swelling, and radicular/neuropathic pain; musculoskeletal pain as the most common type. Potential underlying mechanisms include a disruption of peripheral nociception and alterations in central pain threshold/processing. Genetic polymorphisms in genes that confer pain susceptibility might also play a role in the occurrence of pain in PD. In advanced stage of patients with PD, polyneuropathy could occur in patients using high dosage of levodopa. Pain often correlates to other non-motor symptoms of PD, including depression, sleep, and autonomic symptoms. Dopaminergic drugs, non-dopaminergic medications, botulinum toxin, deep brain stimulation, and physiotherapy have shown some benefits for certain types of PD-related pain. An increased awareness of pain as a common non-motor symptom of PD provides further insights into sensory system dysregulation in this disease. In this review, we aim to summarizes the clinical features of pain in patients with PD and emphasize the latest evidence of pain related to levodopa treatment.

1. Introduction

Pain is a common non-motor symptom in Parkinson's disease (PD), and it is increasingly attracting attention. The characteristics of pain in PD are heterogeneous, both in quality and in its distribution over the body [1]. Depending on the type of pain, the study design, and possibly the race [2], pain prevalence ranges from 24% to over 85% [3–6]. About half of patients with PD have reported moderate to severe pain during the disease course [5,7]. Patients with PD have shown significantly higher pain severity scores than age- and gender-matched controls [8]. Moreover, patients who report pain symptoms were also significantly more likely to report depression and a reduced quality of life [9].

Most PD-related pain is secondary to motor disability (e.g., musculoskeletal or dystonic pain); however, as many as 40% of patients with PD experience “primary pain” in the early stages of PD, before motor symptoms have become prominent [10]. In addition, pain symptoms might predate the onset of motor features by years [10]. Because pain is a common non-motor feature of PD, a thorough understanding related to relevant clinical manifestations, risk factors, potential pathogenic mechanisms, and treatment of pain in patients with PD is needed. The present review summarizes the clinical features of pain in patients with PD. We also emphasize the updated evidence of neuropathy related to chronic levodopa treatment and the managements of pain in PD.

2. Tools for evaluating pain

Pain is analysed in terms of its characteristics, frequency, severity, and interference [8]. The characters of pain can be described as radiating, aching, dull, tension, sharp, boring, penetrating, shooting, throbbing, burning, stabbing, cramping, paresthetic, and akathisia [11]. Several tools are available for evaluating pain in PD, including the visual analogue scale, McGill pain questionnaire [12], and King's PD Pain Scale [10]. Among these pain questionnaires and scales, the King's PD Pain Scale is easy to administer, requiring the investigator to ask the patient questions related to pain and to score both severity and frequency of PD pain [13]. This scale includes questions related to seven domains, including musculoskeletal pain, chronic neuropathic pain, motor fluctuation-related pain, nocturnal pain (such as pain related to restless legs syndrome), orofacial pain, limbs edema/swelling related pain and radicular pain. Each domain is scored by severity (0, none to 3, very severe) multiplied by frequency

* Corresponding author at: No. 7, Chung-Shan South Road, Department of Neurology, National Taiwan University Hospital, Taipei 100, Taiwan.
E-mail address: chlin@ntu.edu.tw. (C.-H. Lin).

http://dx.doi.org/10.1016/j.prdoa.2019.11.004

(0, never to 4, all the time), which results in a sub-score of 0 to12 and sums up to the total score with a theoretical range from 0 to 168. Data from seven domains provide clinicians further information on different types of PD pain, which could be broadly classified as nociceptive and neuropathic patterns. Furthermore, the scale could also capture the information about wearing off-related pain, central, orofacial, and radicular pain.

3. Classification of pain in PD

There is still a lack of consensus regarding the assessment and classification of pain in PD patients. As data regarding the frequency and characteristics of pain in patients with PD has emerged in the past decade (summarized in Table 1), some classification systems of PD-related pain have been proposed. Ford's classification is the most commonly used classification system in clinical practice [14], and it classifies PD pain into the following categories: musculoskeletal pain, radicular/neuropathic pain, dystonia-related pain, akathisia discomfort and central pain. Recently, classifications based on King's Parkinson's Disease Pain Scale were also wildly used [10] and pain was categorized into seven domains as we previously mentioned [13]. Some studies include other painful symptoms, such as oral/genital pain and burning mouth/vaginal syndrome [3,4]. In an Ethiopian study, orofacial pain was categorized as pain when chewing, nocturnal teeth grinding pain, and burning mouth syndrome [15]. Pain around the joints and pain while turning in bed are the most prevalent types; in contrast, burning mouth syndrome and pain due to grinding teeth occur at the lowest frequency. In a study that applied King's PD pain scale [16], the types of pain varied in different countries and ethnicities. For example, in a Pakistani study, non-musculoskeletal pain was reported by 30% of patients [2]; in an Ethiopian study, up to 68% of patients reported musculoskeletal pain [15].

3.1. Musculoskeletal pain

Musculoskeletal pain is the most common type of pain in patients with PD [7,17], arising from muscular, joint and postural aetiologies, including muscle cramps. The prevalence of musculoskeletal pain ranges from 40% to 75% in those patients with PD experiencing pain [10,18–21]. This prevalence rate of pain is much higher in PD patients than that reported in the general population (10%–25%) [18] (Table 1). Musculoskeletal problems are more common in patients with PD than in elderly without PD. PD-related musculoskeletal pain is associated with truncal deformities, such as kyphoscoliosis, camptocormia, Pisa syndrome, dropped head syndrome, bone mineralization disorders (e.g., osteoporosis and bone fractures), and joint disorders, including frozen shoulder, dystonic joints, and joint pain [22]. Musculoskeletal pain can be further classified as spinal-paravertebral pain, joint pain, and lower back pain. Spinal-paravertebral pain is the dominant form of pain [23]. Patients with musculoskeletal pain have reported worse health-related quality of life compared to patients without pain complaints [24].

Patients with PD that have co-morbid osteoarthritis reported specific pain characteristics. They were more likely to have paraesthesia- and akathisia-related pain, and less likely to have aching pain, compared to patients with PD without osteoarthritis [25]. Patients with PD might also display increased thoracic kyphosis and decreased truncal mobility, which can lead to humeral-acromial impingement syndrome and capsulitis. These disorders cause inflammation of the bursa, shoulder pain, and

Table 1
Prevalence and classification of pain in patients with PD in the literature.

