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REVIEW ARTICLE

Diagnosis and Management of Pain in Parkinson's Disease: A New Approach

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Abstract

Pain is a frequent and disabling non-motor feature of Parkinson's disease (PD). The recently proposed PD Pain Classification System (PD-PCS) allows for an association of pain with PD to be determined before being allocated to the main pain mechanism (i.e. nociceptive, neuropathic, and nociplastic). In this article, previous studies on treatments for pain in PD are summarized according to the pain mechanisms. A mechanistic approach to treatment is discussed. We suggest that the first step should be optimizing dopaminergic therapy before other therapy is started. When these treatments remain unsuccessful, further causes of pain must be considered. The role of drugs, invasive treatments, and physiotherapeutic interventions are discussed with a focus on older PD patients and considering polypharmacy, altered pharmacokinetics, and comorbidities.

Key Points

The correct classification of pain syndromes in Parkinson's disease (PD) is crucial for their successful treatment.

Dopaminergic drugs may be useful for most PD-related pain.

Conventional pain therapy may be an option when adjustment of dopaminergic therapy fails.

Drug interactions, altered pharmacokinetics, and comorbidities require a regular follow-up in older patients.

1 Introduction

Chronic pain (i.e. pain of at least 3 months' duration) is a relevant non-motor symptom (NMS) of patients with Parkinson's disease (PD), with impact on health-related quality of life [1, 2]. Especially in older PD patients, pain becomes difficult to diagnose and to treat because of the high prevalence of PD-unrelated pains [3]. Therefore, an association with the disease should be determined before evaluating the therapeutic options. In addition to pains directly associated with PD (e.g. Off-phase pain), pains can also be aggravated by the disease (indirectly related). PD also contributes to pain syndromes not directly related to the extent of dopaminergic stimulation (i.e. cobalamin deficiency, osteoarthrosis).

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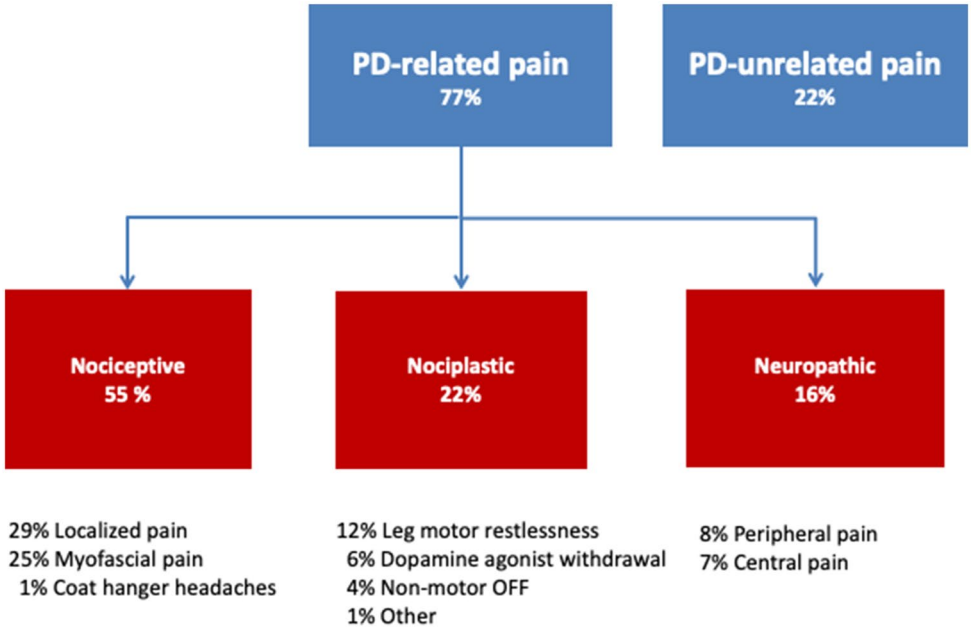

Fig. 1 Prevalence of Parkinson's disease (PD)-related pains (neuropathic, nociceptive, and nociplastic pains with respect to the defined pain syndrome), and PD-unrelated pains (modified with permission from [4])

Finally, patients may be affected by other pain syndromes commonly encountered in older adults (PD-unrelated pains).

A new PD Pain Classification System (PD-PCS) including a questionnaire and an online application has been developed and validated to allow for the attribution of pain to PD, before defining a mechanistic pain descriptor (i.e. neuropathic, nociceptive, and nociplastic) [4] (Fig. 1). Nociplastic pain has been recently introduced as a third mechanistic pain descriptor reflecting pains with an altered nociception that are neither neuropathic nor nociceptive (e.g. primary chronic pains) [5, 6]. In routine care, pain therapy normally implicates first the improvement of the dopaminergic medication (especially for nociceptive and nociplastic pains) before further therapies (e.g. in neuropathic pains) or further diagnostics become mandatory (unrelated or indirectly related pains). Pharmacological treatment of PD in older patients has been presented elsewhere and will be summarized with a focus on pain therapy [7]. Dopaminergic and non-dopaminergic medications with proven effects on pain in PD will be discussed in more detail. Invasive therapies such as levodopa-carbidopa intestinal gel (LCIG) pump therapy and deep brain stimulation (DBS) can be an option in refractory motor and non-motor fluctuations such as pain. Additionally, the pain-relieving role of physiotherapeutic interventions will be taken into consideration. Associated factors (i.e. cognitive function, emotional factors and sleep), polypharmacy and comorbidities are to be considered during regular follow-ups [7].

2 The Older Parkinson's Disease (PD) Patient

The clinical course of PD is largely determined by the motor but also by the non-motor subtype [2, 8]. For example, the tremor-dominant type has a better clinical course with fewer cognitive symptoms [9]. In addition, the recently defined Pain Park non-motor type showed a strong association with sleep dysfunction and dysautonomia, whereas other non-motor symptoms were not independently associated with pain [10, 11]. Along with aging, motor and non-motor symptoms deteriorate with frailty, risks for falls and dysphagia affecting quality of life [12–14]. PD therapy becomes less effective and the occurrence of motor and non-motor fluctuations also leads to increased risks for falls and dysphagia [2]. Multimorbidity affects many PD patients with a large proportion having cardiovascular diseases and cardiovascular risk factors also increasing polypharmacy [15]. Side effects of medication, interactions of drugs as well as non-motor symptoms (cognitive decline, sleep disorders, depression, cardiovascular, and gastrointestinal symptoms) determine the course in later stages [16]. Due to the high prevalence of comorbidities and polypharmacy, these conditions must be considered especially in the pharmacological management of pain.