Author, year	Number of participants	Prevalence of pain	Classification and rate of pain (n, %)
Snider et al., 1976 [18]	101 PD patients 149 non-PD subjects	PD patients (40%) Non-PD participants (8%)	Central pain (PD vs non-PD: 11 vs. 0)_ Burning (PD vs non-PD: 22 vs. 3) Tingling (PD vs non-PD: 21 vs. 1) Numbness (PD vs non-PD: 29 vs. 3)
Goetz et al., 1986 [19]	93 PD patients No controls	PD patients (45%)	Musculoskeletal pain (32, 74%) Dystonic pain (12, 28%) Radicular pain (6, 14%) Akathisia (1, 2%) Thalamic pain (0)
Scott et al., 2000 [95]	93 PD patients No controls	PD patients (41–54%)	Neck pain (Male vs. Female: 54% vs. 45%) Back pain (Male vs. Female: 48% vs. 41%) Muscle cramps (Male vs. Female: 45% vs. 41%)
Tinazzi et al., 2006 [20]	117 PD patients No controls	PD patients (40%)	Musculoskeletal pain (21%) Dystonic pain (8%) Central primary pain (40%) Akathisia (4%)
Negre-Pages et al. 2008 [98]	450 PD patients 98 controls	PD patients with chronic pain (62%) PD patients with non-chronic pain (6%) Controls (58%)	Dystonic pain (36%) Neuropathic pain (7%) Akathisia (5%) Musculoskeletal (2%) Non-PD pain (31%)
Defazio et al., 2008 [99]	402 PD patients 317 controls	PD patients (70%) Controls (63%)	Dystonic pain (7%) Musculoskeletal pain (25%) Peripheral neuropathic pain (5%) Central neuropathic pain (4%)
Beiske et al., 2009 [30]	176 PD patients No controls	PD patients (83%)	Musculoskeletal pain (70%) Radicular/neuropathic pain (20%) Dystonic pain (40%) Central pain (10%)
Hanagasi et al., 2011 [100]	176 PD patients No controls	PD patients (65%)	Musculoskeletal pain (44%) Radicular or neuropathic pain (11%) Dystonic pain (19%) Central pain (13%)
Zambito Marsala et al., 2011 [96]	106 PD patients 51 controls	PD patients (62%)	N.A.
Allen et al. 2016 [97]	176 PD patients No controls	PD patients (81%)	N.A.
Fu et al., 2018 [7]	144 PD patients No controls	PD patients (52%)	N.A.

PD, Parkinson's disease; N.A. not available.

reduced movement [26]. Frozen shoulder is peri-arthritis or adhesive capsulitis, with a spontaneous onset of pain and a gradual restriction in the range of motion. It can appear within 1 or 2 years before the onset of motor features; thus, it can be considered a pre-motor feature of PD [27].

Over 50% of patients with PD report lower back pain, which is often classified as chronic pain [28]. Lower back pain can be caused by muscular imbalances inherent to a movement disorder and by skeletal degeneration. Other types of lower back pain also exist; for example, radicular, dystonic, akathisia-related, or central pain [13]. Risk factors for lower back pain include older age, higher depression score, and PD-related factors, including rigidity and poor posture [29]. Patients with PD that have lower back pain have longer disease durations and higher pain intensities, compared to those without pain. Pain intensity and disability scores are associated with advanced PD stages and higher motor scores, assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) [28].

3.2. Radicular pain

The second next most common type is radicular pain [6,24]. The prevalence of radicular pain in either arms or legs in patients with PD ranges from 5% to 20% [6,18–21,24,30] (Table 1). The symptom of pain may manifest with numbness or weakness in the territory of a nerve root. Truncal abnormalities, co-morbid cervical or lumbar radiculopathies, which may develop during the disease course, can lead to this type of pain [31].

3.3. Dystonic pain

Painful dystonia develops in approximately one-third of patients with PD that receive long-term levodopa treatments [32]. Previous studies have shown that the prevalence of dystonia-related pain ranges from 8% to 50% in patients with PD [10,18–21,24,30–32] (Table 1). There are various clinical features of foot dystonia, ranging from simple forms, such as inversion or hallux extension, to complex forms, with combinations of inversion, plantar and toe flexion, intra-rotation, and dorsal and hallux extension. These pains typically occur in the morning, before the first dose of levodopa, or even during medicated periods. Foot and toe dystonia are very painful and cause walking difficulties [33].

3.4. Polyneuropathy and neuropathic pain

The prevalence of peripheral neuropathy in patients with PD ranges from 37.8 to 55% [34,35], which is greater than that among age-matched controls [40]. Patients with PD have a high prevalence of symmetrical neuropathy, predominantly in sensory axons [36]. The risk of polyneuropathy has been reported to be increased in patients taking high doses of levodopa [37,38]. Kaur et al. described a patient with pre-existing polyneuropathy that developed acute neuropathic pain, related to a treatment of levodopa-carbidopa intestinal gel (LCIG) infusion [39]. Unlike oral levodopa treatments, LCIGs are administered in the lower duodenal tract, where Vitamin B12 is absorbed [40]. In the LCIG group, the degree of neuropathic change was correlated with the amount of weight lost since therapy initiation and with the drug dose [39]. Previous literature including a long-term follow-up (24.36 ± 12.18 months) study in patients receiving LCIG showed that subacute, chronic, and subclinical polyneuropathy ultimately developed while patients were assessed by electrophysiology [40,41].

Patients with LCIG-related polyneuropathy typically respond well to vitamin B12 replacement therapy, without ceasing LCIG treatment [40,41]. It might be advisable to consider vitamin B12 supplementation in patients with PD that require duodenal levodopa infusion therapy.

Therefore, it is suggested that in patients with PD receiving high levodopa doses, pain should be evaluated with quantitative sensory testing, a sympathetic skin response test, and a conventional nerve conduction study to identify the possible levodopa related polyneuropathy.

3.5. Orofacial pain

Orofacial pain is an anatomical classification of pain in patients with PD. Orofacial pain includes pain when chewing, nocturnal teeth grinding pain, and burning mouth syndrome. Pain when chewing is thought to be secondary to temporomandibular joint (TMJ) disorders [42]. The TMJ is innervated by the auriculotemporal nerve, a branch of the mandibular nerve (the largest branch of the trigeminal nerve), which showed pathology in PD. Nocturnal teeth grinding pain can be classified as a musculoskeletal pain in the TMJ joint. PD has been associated with a higher rate of bruxism in patients, either asleep or awake [43]. Burning mouth syndrome is characterized by a painful, intraoral burning sensation, without physical or laboratory correlates. Its prevalence in PD varies from 4% to 24% [44,45]. One case report stated that pramipexole was effective in relieving symptoms [46], but the actual role of dopaminergic medication remains an issue of debate [47].

4. Pain in different stages of PD

4.1. Pain in early PD stages

We defined two stages of PD, according to Hoehn and Yahr stages I-V. Early-stage PD was defined as stages I to III and advanced PD as stages IV and V. In early-stage PD, motor impairment and disease duration were not related to pain severity [2]. Disrupted nociceptive and aberrant processing associated with central and peripheral deafferentation was observed in early-stage PD patients [48]. Pain severity was correlated with affective symptoms, autonomic symptoms, motor complications, female gender, and young age [5]. It remains uncertain whether nociceptive processing is dysfunctional in early-stage PD, when motor symptoms are not prominent. A previous review has highlighted the evidence for disrupted nociceptive processing in patients with early-stage PD [48]. It was hypothesized that aberrant pain processing in early PD was associated with both central and peripheral deafferentation. Furthermore, the development of Lewy body pathology in non-dopaminergic areas of the brainstem contribute to the clinical features of pain in early-stage PD.

4.2. Pain in advanced PD stages

Pain is more common in advanced PD stages. Patients that had PD for more than 5 years reported a 35% higher incidence of pain compared to those with early-stage disease [49]. Moreover, characteristics of pain differ between patients with advanced and early stages of PD. Studies in patients with advanced-stage PD have shown conflicting results. Fu et al. reported a lower frequency of neuropathic pain but a higher frequency of central pain in patients with advanced-stage of PD compared to those with early-stage PD [7]. Fabbri et al. found that pain symptoms in advanced stages did not respond to dopaminergic treatment [49]. Grofik et al. demonstrated that the prevalence of polyneuropathy increased with either longer levodopa treatment durations or advanced disease stages. Among patients with advanced-stage PD, secondary disorders are common, including radicular compression, musculoskeletal deformities and contractures, cramps, dysesthesia, and frozen shoulder [50,51]; these disorders might play an important role in the source of pain.

5. Risk factors for pain in PD

5.1. Clinical risk factors

Clinical risk factors for pain in PD include the female sex [17], an early age of onset [6,21], a long disease duration, motor complications, depressive symptoms, and comorbidities (e.g., diabetes mellitus, osteoporosis, rheumatic disease, degenerative joint disease, arthritis, and disc herniation) [1]. Among these clinical risk factors, the evidence of age in pain of PD is controversial and the results are conflicting [19]. While considering the mean age of PD patients with pain, an increase in the prevalence of

musculoskeletal pain due to combined joint problems and degenerative changes elsewhere in the body would seem to be expected. However, studies have shown that dystonia-related pain was observed at earlier ages. It is noteworthy that age has not systematically been considered in all studies and different age groups may contribute to specific type of pain.

5.2. Depression and other non-motor symptoms in PD

Pain is closely related to other non-motor symptoms, including depression, fatigue, daytime sleepiness, and sleep disorders [17]. Patients with PD that displayed depressive symptoms had significantly higher pain severity and pain interference scores than controls without depressive symptoms [8].

Cognitive dysfunction, evaluated with the Mini-Mental State Examination (MMSE), was not correlated with pain in PD [7]. Nevertheless, in another study, the non-motor symptoms scale showed a correlation between pain and attention/memory [17]; however, in that study, patients with PD were excluded when their MMSE scores were below 24. Interestingly, like other non-motor symptoms, pain is also present in secondary parkinsonism, which is defined as PD that does not respond to levodopa or to the more persistent effects of dopamine substitution treatment. However, pain is more prevalent among patients with PD than among those with secondary parkinsonism [23].

Other non-motor symptoms, like sleep and autonomic symptoms, have shown similar associations. Patients with PD that experienced poor sleep quality displayed higher pain severity scores and higher severity for depression and anxiety. Patients with poor sleep quality characterized pain mainly as radiating, paraesthesia-, and akathisia-related [11]. Compared to patients with PD without pain, those with pain displayed longer sleep latencies, shorter total sleep times, less time in the rapid eye movement stage of sleep, more wakefulness after sleep onset, and poor sleep efficiency. Among patients with PD, sleep architecture also differs in PD patients with and without pain; polysomnography showed that those with pain showed more light sleep (N1) and less deep sleep (N2 and slow-wave sleep) than those without pain [11]. Interestingly, restless leg syndrome was not significantly correlated with depression, anxiety, or pain [11,52].

6. Mechanisms of pain in PD

We broadly classified pain mechanisms into central and peripheral mechanisms. Central causes include a lower pain threshold, altered pain processing, and motor/non-motor fluctuations. Peripheral causes include altered inflammatory signals and levodopa-induced Vitamin B12 deficiency.

6.1. Central mechanisms

In recent years, a growing number of neurophysiological and neuroimaging studies have investigated cerebral responses to pain in patients with early PD. The pain threshold was lower in patients with PD than in healthy controls, and the administration of levodopa significantly raised the pain threshold in PD, but not in controls [53]. Thompson et al. found “pain hypersensitivity” in patients with PD [54]. Tyanzi et al. showed that, accompanied by a marginally reduced heat pain threshold to painful laser stimulation, amplitudes of laser-evoked potentials were also decreased in mild pain-free hemi-parkinsonism patients [55]. The same group examined drug-naïve early-stage PD patients and observed that the decrease in amplitude of laser-evoked potentials occurred in the affected side but not in the unaffected side of PD motor symptoms [56]. Compatible with these findings, our group previously used a contact heat stimulator to record the reduction in amplitude of evoked potentials in a group of PD patients, including those with early-stage PD [57]. These findings are in line with one recent meta-analysis which demonstrated that PD patients are more sensitive to noxious stimuli compared to healthy controls across all sensory modalities when tested in the off-medication state [58].

With laser-evoked potentials, Zambito-Marsala et al. found that pain-free patients with PD had comparable N1, N2, and P2 latencies, but significantly lower N2/P2 amplitudes, compared to controls, regardless of the clinically affected side. Furthermore, Suppa et al. applied transcranial magnetic stimulation in a laser-paired associative stimulation design and found reduced responses in patients with PD, with or without pain, off or on dopaminergic therapy, compared to controls. Those findings suggested that chronic pain in PD was related to abnormal pain-motor integration [61]. They showed that an altered central pain processing mechanism contributed to symptoms of pain in PD.

With functional MRI, Tessitore et al. found that pain processing pathways were functionally re-modulated in drug-naïve patients with PD, even in the absence of clinically overt pain symptoms [59]. This mechanism became more dysfunctional over time. Positron emission tomography revealed abnormalities in sensory discriminative processing and affective motivational processing of pain [60].

The dopaminergic system might be involved in pain modulation, probably through various cortical connections to the basal ganglion, including the limbic system and the sensory cortex [62]. Schestatsky et al. found that cortical processing of nociceptive stimuli was increased during unmedicated periods in patients with PD that had primary central pain, compared to those without pain or controls. However, cortical processing returned to normal during medicated periods (on state) [63]. Pain in PD was also strongly associated with motor fluctuations and dyskinesias, similar to fluctuation-related pain and musculoskeletal pain [51]. Moreover, the severity of pain was significantly correlated with the severity of motor complications [51]. The relationship between pain and non-motor fluctuations might be explained by the involvement of dopaminergic pathways with the descending pain inhibitory system [64].

In animal studies, both nigral and extra-nigral pathology can contribute to abnormal central nociceptive processing [60]. A study using 6-OHDA PD rat model demonstrated that PD was associated with mechanical hypernociception and normal nociception could be restored with apomorphine. PD was also associated with reduced GABAergic activity in the contralateral periaqueductal grey matter (PAG) and reduced enkephalin and μ-opioid receptor activities in bilateral dorsal horns of the spinal cord. Thus, descending analgesic control was impaired in PD [65]. Mylius et al. measured the nociceptive flexion reflex, and their findings suggested that PD was associated with local changes in spinal excitability [66]. Pautrat et al. showed complex tonic and phasic responses to noxious stimuli in the subthalamic nucleus (STN) in a PD rat model [67].

Notably, catechol-*O*-methyltransferase (COMT) inhibitors were recently shown to shorten the nociceptive latencies to thermal stimuli and thresholds of mechanical nociception in rats, implying that low COMT activity is associated with enhanced nociception [68]. COMT metabolizes catecholamines in glial cells, postsynaptic neurons in the brain, peripheral sensory ganglia and spinal cord [69]. Metabolic activity of COMT is determined by genetic polymorphisms, especially the Val108/158Met polymorphism, leading to significant differences in COMT activity [70] and are related to several functional differences including increased sensitivity to pain. For example, one recent study has found that patients with PD that reported pain had higher frequencies of the *COMT* rs4680 “A” allele than patients without pain. However, participants with *COMT* rs4680 “GG” and “GA” genotypes reported significantly higher pain severity than patients with the “AA” genotype [21]. Additionally, pain severity was significantly associated with the *COMT* rs6267 T allele. Li et al. found that the frequencies of the rs6267 “GT/TT” genotype and the “T” allele were higher in patients with PD that had pain than in those without pain [71].