3 Prevalence of Pain in PD

The prevalence of PD-related chronic pain depends on the age of the patient, the stage of the disease as well as on concomitant factors and comorbidities. A quarter of patients

have reported pain as a preceding symptom indicating an early motor stage (i.e. shoulder pain reflecting localized rigor and akinesia) [17]. In intermediate stages, a prevalence of 60% for PD-related pains has been observed [3]. During the disease course, pain prevalence increases together with motor fluctuations and alterations of pain perception affecting up to 80% of the population [18]. With respect to the different types of PD-related pain, nociceptive pain has the highest prevalence followed by nociplastic (a recently defined pain type, see below), and neuropathic pains [4] (Fig. 1). Chronic pain in PD also impacts quality of life and often shows an association with female gender, and Hoehn and Yahr stage [1, 10]. In a recent study, we showed a moderate correlation between the PD-PCS total score and PD-related quality of life. In contrast, when adjusted for other variables, PD-related pains as assessed by King's Parkinson's disease Pain Scale (KPPS) only slightly impact quality of life [19]. This discrepancy might be explained by differences in the sample, as the impact of pain relative to other non-motor symptoms appears to be less marked in the more advanced stages.

PD-unrelated pains seem to have a similar prevalence as seen in the general population of about 22–30% [4, 20]. In contrast, some observations suggest a higher prevalence of 60% and a greater impact on health-related quality of life [3].

4 Pathophysiology of PD-Related Pain

A fluctuation of pain with motor and non-motor fluctuations and thereby with dopaminergic stimulation is often observed with more intense pain in motor and/or non-motor Off phases in the respective regions of the body. Experimental pain sensitivity has been employed to detect altered nociception and pain perception. Accordingly, studies revealed increased pain sensitivity towards various stimuli during the Off phase, further increasing with disease duration and with pain [21–24]. In addition, one study showed an impact of dyskinesia on experimental pain stressing the hypothesis that pain and dyskinesia share similar mechanisms [25]. At the spinal level, increased pain sensitivity (nociception) has been shown to decrease following dopamine replacement therapy

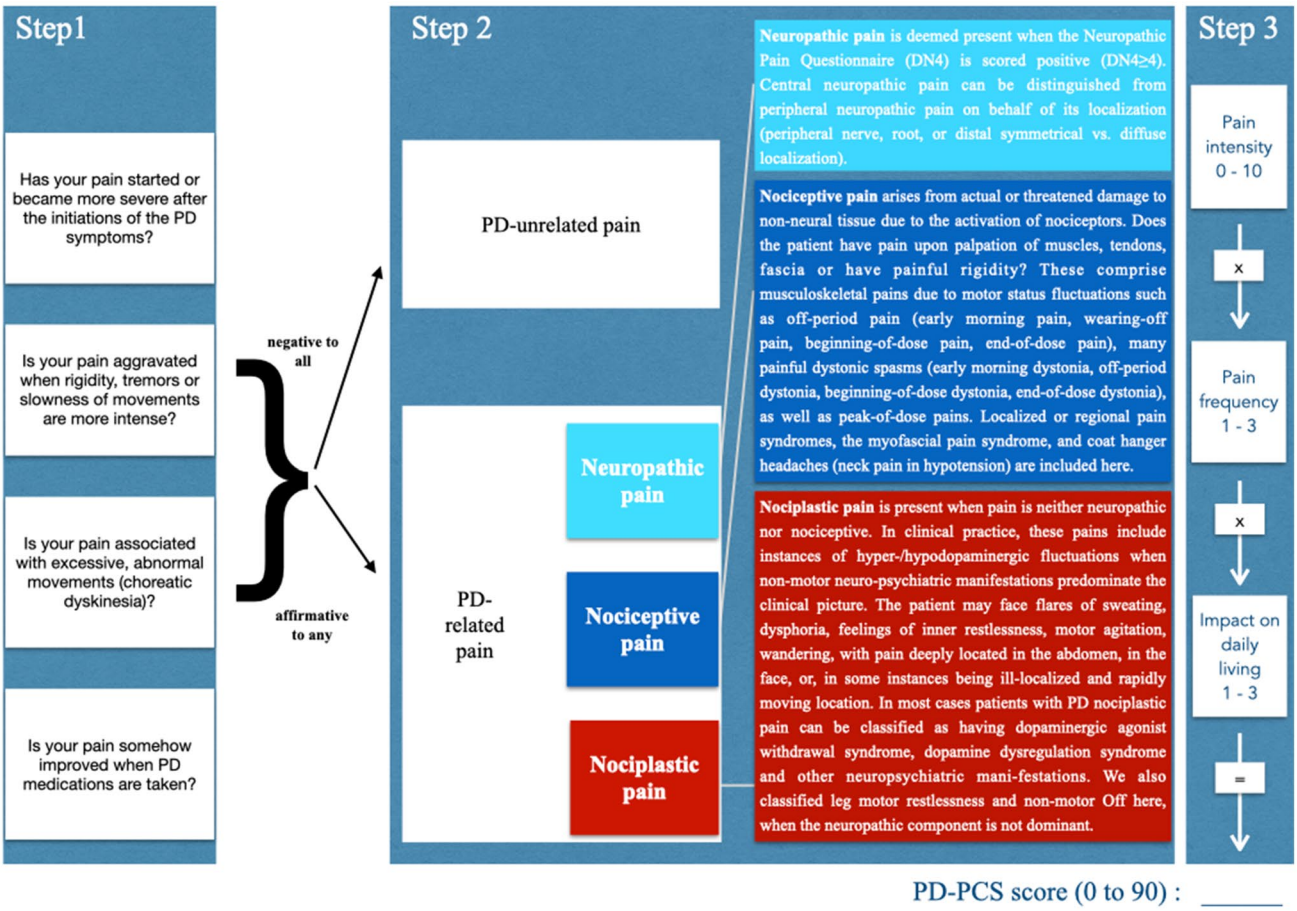

Fig. 2 The Parkinson's Disease–Pain Classification System (PD–PCS) (modified with permission from [4])

[22]. At the cortical level, the activation of the medial and lateral pain network during the Off phase was more pronounced as compared with the On phase in functional MRI [26]. In neuropathic pain, the medial pain pathway is thought to contribute to the perceived pain in contrast to PD patients without pain who rather activate the lateral pain pathway [27]. In these regions, the involvement of monoaminergic systems has been postulated [28]. Decreased descending inhibitory control deriving from mesencephalic descending dopaminergic pathways contributes to increased spinal nociception while other descending inhibitory pathways were not affected, as shown by conditioned pain modulation (CPM) at the spinal level [24]. Lewy bodies in cutaneous nerve fiber endings seem to reduce pain sensitivity in the On phase, whereas Lewy bodies in the spinal dorsal column may have contrary effects for the transmission of nociceptive input [29, 30]. Aging, in general, seems not to influence nociception and pain perception, presumably since reduced descending inhibitory control outweighs reduced afferent input [31]. Only sympathetic skin responses towards pain, reflecting nocifensive responses, were found to be reduced [31].