6.2. Peripheral mechanisms

Recent studies that applied skin biopsy techniques to evaluate the integrity of epidermal nerve fibers have shown that the degeneration of small-diameter sensory nerves and deposition of phosphorylated α-synuclein in cutaneous sensory and autonomic nerves occurs in the early stage of patients with PD [72,73]. Further, another study revealed that the skin of

the extremities most affected by motor symptoms manifest decreased nerve degeneration, with the degree of denervation associated with impaired pain perception [74], suggesting early peripheral pain-sensing small fiber degeneration in the PD process. These findings suggest that peripheral pain-sensing nerves were also perturbed in addition to central processing system in the pain of PD.

Furthermore, one recent study found that plasma interleukin (IL)-1 levels were significantly higher in patients with PD that experienced pain, compared to healthy controls. IL-6, IL-10, and tumour necrosis factor-α (TNF-α) were not significantly different between groups [75]. In addition, IL-1 levels were significantly elevated in patients with high levodopa doses (above 250 mg), high Hoehn and Yahr stages (above stage 2), and high UPDRS part III scores (above 27). A rat PD model showed upregulations of IL-1β, IL-6, and TNF-α receptors in the PAG areas of the brain [76]. That finding indicated that peripheral inflammatory cytokines may associate with central pain modulation in patients with PD.

One of the possible causes contributing to PD polyneuropathy is prolonged levodopa exposure, which causes vitamin B12 deficiency [34]. Methylmalonic acid (MMA) is the precursor of Vitamin B12. Levodopa catabolism is known to be associated with vitamin B12 deficiency and, elevated serum homocysteine [77], and elevated serum MMA. Park et al. found that MMA levels, not Vitamin B12 or homocysteine, were positively correlated with the neuropathy pain scale in patients with PD that had peripheral neuropathy [34].

7. Treatment of pain in PD

7.1. Dopaminergic medications

A series of studies have applied quantitative sensory testing (QST) to evaluate the changes in sensory thresholds in PD patients under treatments of levodopa or dopamine agonists (on-status), and after several hours of treatment withdrawal (off-status). Previous studies have reported that PD with pain would present lower pain threshold compared to pain-free patients [78]. The administration of levodopa markedly raised pain threshold in PD patients but not in healthy subjects [79]. Following studies also revealed that dopamine deficit lowers multimodal pain thresholds that are amenable to correction with levodopa treatment and dosing [60]. A generalized, nonspecific pain may be more responsive to levodopa, compared to radicular, neuropathic, or akathisia-related pain [80]. Clinically, levodopa alleviated pain in some patients, but exacerbated pain in other patients. When pain is associated with worsening motor disability or with fluctuation-dependent dystonia [81], generally, the first step is to adjust the dose of anti-parkinsonian medication [51]. When the pain does not respond to dopaminergic medication adjustments, other causes should be evaluated; for example, pain might be caused by rotator cuff syndrome, frozen shoulder, cervical and lumbar spondylosis, or a cardiorespiratory disorder [51]. Taken together, these findings suggest that PD patients have abnormal sensory and pain thresholds, and pain could be partially relieved after the administration of dopaminergic medications. Whether the dopamine has a real antinociceptive effect or only a pain modulation effect remains further investigations.

7.2. Non-dopaminergic medications

The most common medication for musculoskeletal pain is NSAID, followed by opioids and COX-2 selective NSAIDs. Few patients receive anticonvulsants, triptan, or anti-depressants [28]. Duloxetine is an option for central or primary pain [51]. An early meta-analysis showed that duloxetine and rotigotine could effectively treat pain in PD [82]. Qureshi et al. performed a meta-analysis on pain treatments in PD. The greatest reductions in pain were found with safinamide, followed by cannabinoids, opioids, and COMT inhibitors. Pardoprunox showed moderate effects, and dopaminergic agonists showed the weakest effects [83]. Safinamide mechanisms include both dopaminergic (reversible monoamine oxidase B inhibition) and non-dopaminergic (sodium channel blockade to modulate abnormal glutamate release) pathways. Safinamide was shown to reduce pain over the long term [84].

In addition, a combination of the opiate agonist oxycodone and the peripheral opiate antagonist naloxone, named Targinact, has been proven to be effective in the treatment of pain in PD [85]. Currently, some new medications are under investigation. Tapentadol is a relatively new opioid agent. It has reduced affinity for the μ-opioid receptor, and it inhibited serotonin/noradrenaline reuptake. It showed potential efficacy for treating pain in PD [86].

7.3. Botulinum toxin

Rieu et al. used botulinum toxin A to treat painful foot dystonia. They observed significant reductions in pain and dystonia compared to baseline, but no improvement compared to a placebo group [33]. A randomized double-blind crossover study tested botulinum toxin type A for limb pain in advanced PD. This treatment did not significantly reduce the pain score in the pain group; however, a subgroup analysis showed that it significantly improved dystonic pain [87].

7.4. Deep brain stimulation

Deep brain stimulation (DBS) might alleviate pain in patients with PD. Pain was successfully alleviated with DBS in both the globus pallidus internus (GPi) and subthalamic nucleus (STN), with follow-up durations ranging from 3 months to 2 years [88]. Several studies have shown that STN-DBS could relieve pain in more than 80% of PD patients during the off periods [88,89]. Furthermore, STN-DBS could significantly increase subjective pain threshold and reduced pain-induced cortical activity in PD patients with pain, while it had no effect in PD patients without pain complaints [89]. The greatest improvements were noted in dystonic and musculoskeletal pain, followed by central and neuropathic pain [88]. DBS might have a direct anti-nociceptive effect, by stimulating or modulating the basal ganglion circuitry [88]. Bilateral STN-DBS improved pain, particularly pain related to dystonia, in 50% of patients with PD after a mean follow-up period of 5 years [12]. Smith et al. described a mean improvement of 31.7% in the pain score for lower back pain, at both 6 months and 1 year after bilateral STN-DBS [12]. However, Fabbri et al. showed that long-term (4.6 ± 1.3 years) use of STN-DBS could not significantly improve pain but statistical improvement of anxiety and fatigue [90]. These findings suggest future longitudinal studies on the long-term effects of STN-DBS on pain in PD patients are needed.

The effects of stimulation to other targets such as GPi on pain relief have been much less frequently investigated. Unilateral GPi-DBS has been reported to improve contralateral pain by 80% and limb dystonia by 90% [50]. With bilateral GPi-DBS, scores for dystonia were improved by 86%, for pain by 90%, for cramps by 90% and for dysesthesia by 88% [88]. These observations suggest GPi-DBS is most beneficial in relieving dystonia and dystonic pain in patients with PD.

7.5. Non-invasive cortical stimulation

Non-invasive cortical stimulation, including transcranial direct current stimulation and transcranial alternating current stimulation, are currently under investigation for treating pain in PD. Direct cortical stimulation may improve symptoms of pain in PD [91]. Repetitive transcranial magnetic stimulation might be effective for relieving painful dystonia in unmedicated patients with PD [100].

7.6. Other treatments

Total knee arthroplasty might partially alleviate pain for long periods (up to 3 years) for PD patients with musculoskeletal pain coming from bony degenerative changes. However, the functional outcome appeared to deteriorate post-operatively, over the long term [92]. Similarly, reverse shoulder arthroplasty, designed to provide inherent shoulder constraint,

reduced shoulder pain for PD patients with musculoskeletal pain coming from degenerative changes of shoulder joints, but clinical function was inferior compared to controls [93]. Non-pharmacological therapies, including multidisciplinary team care, electrical stimulation, were found to alleviate pain effectively [83]. Tai chi is a series of aquatic exercises, based on a combination of tai-chi and qi-qong concepts. Perez de la Cruz found that pain significantly improved after 1 month of aquatic ai chi training in patients with mild to moderate PD [94].

8. Conclusions

Pain is a heterogeneous symptom in PD. Different types of pain have different clinical impacts, ranging from central pain to peripheral pain, including polyneuropathy. The characteristics, severity, and distribution of pain varies with gender, race, and disease stage. Genetic polymorphisms might also play a role in pain severity. Therefore, pain in PD is suggested to be treated with different strategies. An increasing awareness of symptom of pain in PD would provide a further insight into the exploration of dysregulation of the sensory system in the pathophysiology of this disease.

Funding support

We thank the National Taiwan University Hospital and E-Da University Hosptial (106-EDN06 and 107-EDN14) for funding this work.

Author contributions

Conception and design of the study: CH Lin.
Acquisition and interpretation of data from literature review: YC Tai.
Drafting the article: YC Tai.
Revising it critically for important intellectual content: CH Lin.
Final approval of the version to be submitted: YC Tai and CH Lin.

Declaration of competing interest

Both authors (Dry YC Tai and Dr. CH Lin) declare no financial disclosures or conflicts of interest related to this study.

References

[1] G. Defazio, M. Tinazzi, A. Berardelli, How pain arises in Parkinson's disease? Eur. J. Neurol. 20 (2013) 1517–1523.
[2] S. Mukhtar, R. Imran, M. Zaheer, H. Tariq, Frequency of non-motor symptoms in Parkinson's disease presenting to tertiary care centre in Pakistan: an observational, cross-sectional study, BMJ Open 8 (2018), e019172.
[3] A.D. Ha, J. Jankovic, Pain in Parkinson's disease, Mov. Disord. 27 (2012) 485–491.
[4] A. Antonini, M. Tinazzi, G. Abbruzzese, A. Berardelli, K.R. Chaudhuri, G. Defazio, J. Ferreira, P. Martinez-Martin, C. Trenkwalder, O. Rascol, Pain in Parkinson's disease: facts and uncertainties, Eur. J. Neurol. 25 (2018) 917–e969.
[5] M.A. Silverdale, C. Kobylecki, L. Kass-Iliyya, P. Martinez-Martin, M. Lawton, S. Cotterill, K.R. Chaudhuri, H. Morris, F. Baig, N. Williams, L. Hubbard, M.T. Hu, D.G. Grosset, U.K.P.s.P.S. Collaboration, A detailed clinical study of pain in 1957 participants with early/moderate Parkinson's disease, Parkinsonism Relat. Disord. DOI https://doi.org/10.1016/j.parkreldis.2018.06.001(2018).
[6] S.M. Choi, B.C. Kim, H.J. Jung, G.J. Yoon, K.W. Kang, K.H. Choi, J.T. Kim, S.H. Lee, M.S. Park, M.K. Kim, K.H. Cho, Impact of pain and pain subtypes on the quality of life of patients with Parkinson's disease, J. Clin. Neurosci. 45 (2017) 105–109.
[7] Y.T. Fu, C.J. Mao, L.J. Ma, H.J. Zhang, Y. Wang, J. Li, J.Y. Huang, J.Y. Liu, C.F. Liu, Pain correlates with sleep disturbances in Parkinson's disease patients, Pain Pract. 18 (2018) 29–37.
[8] A.Q. Rana, A.R.M. Qureshi, A. Haris, M.A. Danish, M.S. Furqan, O. Shaikh, Z. Sarfraz, R. Rana, Negative impact of severity of pain on mood, social life and general activity in Parkinson's disease, Neurol. Res. 40 (2018) 1054–1059.
[9] A.Q. Rana, A. Kabir, M. Jesudasan, I. Siddiqui, S. Khondker, Pain in Parkinson's disease: analysis and literature review, Clin. Neurol. Neurosurg. 115 (2013) 2313–2317.
[10] C.H. Lin, R.M. Wu, H.Y. Chang, Y.T. Chiang, H.H. Lin, Preceding pain symptoms and Parkinson's disease: a nationwide population-based cohort study, Eur. J. Neurol. 20 (2013) 1398–1404.
[11] A.Q. Rana, A.R.M. Qureshi, Y. Shamli Oghli, Y. Saqib, B. Mohammed, Z. Sarfraz, R. Rana, Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity, and correlates with pain intensity and quality, Neurol. Res. 40 (2018) 696–701.
[12] H. Smith, L. Gee, V. Kumar, A. Ramirez-Zamora, J. Durphy, E. Hanspal, A. Barba, E. Molho, D. Shin, J.G. Pilitsis, Deep brain stimulation significantly decreases disability from low back pain in patients with advanced Parkinson's disease, Stereotact. Funct. Neurosurg. 93 (2015) 206–211.
[13] K.R. Chaudhuri, A. Rizos, C. Trenkwalder, O. Rascol, S. Pal, D. Martino, C. Carroll, D. Paviour, C. Falup-Pecurariu, B. Kessel, M. Silverdale, A. Todorova, A. Sauerbier, P. Odin, A. Antonini, P. Martinez-Martin, Europar, I.N.M.P.D.S.G. the, King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation, Mov. Disord. 30 (2015) 1623–1631.
[14] B. Ford, Pain in Parkinson's disease, Mov. Disord. 25 (Suppl. 1) (2010) S98–103.
[15] J.O. Hirsi, Y.M. Yifru, G.Z. Metaferia, J.H. Bower, Prevalence of pain in patients with Parkinson's disease in Addis Ababa, Ethiopia, Parkinsonism Relat. Disord. DOI https://doi.org/10.1016/j.parkreldis.2018.09.030(2018).
[16] P. Martinez-Martin, J. Manuel Rojo-Abuin, A. Rizos, C. Rodriguez-Blazquez, C. Trenkwalder, L. Perkins, A. Sauerbier, P. Odin, A. Antonini, K.R. Chaudhuri, E. Kpps, I.N.M.P.D.S.G. the, distribution and impact on quality of life of the pain modalities assessed by the King's Parkinson's disease pain scale, NPJ Parkinsons, Dis. 3 (2017) 8.
[17] G. Defazio, A. Antonini, M. Tinazzi, A.F. Gigante, S. Pietracupa, R. Pellicciari, M. Bloise, R. Bacchin, A. Marcante, G. Fabbrini, A. Berardelli, Relationship between pain and motor and non-motor symptoms in Parkinson's disease, Eur. J. Neurol. 24 (2017) 974–980.
[18] S.R. Snider, S. Fahn, W.P. Isgreen, L.J. Cote, Primary sensory symptoms in parkinsonism, Neurology 26 (1976) 423–429.
[19] C.G. Goetz, C.M. Tanner, M. Levy, R.S. Wilson, D.C. Garron, Pain in Parkinson's disease, Mov. Disord. 1 (1986) 45–49.
[20] M. Tinazzi, C. Del Vesco, E. Fincati, S. Ottaviani, N. Smania, G. Moretto, A. Fiaschi, D. Martino, G. Defazio, Pain and motor complications in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 77 (2006) 822–825.
[21] C.H. Lin, K.R. Chaudhuri, J.Y. Fan, C.I. Ko, A. Rizos, C.W. Chang, H.I. Lin, Y.R. Wu, Depression and Catechol-O-methyltransferase (COMT) genetic variants are associated with pain in Parkinson's disease, Sci. Rep. 7 (2017) 6306.
[22] M.L. Rabin, M.C. Earnhardt, A. Patel, I. Ganihong, R. Kurlan, Postural, bone, and joint disorders in Parkinson's disease, Mov. Disord. Clin. Pract. 3 (2016) 538–547.
[23] M.A.S. Zella, C. May, T. Muller, M. Ahrens, L. Tonges, R. Gold, K. Marcus, D. Woitalla, Landscape of pain in Parkinson's disease: impact of gender differences, Neurol. Res. DOI 10.1080/01616412.2018.1531208(2018) 1-11.
[24] Y.E. Kim, H.J. Kim, J.Y. Yun, W.W. Lee, H.J. Yang, J.M. Kim, B. Jeon, Musculoskeletal problems affect the quality of life of patients with Parkinson's disease, J, Mov. Disord. 11 (2018) 133–138.
[25] A.Q. Rana, A.R. Qureshi, S. Akhter, Y. Ingar, A. Ayub, I. Abdullah, O. Madhosh, Z. Sarfraz, M.B. Rana, R. Rana, Osteoarthritis increases paresthestic and akathisic pain, anxiety case-ness, and depression severity in patients with Parkinson's disease, Front. Neurol. 9 (2018) 409.
[26] R. Papalia, G. Torre, G. Papalia, M.H. Baums, P. Narbona, V. Di Lazzaro, V. Denaro, Frozen shoulder or shoulder stiffness from Parkinson disease?, Musculoskelet. Surg. DOI https://doi.org/10.1007/s12306-018-0567-3(2018).
[27] D. Riley, A.E. Lang, R.D. Blair, A. Birnbaum, B. Reid, Frozen shoulder and other shoulder disturbances in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 52 (1989) 63–66.
[28] I. Galazky, C. Caspari, H.J. Heinze, J. Franke, The prevalence of chronic low back pain and lumbar deformities in patients with Parkinson's disease: implications on spinal surgery, Eur. Spine J. DOI https://doi.org/10.1007/s00586-018-5748-0(2018).
[29] E.A. Ozturk, B.G. Kocer, Predictive risk factors for chronic low back pain in Parkinson's disease, Clin. Neurol. Neurosurg. 164 (2018) 190–195.
[30] A.G. Beiske, J.H. Loge, A. Ronningen, E. Svensson, Pain in Parkinson's disease: prevalence and characteristics, Pain 141 (2009) 173–177.
[31] M.A. Adams, B.J. Freeman, H.P. Morrison, I.W. Nelson, P. Dolan, Mechanical initiation of intervertebral disc degeneration, Spine (Phila Pa 1976) 25 (2000) 1625–1636.
[32] M. Kodama, T. Kasahara, M. Hyodo, K. Aono, M. Sugaya, Y. Koyama, K. Hanayama, Y. Masakado, Effect of low-frequency repetitive transcranial magnetic stimulation combined with physical therapy on L-dopa-induced painful off-period dystonia in Parkinson's disease, Am. J. Phys. Med. Rehabil. 90 (2011) 150–155.
[33] I. Rieu, B. Degos, G. Castelnovo, C. Vial, E. Durand, B. Pereira, M. Simonetta-Moreau, S. Sangla, F. Fluchere, D. Guehl, P. Burbaud, C. Geny, D. Gayraud, F. Ory-Magne, F. Bouhour, E. Llinares, P. Derost, A. Marques, F. Durif, Incobotulinum toxin A in Parkinson's disease with foot dystonia: a double blind randomized trial, Parkinsonism Relat. Disord. 46 (2018) 9–15.
[34] J.S. Park, D. Park, P.W. Ko, K. Kang, H.W. Lee, Serum methylmalonic acid correlates with neuropathic pain in idiopathic Parkinson's disease, Neurol. Sci. 38 (2017) 1799–1804.
[35] J.K. Adewusi, M. Hadjivassiliou, A. Vinagre-Aragon, K.R. O'Connor, A. Khan, R.A. Grunewald, P. Zis, Peripheral neuropathic pain in idiopathic Parkinson's disease: prevalence and impact on quality of life; a case controlled study, J. Neurol. Sci. 392 (2018) 3–7.
[36] Z. Chovancova, P. Kanovsky, J. Dufek, M. Nevrly, P. Otruba, Peripheral nerve involvement and severity of motor disorder in Parkinson's disease: a correlational study, Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 153 (2009) 59–62.
[37] T. Kimber, P. Blumbergs, P. Thompson, Severe ataxic polyneuropathy associated with chronic levodopa use in Parkinson's disease, Parkinsonism Relat. Disord. 19 (2013) 847–849.
[38] C. Conradt, D. Guo, A. Miclea, T. Nisslein, C. Ismail, K. Chatamra, F. Andersohn, Increased prevalence of polyneuropathy in Parkinson's disease patients: an observational study, J. Park. Dis. 8 (2018) 141–144.