5 Diagnosing Pain in PD

Due to the high prevalence of pain in older adults as well as of pain associated with PD, the diagnosis of pain related to PD can be a challenge for the clinician [3]. This difficulty derives also from fluctuation of pain along with the fluctuation of PD symptoms, concomitant factors related to pain processing and perception (i.e. depressive symptoms and cognitive decline), and further PD-related symptoms in the actual clinical focus.

We suggest first assessing motor and non-motor symptoms by using the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) [32], the MDS Non-Motor Rating Scale (MDS-NMS) [33], and a motor diary to determine the functional staging of the patient across the day. This allows the calculation of On time, Off time, and time spent with disabling or non-disabling dyskinesias [34]. As a next step, the relation with PD can be determined either by questions from the NMS scale (NMSS) and the NMS questionnaire (pain during the Off phase, improvement by medication, and exclusion of further causes) [35, 36], or by using the more recent PD-PCS [4] (Fig. 2). This novel pain questionnaire follows the propositions of Quinn et al., Wasner and Deuschl, as well as of Marques et al. [37–39] and includes questions from the non-motor symptom scale and the questionnaire for the association of pain with PD [35, 36]. Here, the first step is to determine if the patient's pain is directly related to or aggravated by PD (indirectly related) (illustrative cases in Figs. 3, 4). The relation with PD is determined by the concomitant beginning or aggravation of pain with motor symptoms, improvement of pain by dopaminergic drugs, the increase of pain during the Off phase, and/or the occurrence of pain during choreiform dyskinesia [40]. If one of those four questions apply, a relation with PD is assumed. The underlying pain mechanism can be determined in a hierarchical manner in step 2 as suggested by the International Association for the Study of Pain (IASP). Neuropathic pain (central or peripheral) can be detected first by using the Douleur neuropathique questionnaire 4 (DN4) [41], before nociceptive and nociplastic pains are assessed. In step 3, pain intensity, frequency, and level of interference with activities of daily living can be scored. A final score that ranges from 0 to 90 can then be obtained by multiplying these scores for the three categories of pain. As an alternative rater-based approach, the KPPS can be employed, which distinguishes seven different PD-related pain domains [42, 43].

In general, a mechanism-based classification facilitates further diagnosis and mechanisms-based therapy. As a first step, we suggest optimization of the antiparkinsonian medication regimen [40]. If pain persists after this, a weak correlation with motor and/or non-motor fluctuations in PD can be assumed, and other treatments will be necessary. This

Fig. 3 Clinical case 1

A 74-year-old male patient suffering from PD for 10 years presented with a diffuse ache of the abdominal region and painful paresthesia of the feet. These symptoms started many years before and had worsened ever since. His medical history included polyneuropathy of unknown origin, depression, and sciatica. His current treatment consisted of 1100 mg L-dopa, 150 mg pregabalin, and 30 mg duloxetine/day.

He reported a worsening of abdominal pain during wearing-off phases and an improvement by dopaminergic treatment. This was confirmed by careful assessment employing the PD-PCS. Due to interior restlessness and after the exclusion of neuropathic and nociceptive pains, the present pain was diagnosed as nociplastic non-motor off pain with a PD-PCS score of 45.

The reduction of the off-phase duration by an increase of the dopaminergic drug dosing frequency contributed to a substantial relief in the abdominal pain. According to the PD-PCS assessment, painful paresthesia of the feet were not related to PD and had a neuropathic character. A severe cobalamin deficiency was diagnosed and treated.

Fig. 4 Clinical case 2

A 42-year-old female patient with early-onset PD complained about pain in the lower limbs in the morning before medication intake occurring since the diagnosis of PD 5 years ago. Furthermore, she describes a severe generalized pain since taking a combination of entacapone and L-dopa for some months during the whole day.
The first pain occurred during the off phase and improved with dopaminergic medication, whereas her second pain occurred during the on phase together with slight choreatic dyskinesia and worsened by the intake of the combination of entacapone and L-dopa. The leg pain was classified as nociceptive off dystonia. It was markedly reduced by adding a rotigotine patch. Due to severe neuropsychiatric symptoms after the exclusion of neuropathic and nociceptive pain, the second was classified as nociplastic with a PD-PCS score of 72 (maximum 90). This severe generalized pain was resolved along with a reduction of dyskinesia by stopping entacapone.

case, which may be more relevant for nociceptive pains, requires the consideration of mechanism-based therapies, and of the presence of PD-unrelated pain. In addition, a rating for pain intensity as well as for the impact on quality of life is suggested as provided within the proposed questionnaires [4, 42, 44]. However, in older adults with comorbidities, pain assessment using dedicated questionnaires often becomes difficult. Here, scales like verbal analogue scales for pain intensity and non-verbal scales should be employed in order to address relevant pain not adequately communicated [45].

5.1 Pains Related to PD

The PD-PCS can help to classify PD-related pains into one of the three mechanistic pain descriptors including all previously mentioned pains attributed to PD (i.e. nociceptive, neuropathic, and nociplastic pains) (Figs 1, 2) [4]. Neuropathic pain is defined as pain syndrome due to a lesion or disease of the somatosensory nervous system [46]. It includes a peripheral (e.g. distributed according to dermatomes) and a central subtype (i.e. following an atypical or a 'central' distribution, such as hemibody) [47]. Nociceptive pain, arising from actual or threatened damage of non-neural tissue due to the activation of nociceptors with increased sensitivity to palpation [48], can be subdivided into localized pains, myofascial pain syndrome, and coat hanger headaches. These pains often occur during an Off phase and may have a dystonic component. Nociplastic pain has been introduced as a third mechanistic pain descriptor for pains deriving from an alteration of nociceptive processing as described in primary pain syndromes [5, 48]. Following the definition from IASP, it is diagnosed after neuropathic and nociceptive pains are excluded [4]. In PD, nociplastic pains are usually part of a broader neuro-psychiatric disturbance including non-motor fluctuations such as dopamine agonist withdrawal syndrome or dopaminergic dysregulation syndrome, reflecting an altered dopaminergic receptor stimulation. We also classified leg motor restlessness and the non-motor Off here when the neuropathic component was not dominant.

5.2 Pains Unrelated to PD

Pains unrelated or indirectly-related (i.e. aggravated) to PD may occur with a higher frequency than in the general population [49]. Altered posture, falls, osteoporosis, and sensory polyneuropathy connected with cobalamin deficiency may increase the prevalence of PD-unrelated pains [50] compared with the general population as shown in one study compared to others [3, 4, 20].