[39] H. Kaur, K. Bhatia, A. Yelam, A. Shukla, I. Asher, R. Govindarajan, Infusion-rate-dependent acute neuropathic pain with Duopa in a patient with Parkinson's disease and pre-existing neuropathy, Cureus 10 (2018), e3055.
[40] M. Onofrj, L. Bonanni, G. Cossu, D. Manca, F. Stocchi, A. Thomas, Emergencies in parkinsonism: akinetic crisis, life-threatening dyskinesias, and polyneuropathy during L-Dopa gel treatment, Parkinsonism Relat. Disord. 15 (Suppl. 3) (2009) S233–S236.
[41] A. Uncini, R. Eleopra, M. Onofrj, Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management, J. Neurol. Neurosurg. Psychiatry 86 (2015) 490–495.
[42] G.G. Demerjian, A.B. Sims, B.C. Stack, Proteomic signature of temporomandibular joint disorders (TMD): toward diagnostically predictive biomarkers, Bioinformation 5 (2011) 282–284.
[43] M.C. Verhoeff, F. Lobbezoo, P. Wetselaar, G. Aarab, M. Koutris, Parkinson's disease, temporomandibular disorders and bruxism: a pilot study, J. Oral Rehabil. 45 (2018) 854–863.
[44] Y. Zlotnik, Y. Balash, A.D. Korczyn, N. Giladi, T. Gurevich, Disorders of the oral cavity in Parkinson's disease and parkinsonian syndromes, Parkinsons. Dis. 2015 (2015) 379482.
[45] D. Bonenfant, P.H. Rompre, N. Rei, N. Jodoin, V.L. Soland, V. Rey, C. Brefel-Courbon, F. Ory-Magne, O. Rascol, P.J. Blanchet, Characterization of burning mouth syndrome in patients with Parkinson's disease, J. Oral facial, Pain Headache 30 (2016) 318–322.
[46] J. Stuginski-Barbosa, G.G. Rodrigues, M.E. Bigal, J.G. Speciali, Burning mouth syndrome responsive to pramipexol, J. Headache Pain 9 (2008) 43–45.
[47] E.A. Coon, R.S. Laughlin, Burning mouth syndrome in Parkinson's disease: dopamine as cure or cause? J. Headache Pain 13 (2012) 255–257.
[48] M.T. Tseng, C.H. Lin, Pain in early-stage Parkinson's disease: implications from clinical features to pathophysiology mechanisms, J. Formos. Med. Assoc. 116 (2017) 571–581.
[49] M. Fabbri, M. Coelho, L.C. Guedes, I. Chendo, C. Sousa, M.M. Rosa, D. Abreu, N. Costa, C. Godinho, A. Antonini, J.J. Ferreira, Response of non-motor symptoms to levodopa in late-stage Parkinson's disease: results of a levodopa challenge test, Parkinsonism Relat. Disord. 39 (2017) 37–43.
[50] T.J. Loher, J.M. Burgunder, S. Weber, R. Sommerhalder, J.K. Krauss, Effect of chronic pallidal deep brain stimulation on off period dystonia and sensory symptoms in advanced Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 73 (2002) 395–399.
[51] M. Coelho, J. Ferreira, M. Rosa, C. Sampaio, Treatment options for non-motor symptoms in late-stage Parkinson's disease, Expert. Opin. Pharmacother. 9 (2008) 523–535.
[52] A.Q. Rana, A.R.M. Qureshi, N. Rahman, A. Mohammed, Z. Sarfraz, R. Rana, Disability from pain directly correlated with depression in Parkinson's disease, Clin. Neurol. Neurosurg. 160 (2017) 1–4.
[53] T. Prell, Structural and functional brain patterns of non-motor syndromes in Parkinson's disease, Front. Neurol. 9 (2018) 138.
[54] T. Thompson, K. Gallop, C.U. Correll, A.F. Carvalho, N. Veronese, E. Wright, B. Stubbs, Pain perception in Parkinson's disease: a systematic review and meta-analysis of experimental studies, Ageing Res. Rev. 35 (2017) 74–86.
[55] M. Tinazzi, C. Del Vesco, G. Defazio, E. Fincati, N. Smania, G. Moretto, A. Fiaschi, D. Le Pera, M. Valeriani, Abnormal processing of the nociceptive input in Parkinson's disease: a study with CO2 laser evoked potentials, Pain 136 (2008) 117–124.
[56] M. Tinazzi, S. Recchia, S. Simonetto, G. Defazio, S. Tamburin, G. Moretto, A. Fiaschi, R. Miliucci, M. Valeriani, Hyperalgesia and laser evoked potentials alterations in hemiparkinson: evidence for an abnormal nociceptive processing, J. Neurol. Sci. 276 (2009) 153–158.
[57] C.H. Lin, C.C. Chao, S.W. Wu, P.C. Hsieh, F.P. Feng, Y.H. Lin, Y.M. Chen, R.M. Wu, S.T. Hsieh, Pathophysiology of small-fiber sensory system in Parkinson's disease: skin innervation and contact heat evoked potential, Medicine (Baltimore) 95 (2016), e3058.
[58] S. Sung, N. Vijiaratnam, D.W.C. Chan, M. Farrell, A.H. Evans, Pain sensitivity in Parkinson's disease: systematic review and meta-analysis, Parkinsonism Relat. Disord. 48 (2018) 17–27.
[59] A. Tessitore, A. Russo, R. De Micco, M. Fratello, G. Caiazzo, A. Giordano, M. Cirillo, G. Tedeschi, F. Esposito, Central pain processing in "drug-naive" pain-free patients with Parkinson's disease, Hum. Brain Mapp. 39 (2018) 932–940.
[60] P.J. Blanchet, C. Brefel-Courbon, Chronic pain and pain processing in Parkinson's disease, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 87 (2018) 200–206.
[61] A. Suppa, C. Leone, F. Di Stasio, L. Marsili, A. Di Santo, A. Biasiotta, S. La Cesa, A. Truini, G. Cruccu, A. Berardelli, Pain-motor integration in the primary motor cortex in Parkinson's disease, Brain Stimul. 10 (2017) 806–816.
[62] V. Mylius, D. Ciampi de Andrade, R.G. Cury, M. Teepker, U. Ehrt, K.M. Eggert, S. Beer, J. Kesselring, M. Stamelou, W.H. Oertel, J.C. Moller, J.P. Lefaucheur, Pain in Parkinson's disease: current concepts and a new diagnostic algorithm, Mov. Disord. Clin. Pract. 2 (2015) 357–364.
[63] P. Schestatsky, H. Kumru, J. Valls-Sole, F. Valldeoriola, M.J. Marti, E. Tolosa, M.L. Chaves, Neurophysiologic study of central pain in patients with Parkinson disease, Neurology 69 (2007) 2162–2169.
[64] W. Grashorn, O. Schunke, C. Buhmann, K. Forkmann, S. Diedrich, K. Wesemann, U. Bingel, Influence of dopaminergic medication on conditioned pain modulation in Parkinson's disease patients, PLoS One 10 (2015), e0135287.
[65] R.A. Domenici, A.C.P. Campos, S.T. Maciel, M.B. Berzuino, M.S. Hernandes, E.T. Fonoff, R.L. Pagano, Parkinson's disease and pain: modulation of nociceptive circuitry in a rat model of nigrostriatal lesion, Exp. Neurol. 315 (2019) 72–81.
[66] V. Mylius, S. Pee, H. Pape, M. Teepker, M. Stamelou, K. Eggert, J.P. Lefaucheur, W.H. Oertel, J.C. Moller, Experimental pain sensitivity in multiple system atrophy and Parkinson's disease at an early stage, Eur. J. Pain 20 (2016) 1223–1228.