5.3 Factors Influencing Pain in PD

Influencing factors can be assessed by using the MDS-NMS scale and when necessary by using dedicated questionnaires for the assessment of mood and cognition [e.g. Hospital Anxiety and Depression Scale (HADS) and Montreal Cognitive Assessment (MoCA)] [33, 51, 52]. These factors are of great importance because they influence pain perception and communication. Pain in PD patients is often insufficiently treated. Reasons may be underreporting by the patients, or predominance of other symptoms (e.g. severe motor Off phase or cognitive deficits) [13]. In this context, experimental studies revealed that pain perception is not reduced in dementia, but that communication is limited, which requires dedicated verbal or non-verbal assessment tools such as the Pain Assessment in Advanced Dementia (PAINAD) scale [45, 53]. When depression and pain occur simultaneously, a mutual negative influence should be considered due to the implication of similar neurotransmitters in both conditions [54]. Moreover, it has been demonstrated by using the NMSS that cardiovascular symptoms and sleep, in particular, correlate with pain in PD [10]. Thus, these NMS require further attention with respect to their negative influence on pain, implicating a detailed assessment

of sleep and cardiovascular symptoms (e.g. orthostatic hypotension).

6 Treatment of Pain

Treatment of pain in PD should be tailored to the mechanism of pain (i.e. nociceptive, neuropathic, or nociplastic [4]). These are the major pain syndromes [37]. There are no studies assessing the herein proposed mechanistic therapy in PD. Notwithstanding, in the present text we classify previous studies according to the assumed pain mechanism.

With respect to pain related to PD, no recommendations have been given so far by the Non-Motor PD study group of the Movement Disorders Society (MDS) in 2019 [55]. Insufficient evidence was found in one negative study for the combination of oxycodone/naloxone prolonged-release formulation [56]. Because of positive effects during the study and the almost significant effect at the primary endpoint, it was considered possibly useful with a monitoring of gastrointestinal symptoms (see below). Insufficient evidence was seen for the rotigotine patch according to the first results of one study [57]. Most studies did not target pain but reported pain as part of health-related quality of life and/or non-motor symptom questionnaires. Hence, recent studies measured pain by using visual analogue scales (VAS) or the KPPS. These studies revealed promising results of various approaches, which will be detailed in the following sections. Studies targeting motor symptoms of PD will be discussed first.

6.1 Effects of Dopaminergic Drugs on Pain in PD

The first step in the treatment of PD-related pain should be the adequate control of motor and non-motor symptoms by optimizing the dopaminergic medication schedule with attention on side effects. Studies targeting pain in PD are selected according to the assumed pain mechanism or the motor symptom treated (Table 1). All PD-related pain syndromes included under the respective mechanism are mentioned in Fig. 1.

6.1.1 Nociceptive Pain

6.1.1.1 Levodopa The effect of L-dopa on pain (mainly nociceptive and neuropathic) has been assessed in an open-label study of 15 patients reporting a pain reduction of 51% in the On phase as compared with the Off phase (VAS) and a correlation of motor improvements with pain decrease [58]. An evaluation of the Wearing-Off Questionnaire (WOQ-9) showed that motor and non-motor wearing-off pain respond differently to dopaminergic treatment [59]. Motor pain (muscle cramping) improved in 57%, whereas non-motor pain improved in 46% following the next dosage.

6.1.1.2 Dopamine Agonists *Rotigotine* Two randomized controlled trials (RCTs) evaluated the effect of the 24-h rotigotine transdermal patch on motor symptoms and non-motor symptoms [60, 61]. The analyses of the RECOVER study for unsatisfactory control of early morning symptoms revealed improved motor function, sleep and pain (Likert scale) after 4 weeks of maintenance [61]. Post-hoc analyses of patients with pain showed greater effects in those with motor symptom and sleep quality improvements [62].

The second study examined 12 weeks of rotigotine on non-motor symptoms in patients with an NMSS score of at least 40 [60]. This study revealed positive effects on the mood/apathy and miscellaneous domain of the NMSS (significant effect on excessive sweating but non-significant effect on unexplained pain) domain as well as on the UPDRS III and on quality of life [subdomains of the Parkinson's Disease Questionnaire-39 (PDQ-39) were not given].

Pramipexole An RCT targeting depressive symptoms in PD revealed that improved depression accounts for a major part of improvements induced by pramipexole [63]. The PDQ-39 did not show significant effects but the EQ-5D did. However, no significant effect in the pain subdomain was seen.

6.1.1.3 COMT Inhibitor *Entacapone* An RCT showed significant effects on health-related quality of life by the addition of entacapone for 26 weeks in patients with stable L-dopa response [64]. However, no significant effects on the pain subdomain were seen.

6.1.1.4 MAO-B Inhibitor *Safinamide* In addition to the reversible inhibition of the MAO-B, safinamide inhibits glutamate release by blocking voltage-dependent sodium channels [65]. Therefore, additional effects on pain transmission can be expected.

An RCT of safinamide for 24 weeks in patients with motor fluctuations and relevant Off time revealed increase of On time for the 50- and 100-mg dosages, improved quality of life (PDQ-39) as well as improved bodily discomfort for the 100-mg dosage only [66]. The post-hoc analyses of two trials showed slightly fewer concomitant pain drugs as well as a slight reduction in muscle cramps and hot or cold sensations (items of the PDQ-39) [67]. The 2-year extension study as well as the post-hoc analyses of PD-related quality of life showed similar effects [68, 69].

A 12-week open-label study in 13 patients with musculoskeletal ($N = 13$) and neuropathic pain ($N = 7$), and with motor fluctuations showed significant effects of safinamide 100 mg on the KPPS, the Brief Pain Inventory (BPI), and the Numeric Rating Scale (NRS) [70].

Table 1 Studies investigating pain in PD by using dopaminergic drugs

Study	Drug	Study design/sample size per group	Inclusion criteria	Primary outcome/pain-related outcome	Group differences in the outcomes	Main pain mechanisms	Comments
Nebe and Ebersbach [58]	L-Dopa	ON vs OFF *N* = 15	Motor fluctuations and pain	UPDRS III Pain VAS	− 14 − 3.6 (< 0.01)	Nociceptive Lower body pain	Changes in motor performance correlated with improvements in pain (< 0.05)
Olanow et al. [64]	Entacapone 200 mg added to each L-dopa dose or placebo for 26 wk	RCT *N* = 373/377	stable L-dopa response without motor fluctuations	UPDRS III PDQ-39 SF-36 pain domain	no difference 0.9 (< 0.001) − 0.1 (NS)	Not determined	Slight improvement in Quality of life
Trenkwalder et al. [61]	Rotigotine 2–16 mg/24 h or placebo for 4 wk	RCT *N* = 190/97	Early morning symptoms	UPDRS III PDSS-2 Pain Likert scale	− 3.55 (< 0.001) − 4.26 (< 0.0001) − 0.77 (< 0.001)	Nociceptive	
Kassubek et al. [62]	Post-hoc analyses	Patients with pain *N* = 178/89		Likert scale Moderate to severe pain	− 0.88 (< 0.05) − 1.38 (< 0.05)		UPDRS III and PDSS-2 responders had greater effects
Antonini et al. [60]	Rotigotine 1–16 mg/24 h or placebo for 12 wk	RCT *N* = 211/122	NMSS ≥ 40	NMSS NMSS domains Mood/apathy Miscellaneous PDQ-39 UPDRS III	− 3.58 (NS) − 1.81 (< 0.05) − 1.04 (< 0.05) − 2.79 (< 0.05) − 2.6 (< 0.01)	Nociplastic?	In the miscellaneous domain pain decrease not significant
Barone et al. [63]	Pramipexole 0.125–1 mg/3× daily or placebo for 12 wk	RCT *N* = 139/148	GDS ≥ 5 and UPDRS I depression item ≥ 2	BDI UPDRS III PDQ-39 EuroQol	–1.9 (< 0.05) − 2.2 (< 0.005) − 1.3 (NS) 0.04 (< 0.05)	Depression	No group differences concerning pain were seen in the EuroQol
Borgohain et al. [66]	Safinamide 50–100 mg/d or placebo for 24 wk	RCT N1 = 224 N2 = 223 Placebo *N* = 222	Motor fluctuations at least 1.5 h Off time	On without troublesome dyskinesia UPDRSIII PDQ-39 100 mg Bodily discomfort	0.51 h (50 mg) (< 0.05) 0.55 h (100 mg) (< 0.05) –1.8 (50 mg) (< 0.05) − 2.6 (100 mg) (< 0.001) − 16.5 (< 0.05) − 3.3 (< 0.05)	Nociceptive	