[67] A. Pautrat, M. Rolland, M. Barthelemy, C. Baunez, V. Sinniger, B. Piallat, M. Savasta, P.G. Overton, O. David, V. Coizet, Revealing a novel nociceptive network that links the subthalamic nucleus to pain processing, eLife 7 (2018).
[68] A.G. Nackley, K.S. Tan, K. Fecho, P. Flood, L. Diatchenko, W. Maixner, Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors, Pain 128 (2007) 199–208.
[69] P.T. Mannisto, S. Kaakkola, Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors, Pharmacol. Rev. 51 (1999) 593–628.
[70] B. Boudikova, C. Szumlanski, B. Maidak, R. Weinshilboum, Human liver catechol-O-methyltransferase pharmacogenetics, Clin. Pharmacol. Ther. 48 (1990) 381–389.
[71] W. Li, Y. Chen, B. Yin, L. Zhang, Pain in Parkinson's disease associated with COMT gene polymorphisms, Behav. Neurol. 2014 (2014) 304203.
[72] V. Donadio, A. Incensi, V. Leta, M.P. Giannoccaro, C. Scaglione, P. Martinelli, S. Capellari, P. Avoni, A. Baruzzi, R. Liguori, Skin nerve alpha-synuclein deposits: a biomarker for idiopathic Parkinson disease, Neurology 82 (2014) 1362–1369.
[73] N. Wang, C.H. Gibbons, J. Lafo, R. Freeman, Alpha-Synuclein in cutaneous autonomic nerves, Neurology 81 (2013) 1604–1610.
[74] M. Nolano, V. Provitera, A. Estraneo, M.M. Selim, G. Caporaso, A. Stancanelli, A.M. Saltalamacchia, B. Lanzillo, L. Santoro, Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation, Brain 131 (2008) 1903–1911.
[75] D. Li, X. Song, H. Huang, H. Huang, Z. Ye, Association of Parkinson's disease-related pain with plasma interleukin-1, interleukin-6, interleukin-10, and tumour necrosis factor-alpha, Neurosci. Lett. 683 (2018) 181–184.
[76] X. Zhuang, Y. Chen, X. Zhuang, T. Chen, T. Xing, W. Wang, X. Yang, Contribution of pro-inflammatory cytokine signaling within midbrain periaqueductal gray to pain sensitivity in Parkinson's disease via GABAergic pathway, Front. Neurol. 7 (2016) 104.
[77] M. Andreasson, L. Brodin, J.M. Laffita-Mesa, P. Svenningsson, Correlations between methionine cycle metabolism, COMT genotype, and polyneuropathy in L-Dopa treated Parkinson's disease: a preliminary cross-sectional study, J. Park. Dis. 7 (2017) 619–628.
[78] R. Djaldetti, A. Shifrin, Z. Rogowski, E. Sprecher, E. Melamed, D. Yarnitsky, Quantitative measurement of pain sensation in patients with Parkinson disease, Neurology 62 (2004) 2171–2175.
[79] C. Brefel-Courbon, P. Payoux, C. Thalamas, F. Ory, I. Quelven, F. Chollet, J.L. Montastruc, O. Rascol, Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study, Mov. Disord. 20 (2005) 1557–1563.
[80] A.Q. Rana, D. Qureshi, W. Sabeh, A. Mosabbir, E. Rahman, Z. Sarfraz, R. Rana, Pharmacological therapies for pain in Parkinson's disease - a review paper, Expert. Rev. Neurother. 17 (2017) 1209–1219.
[81] E. Schaeffer, D. Berg, Dopaminergic therapies for non-motor symptoms in Parkinson's disease, CNS Drugs 31 (2017) 551–570.
[82] S. Perez-Lloret, M.V. Rey, E. Dellapina, J. Pellaprat, C. Brefel-Courbon, O. Rascol, Emerging analgesic drugs for Parkinson's disease, Expert. Opin. Emerg. Drugs 17 (2012) 157–171.
[83] A.R. Qureshi, A.Q. Rana, S.H. Malik, S.F.H. Rizvi, S. Akhter, C. Vannabouathong, Z. Sarfraz, R. Rana, Comprehensive examination of therapies for pain in Parkinson's disease: a systematic review and meta-analysis, Neuroepidemiology 51 (2018) 190–206.
[84] C. Cattaneo, J. Kulisevsky, V. Tubazio, P. Castellani, Long-term efficacy of safinamide on Parkinson's disease chronic pain, Adv. Ther. 35 (2018) 515–522.
[85] C. Trenkwalder, K.R. Chaudhuri, P. Martinez-Martin, O. Rascol, R. Ehret, M. Valis, M. Satori, A. Krygowska-Wajs, M.J. Marti, K. Reimer, A. Oksche, M. Lomax, J. DeCesare, M. Hopp, P.s. group, prolonged-release oxycodone-naloxone for treatment of severe pain in patients with Parkinson's disease (PANDA): a double-blind, randomised, placebo-controlled trial, Lancet Neurol. 14 (2015) 1161–1170.
[86] U. Freo, M. Furnari, C. Ori, Effects of tapentadol on pain, motor symptoms and cognitive functions in Parkinson's disease, J. Pain Res. 11 (2018) 1849–1856.
[87] V. Bruno, M.E. Freitas, D. Mancini, J.P. Lui, J. Miyasaki, S.H. Fox, Botulinum toxin type a for pain in advanced Parkinson's disease, Can. J. Neurol. Sci. 45 (2018) 23–29.
[88] M.M. Kurtis, T. Rajah, L.F. Delgado, H.S. Dafsari, The effect of deep brain stimulation on the non-motor symptoms of Parkinson's disease: a critical review of the current evidence, NPJ Parkinsons. Dis. 3 (2017) 16024.
[89] H.S. Dafsari, M. Silverdale, M. Strack, A. Rizos, K. Ashkan, P. Mahlstedt, L. Sachse, J. Steffen, T.A. Dembek, V. Visser-Vandewalle, J. Evans, A. Antonini, P. Martinez-Martin, K. Ray-Chaudhuri, L. Timmermann, Europar, I.N.M.P.D.S.G. the, Nonmotor symptoms evolution during 24 months of bilateral subthalamic stimulation in Parkinson's disease, Mov. Disord. 33 (2018) 421–430.
[90] M. Fabbri, M. Coelho, L.C. Guedes, M.M. Rosa, D. Abreu, N. Goncalves, A. Antonini, J.J. Ferreira, Acute response of non-motor symptoms to subthalamic deep brain stimulation in Parkinson's disease, Parkinsonism Relat. Disord. 41 (2017) 113–117.
[91] A. Lavano, G. Guzzi, D. Chirchiglia, Cortical neuromodulation for neuropathic pain and Parkinson disease: where are we? Neurol. Neurochir. Pol. 52 (2018) 75–78.
[92] M. Ashraf, S. Priyavadhana, S.N. Sambandam, V. Mounasamy, O.P. Sharma, Total knee arthroplasty in patients with Parkinson's disease- a critical analysis of available evidence, Open Orthop. J. 11 (2017) 1087–1093.
[93] M.C. Cusick, R.J. Otto, R.E. Clark, M.A. Frankle, Outcome of reverse shoulder arthroplasty for patients with Parkinson's disease: a matched cohort study, Orthopedics 40 (2017) e675–e680.
[94] S. Perez de la Cruz, Effectiveness of aquatic therapy for the control of pain and increased functionality in people with Parkinson's disease: a randomized clinical trial, Eur. J. Phys. Rehabil. Med. 53 (2017) 825–832.
[95] B. Scott, A. Borgman, H. Engler, B. Johnels, S.M. Aquilonius, Gender differences in Parkinson's disease symptom profile, Acta Neurol. Scand. 102 (2000) 37–43.
[96] S. Zambito Marsala, M. Tinazzi, R. Vitaliani, S. Recchia, F. Fabris, C. Marchini, A. Fiaschi, G. Moretto, B. Giometto, A. Macerollo, G. Defazio, Spontaneous pain,