Table 1 (continued)

Study	Drug	Study design/sample size per group	Inclusion criteria	Primary outcome/pain-related outcome	Group differences in the outcomes	Main pain mechanisms	Comments
Cattaneo et al. [67]	Post-hoc analyses 100 mg/d for 24 wk	RCT		PDQ-39			
				No concomitant pain drugs	76 vs 70% (< 0.05)		
				Muscle cramps	−0.19 (< 0.001)		
				Pains in joints or body	− 0.09 (NS)		
				Hot or cold	− 0.15 (< 0.01)		
Borgohain et al. [68]	Safinamide 50–100 mg/d or placebo for 2 y	RCT	Motor fluctuations at least 1.5 h Off time	On without troublesome dyskinesia	0.67 h (50 mg) (< 0.005) 0.83 h (100 mg) (< 0.001)	Nociceptive	
Cattaneo et al. [69]	Post-hoc analyses 100 mg/d for 2 y			PDQ-39			
				No concomitant pain drugs	− 26%		
				Muscle cramps	− 0.23 (< 0.01)		
				Hot or cold	− 0.14 (< 0.05)		
				Bodily discomfort	− 3.69 (< 0.001)		
Geroin et al. [70]	Safinamide 100 mg/daily for 12 wk	Open-label study $N = 13$	Motor fluctuations and pain ≥4 NRS	KPPS score	− 19.3 (< 0.05)	Nociceptive ($N = 13$) and neuropathic ($N = 7$)	Not placebo controlled
				BPI intensity	− 11.8 (< 0.05)		
				NRS	− 4.6 (<0.05)		
				UPDRS III	− 8.5 (< 0.05)		
				PDQ-39	− 11.2 (< 0.05)		
				Bodily discomfort	− 4.5 (< 0.05)		

BDI Beck Depression Index, *BPI* Brief-Pain Inventory, *GDS* geriatric depression scale, *KPPS* King's Parkinson Pain Scale, *NMSS* Non-Motor Symptoms Scale, *NRS* Numeric Rating Scale, *NS* not significant, *PDSS-2* PD Sleep Scale 2, *PDQ-39* Parkinson's Disease Questionnaire-39, *RCT* randomized controlled trial, *UPDRS* Unified PD Rating Scale, *VAS* visual analogue scale

An additional observational safety study over 1 year including patients older than 75 years showed significant improvements in motor function in 45% of the patients [71]. In older adults with PD, dyskinesia was the most frequent side effect. Adverse events (AEs) were similar to patients younger than 75 years, while serious AEs (SAEs) occurred more often in patients aged > 75 years (13.6 vs 7.7%). Patients with comorbidities had higher rates of AEs and SAEs. No serotoninergic syndromes were reported despite an intake of antidepressant drugs in 28% of the patients.

6.1.2 Nociplastic Pain

A similar approach to the one recommended for nociceptive pain may also be applied to nociplastic pain with a predominance in the Off phase. Therefore, optimization of the antiparkinsonian drug regimen should be the first therapeutic option. No recommendations can be given at the present time for pain not responding to optimized dopaminergic therapy.

6.1.3 Neuropathic Pain

So far, no double-blind RCT has reported effects of dopaminergic drugs on neuropathic pain. Notwithstanding, in the open-label study of safinamide, an improvement in pain was seen in seven patients with neuropathic pain [70]. Since central neuropathic and nociplastic pains result from central pain augmentation due to dopamine depletion, we suggest increasing dopaminergic stimulation when a clear relation with PD can be assumed. This hypothesis should be tested in appropriate double-blind controlled trials.

6.1.4 Treatment of PD in Older Adults: General Remarks

Beyond the therapy of motor and non-motor symptoms, PD therapy in older adults should respect altered pharmacokinetics, polypharmacy as well as comorbidities [7].

Concerning levodopa, older women were found to have higher plasma concentrations and a longer drug half-life [72]. Additional orthostatic symptoms may occur in relation to L-dopa intake [73], and L-dopa can further lead to cobalamin deficiency causing polyneuropathy [50]. Also, the impact of gastroparesis in PD leading to a reduced bioavailability should not be neglected [74]. Proteins using similar intestinal transport proteins should not be taken simultaneously but rather with a delay of 60 min before or 30 min after levodopa intake.

Because of the higher frequency of side effects of dopamine agonists, older patients are preferably treated with levodopa. However, if carefully monitored, dopamine agonists can reduce the levodopa dosage, presumably enlarging the interval until motor fluctuations occur. Side effects show a large inter-individual difference and even a low dosage may induce hallucinations, impulse control disorders as well as dizziness [75]. When dopamine agonists are taken together with centrally acting agents, sleepiness may further increase. Risk factors for the development of impulse control disorders include elevated dopamine agonist dosages as well as psychiatric comorbidities [76]. For pramipexole, reduced renal function must be taken into account (for ropinirole only in patients with hemodialysis) [77], while liver function should be considered for ropinirole and rotigotine [78].

COMT and MAO-B inhibitors reduce the degradation of levodopa and thereby increase and prolong its bioavailability. Thus, lower levodopa dosages are required. In addition, the degradation of catecholamines is reduced, which has to be considered when given simultaneously with antidepressants (increased risk for serotonin syndrome). COMT inhibitors may cause dyskinesia when given early [79] and they inhibit CYP2C9, which may lead to increased plasma levels of various agents (e.g. warfarin, diclofenac, ibuprofen, sartans) [80]. The new COMT inhibitor, opicapone, can be administered instead of entacapone only once daily [81]. MAO-B inhibitors are recommended as monotherapy in early PD but also as add-on therapy in advanced stages [82]. The combination with serotoninergic agents increases the risk for serotonin syndrome, which has not been observed in a recent retrospective study [83]. For rasagiline, metabolism via CYP1A2 may lead to increased plasma levels by inhibitors. Rasagiline and safinamide should not be given in liver insufficiency and selegiline not in renal insufficiency [84].

Amantadine, an NMDA-receptor antagonist often employed for the treatment of dyskinesia [85] or in akinetic crises, should not be given together with other QTc-prolonging drugs or in patients with a history of arrhythmias [86]. In addition, renal function, as well as anticholinergic side effects, must be considered.

6.2 Treatment of PD-Related Pain with Non-Dopaminergic Drugs

When pain does not respond to an optimization of the dopaminergic drug regimen, further pain therapy should be envisaged. To date, only three studies have targeted pain in PD [56, 87, 88]. In clinical practice, NSAIDs have been prescribed very often [89]. Table 2 lists studies investigating pain in PD by using non-dopaminergic drugs.

6.2.1 Nociceptive Pain

6.2.1.1 NSAIDs So far, no studies have been performed on the effects of NSAIDs and related drugs on pain in PD. In an observational study, 55% of the PD patients with pain were treated with painkillers [89]. NSAIDs contributed to 60% of the painkillers used, followed by paracetamol (22%), meta-

mizole (16%), and opioid derivates (9%). A 78% efficacy was reported by the patients.

6.2.1.2 Oxycodone/naloxone A 16-week RCT with prolonged-release oxycodone–naloxone in a dosage of 2 × 5/2.5 mg up to 2 × 20/10 mg failed to show a significant effect on the primary outcome (0.6; $p = 0.058$) in PD patients with severe pain (NRS ≥6) but demonstrated a significant improvement after 4, 8 and 12 weeks, especially in patients with musculoskeletal (NRS −0.9) and nocturnal pains (NRS −1.6) [56]. Responder rates were higher in the verum group (48 vs 34%) but drop-out rates were also higher, mainly due to nausea and constipation (17% vs 9% and 17% vs 6%).

6.2.1.3 Tapentadol In a retrospective analysis of 21 PD patients treated with tapentadol (average dosage 200 mg) over 6 months, a mean pain reduction of about 50% was seen with a good tolerability and no cognitive side effects [90]. In addition, mood as well as quality of life improved. In this retrospective study, patients with different pains were included (mostly nociceptive and mixed pains according to the painDETECT questionnaire).

6.2.1.4 Cannabinoids Significant positive short-term effects of a single dose of medical cannabis were seen with respect to motor function and pain as well as for experimental pain measures [91]. Large clinical trials failed to confirm such positive effects often given in open-label studies in other indications [92, 93]. One small RCT revealed an improvement in PD-related quality of life with cannabidiol (CBD) 300 mg, but showed no significant effect on pain [94]. Another RCT of tetrahydrocannabinol (THC)/CBD showed no significant effects on dyskinesia and failed to show significant effects on pain [95]. In a recent survey of patients in Germany, PD-related use of medical cannabis was reported by 8.4%, and 40% of them reported relief from pain and muscle cramps [96].

6.2.1.5 Botulinum toxin Two RCTs assessed the effects of botulinum toxin on two different types of limb pain. One RCT investigated whether the injection of 100 U into the flexor digitorum longus or the flexor digitorum brevis muscle improves toe dystonia [97]. Positive effects on dystonia as well as on pain compared with placebo were seen for both sites but with greater effects for the injection of the flexor digitorum longus muscle also lasting beyond the second injection after 3 months. The authors conclude that a simultaneous injection in both muscles may have even greater effects. The other study failed to show significant effects on limb pain not responsive to levodopa compared with placebo when the muscles of the affected limb were injected with an average dosage of about 242 U (without specifying the respective muscles) [98].

6.2.2 Neuropathic and Nociplastic Pains

6.2.2.1 Duloxetine Beyond its use for the treatment of major depression, duloxetine is an SNRI with proven effects on pain in diabetic neuropathy [99] as well as in chronic musculoskeletal pain [100]. One open-label study employing duloxetine 30–60 mg for 6 weeks in 20 PD patients with assumed central pain revealed a relevant clinical effect on various pain measures [87]. The high drop-out rate (starting dose 60 mg), the open-label design as well as the definition of central PD-related pain must be considered. Usually, a better tolerability can be reached by slow titration. A recent RCT of duloxetine 40 mg for 10 weeks in a group of selected patients with PD-related pains could not replicate the results of this previous study [88]. The study showed positive effects on various aspects of quality of life independently from effects on depression. Lower pain intensities (VAS 5) and the inclusion of all PD–related pains was assumed to account for these negative findings.

6.2.3 Treatment of Pain in Older Adults: General Remarks

With respect to pain medications in PD, limitations exist for their use in geriatric patients. An individualized pain therapy should be envisaged considering altered pharmacokinetics, which requires a reduced dosage depending on liver and renal function [101]. Pharmacotherapy should "start low and go slow" and be given only for a short period. Each agent has some limitations; for example, topical agents should be preferred in cases of osteoarthritis. Interactions with low-dose aspirin must be considered, and thus an interval of 1–2 h can reduce risks for interactions with other NSAIDs. COX-2 inhibitors should be preferred due to a reduced risk for gastrointestinal bleeding. Prophylactic treatment with PPIs could be envisaged, but interactions of PPIs with other medications have to be taken into account. Due to the nephrotoxicity of NSAIDs, paracetamol in doses up to 2 g/day is preferred in older persons without liver dysfunction. Vasoconstrictor effects of NSAIDs in ischemic heart disease and stroke should be taken into account. Also, metamizole can be considered with special care for orthostatic hypotension and myelotoxicity. Prolonged-release opioids in lowest dosages preferably applied together with an antagonist (to reduce gastrointestinal side effects) should be used according to the pain mechanism and the WHO steps but not for longer than 3–6 months. An opioid rotation may be useful, when the pain does not respond (e.g. with tapentadol). Tricyclic antidepressants should be given with caution due to anticholinergic side effects, especially on cognition. Duloxetine in