pain threshold, and pain tolerance in Parkinson's disease, J. Neurol. 258 (2011) 627–633.

[97] N.E. Allen, C.M. Wong, C.G. Canning, N. Moloney, The association between Parkinson's disease motor impairments and pain, Pain Med. 17 (2016) 456–462.

[98] L. Negre-Pages, W. Regragui, D. Bouhassira, H. Grandjean, O. Rascol, P.S.G. DoPaMi, Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey, Mov. Disord. 23 (2008) 1361–1369.

[99] G. Defazio, A. Berardelli, G. Fabbrini, D. Martino, E. Fincati, A. Fiaschi, G. Moretto, G. Abbruzzese, R. Marchese, U. Bonuccelli, P. Del Dotto, P. Barone, E. De Vivo, A. Albanese, A. Antonini, M. Canesi, L. Lopiano, M. Zibetti, G. Nappi, E. Martignoni, P. Lamberti, M. Tinazzi, Pain as a nonmotor symptom of Parkinson disease: evidence from a case-control study, Arch. Neurol. 65 (2008) 1191–1194.

[100] H.A. Hanagasi, S. Akat, H. Gurvit, J. Yazici, M. Emre, Pain is common in Parkinson's disease, Clin. Neurol. Neurosurg. 113 (2011) 11–13.