Table 2 Studies investigating pain in PD by using non-dopaminergic drugs

Study	Drug	Study design/sample size per group	Inclusion criteria	Primary outcome/pain-related outcome	Outcomes group differences	Associated factors	Main pain mechanisms	Comments
Trenkwalder et al. [56]	Oxycodone/naloxone 2 × 5/2.5 mg until 20/10 mg for 16 wk	RCT $N = 93/109$	Hoehn and Yahr stage II–IV patients with severe pain (NRS ≥ 6) in a subsection of the KPPS stable medication	NRS	− 0.6 ($p = 0.058$) 16 wk − 0.6 ($p = 0.018$) 4 wk − 0.7 ($p = 0.011$) 8 wk − 0.7 ($p = 0.021$) 12 wk	76% musculoskeletal 22% PD-related pain 30% fluctuation-related 30% nocturnal pain 2% orofacial pain 19% limb pain 48 vs 34%	Nociceptive	Slight effects Drop-out rates higher in the verum group (33% vs 29%) due to nausea (17% vs 9%) and constipation (17% vs 6%)
				Responder rate	− 0.9 musculoskeletal − 1.6 nocturnal pain			
				CGI-I	36 vs 27%			
				NMSS	NS			
				PDSS-2	NS			
Djaldetti et al. [87]	Duloxetine 60 mg for 6 wk, reduction to 30 mg when side effects	Open-label $N = 20$	Constant central PD-related pain (exclusion of other pains) for at least 30 d not relieved by NSAIDs	McGill pain quest, SF	− 5.7 ($p < 0.01$)	65% of the patients reported improvements in pain	Neuropathic	7 patients reported adverse events started by 60 mg, drop-out rate 35% open-label design
				BPI	− 22.6 ($p < 0.001$)			
				BDI	− 0.9 (NS)			
				PDQ-39	5.5 (NS)			
				UPDRSIII On	1.0 (NS)			
				VAS	− 3.4 ($p < 0.0001$)			
				Warm sensation	NS			
				Heat pain threshold	NS			
Iwaki et al. [88]	Duloxetine 40 mg for 10 wk	RCT N1 = N2 = 23	PD patients with PD-related pain (exclusion of other causes), no antidepressants	VAS	1.09 (NS)	PDQ-39 subdomains improved independently from BDI score changes	PD-related pains	7 patients in the verum and 2 patients in the placebo group discontinued due to side effects
				TUG	− 0.72 (NS)			
				McGill pain quest, SF	− 0.43 (NS)			
				BDI	− 0.78			
				UPDRS III	− 1.17 ($p < 0.05$)			
				PDQ-39				
				ADL	− 9.6 ($p < 0.05$)			
				Emotional	− 13.04 ($p < 0.01$)			
				Communication	− 7.25 ($p < 0.05$)			

Table 2 (continued)

Study	Drug	Study design/sample size per group	Inclusion criteria	Primary outcome/pain-related outcome	Outcomes group differences	Associated factors	Main pain mechanisms	Comments
Chagas et al. [94]	CBD 75/300 mg for 6 wk	RCT N1 = N2 = N3 = 7	Hoehn and Yahr I–III Stable medication No psychiatric comorbidity	UPDRS (I–IV) On	NS	No side effects reported	Not given	Small sample size ANOVA of PDQ-9 revealed significant effect for 300 mg (stigma, social support and cognition)
				PDQ-9 75 mg	3.5 ($F = 4.142$ $p < 0.05$)			
				PDQ-9 300 mg	19.07 ($F = 4.142$ $p < 0.05$)			
Carrol et al. [95]	THC and CBD 2 × 2.5/1.25 mg adapted to the body weight and effects max 0.25 mg THC/kg for 4 wk	RCT cross-over $N = 19$	UPDRS IV (items 32–34) ≥2	UPDRS IV (items 32-34)	0.5 (NS)	Mild adverse events: 37 in the verum group and 15 in the placebo group	Nociceptive	Low drop-out rate 11%
				Dyskinesia (ADL)	− 1.1 (NS)			
				Bain dyskinesia scale	− 0.7 (NS)			
				Rush dyskinesia scale	− 1.5 (NS)			
				PDQ-39	− 0.7 (NS)			
				McGill Pain quest	− 1.8 (NS)			
Rieu et al. [97]	Incobotulinum A 100 IU flexor digitorum longus or brevis muscle or placebo 2× with 3 mo interval	RCT N1 = 16 N2 = 13 N3 = 16	Food dystonia (prolonged plantar flexion of toe dystonia)	CGIC	0.51 ($p = 0.039$) Percentage improved: flexor digitorum longus 62 and 69% (week 6 and 18) flexor digitorum brevis 47 and 56%	Mild adverse effects	Nociceptive	Better effects were seen for the injection of the flexor digitorum longus muscle; injection into both muscles at the same time might be more effective
				Dystonia severity	$p < 0.001$ week 6 $p < 0.001$ week 18			
				Pain	$p < 0.001$ week 6 $p < 0.01$ week 18			

Table 2 (continued)

Study	Drug	Study design/sample size per group	Inclusion criteria	Primary outcome/pain-related outcome	Outcomes group differences	Associated factors	Main pain mechanisms	Comments
Bruno et al. [98]	Botulinum toxin type A Average of 242 U ×1 Painful limb muscles not specified	RCT cross-over $N = 12$	Advanced PD Hoehn and Yahr stage III–IV Painful limbs not responding to levodopa	NRS week 4	− 1.75 ($p < 0.05$) − 0.58 (NS when compared with placebo)	Dystonic pain − 2.66 Musculoskeletal − 1.41	Nociceptive	Improvement in pain is not significant when compared with placebo
				Responder	Verum 58% vs. placebo 42%			
				NRS week 12	NS			
				VAS week 12	NS			
				CGI	Group differences NS			
				MDS-UPDRS	NS			
				PDQ-39	NS			

ADL activities of daily living, *BDI* Beck Depression Index, *BPI* Brief-Pain Inventory, *CBD* cannabidiol, *CGI-I* Clinical Global Impression Scale—Improvement, *KPPS* King's Parkinson Pain Scale, *MDS* Movement Disorders Society, *NMSS* Non-Motor Symptoms Scale, *NRS* Numeric Rating Scale, *NS* not significant, *NSAIDs* non-steroidal anti-inflammatory drugs, *PD* Parkinson's Disease, *PDQ-39* Parkinson's Disease Questionnaire, *PDSS-2* PD Sleep Scale 2, *RCT* randomized controlled trial, *THC* tetrahydrocannabinol, *TUG* Timed Up and Go test, *UPDRS* Unified PD Rating Scale, *VAS* visual analogue scale

low dosages can be considered as add-on therapy depending on the pain type. Low dosages of gabapentin and pregabalin for neuropathic pain should be employed due to reduced renal function in older persons. The FORTA (Fit fOR The Aged) classification supports the adaptation of medication in geriatric patients to avoid over- or under-treatment, as well as mistreatment, by defining indispensable (A), beneficial (B), and questionable drugs (C), as well as drugs to be avoided (D) [102, 103]. Its use in PD patients revealed severe interactions in 12% and moderate to severe interactions in 81%, supporting its usefulness in older PD patients [104].

6.3 Invasive Treatments

6.3.1 Deep Brain Stimulation (DBS)

Deep Brain Stimulation (DBS) is performed by the surgical implantation of electrodes into the brain (usually bilaterally) connected to an extension wire and to an implanted pulse generator (usually located subcutaneously on the chest) [105]. The system provides electrical stimulation to a relatively restricted area of the brain in contact with the tip of the implanted electrode and its adjacent contacts. The most common targets include the subthalamic nucleus (STN) and the globus pallidus pars interna (GPi). Electrical stimulation of these targets provokes the net functional effect of a reversible lesion depending on the stimulation parameters controlled by telemetry. The main indications of DBS are motor fluctuations refractory to levodopa replacement therapy such as dyskinesia, unpredictable Off periods and wearing-off. It has been previously shown that as well as the beneficial effects of DBS on motor symptoms, NMS symptoms such as pain and gastrointestinal disturbances may also improve after surgery. In fact, it has been shown that pain improvement after STN-DBS may have an important role in the overall improvement in quality of life after surgery [106]. Patients with PD have lower than normal pain thresholds, which can be partially reverted by L-dopa administration [24, 26, 107], but also by turning on the STN-DBS system [108]. Also, it seems that specific regions within the STN may favor pain-relieving effects of DBS when used as the main target [109]. To date, NMS control is not a formal indication of DBS, but pain improvement does occur in a large majority of patients after surgery in the long term, especially musculoskeletal (nociceptive) types of pain.

6.3.2 Levodopa-Carbidopa Intestinal Gel (LCIG)

In the last decades, it has been shown that infusion gel of levodopa-carbidopa provides more stable blood levels of levodopa compared with its oral administration in patients experiencing motor fluctuations [110]. Indeed, classical studies have demonstrated the positive effects of L-dopa gel

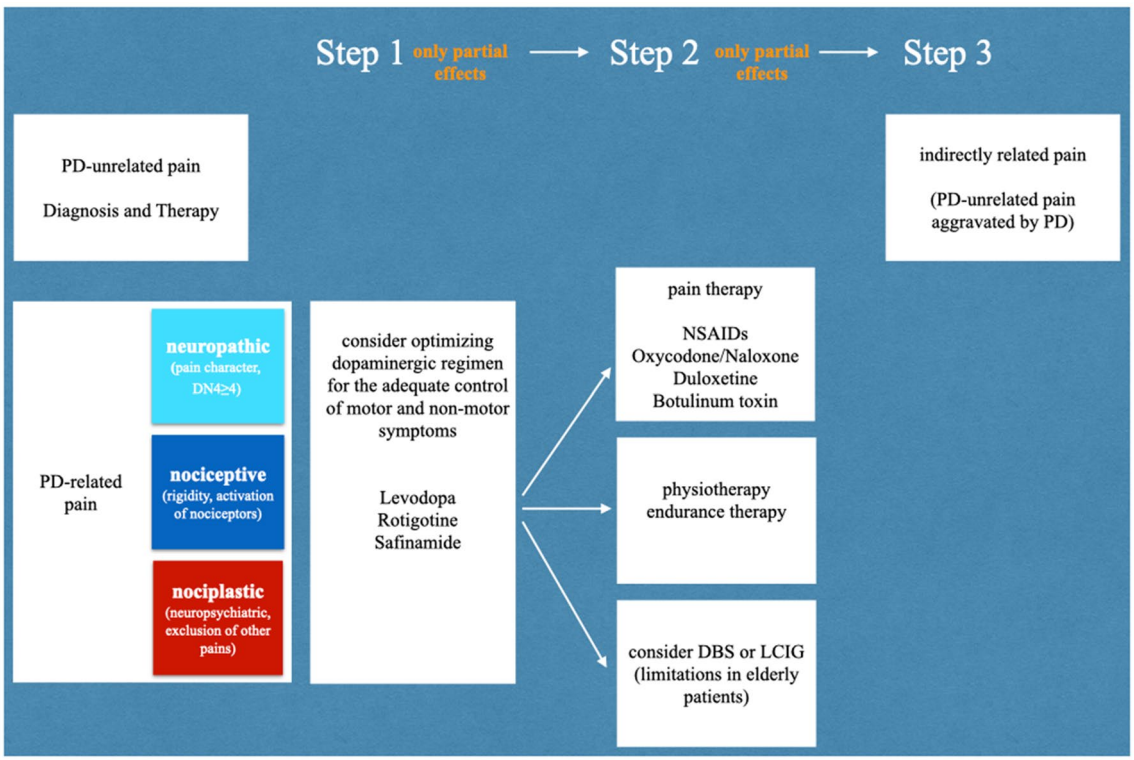

Fig. 5 Algorithm for the therapy of Parkinson's disease (PD)-related pains according to the PD–Pain Classification System (PD–PCS)

infusion in controlling otherwise refractory motor symptoms [111]. Lately, it has been shown that this same strategy would also ameliorate NMS [112]. There is a large body of evidence indicating that L-dopa gel infusion can attenuate several NMS such as mood, sleep, and cognition. Its effects on PD-related pain have been assessed in a small number of uncontrolled studies. The GLORIA registry and Buongiorno et al. have shown an improvement in muscle cramps and painful paresthesias in the long term [112, 113]. Importantly, abdominal cramps have been reported as a side effect of L-dopa gel infusion, affecting 3.1% of patients, along with weight loss, which affected 5.6% of a large cohort of advanced PD patients under long-term L-dopa gel infusion [114]. A recent study also suggested benefits in older PD patients, but dropout rates of about 20% are usually seen [115].

6.4 Physiotherapeutic Interventions

The advantage of physiotherapeutic interventions compared with pharmacological interventions are the positive effects on multiple parameters leading to an increase in quality of life as well as life expectancy with negligible side effects and drug interactions. Based on immediate and prolonged exercise-induced hypoalgesia [116], a clinical study demonstrated outstanding effects on pain and motor function from long-lasting regular Nordic walking or walking (endurance therapy, 70 minutes, 3 times weekly for 6 months), but not of flexibility training [117].

7 Summary of Recommendations (Fig. 5)

No RCT of dopaminergic drugs targeting pain as the primary outcome has been published so far. Effects of L-DOPA were evaluated in a single open-label study and in clinical observations. Only one RCT targeting early morning symptoms with transdermal applied rotigotine showed significant effects on pain, especially in those patients with moderate to severe pain, but this was a secondary outcome and the sample included patients both with and without pain. Pramipexole did not show significant effects on pain in depressive patients. Despite negative results in a study targeting pain with entacapone in stable patients, the drug might still have a place in the treatment of wearing-off related pain, but this has not been assessed so far [79]. Safinamide is a promising drug with a potential to reduce Off time and with a slight analgesic effect. With respect to older PD patients, the treatment recommendations favor the use of L-DOPA as compared with agonists. Notwithstanding, rotigotine transdermal patch may be useful in older PD patients for early morning pain associated with sleep disorders if side effects are carefully monitored. Safinamide can also be suggested as a treatment with a good side-effect profile in older persons, when relevant Off phases occur.

When optimizing the antiparkinsonian drug regimen, NMS should be targeted specifically. Indeed, pain, as well as other NMS, are only partially relieved by improvements in motor symptom control. DBS studies showed that the pain correlates rather with motor fluctuations and not with the motor score [106]. Accordingly, a recent classification using a similar mechanistic approach suggests a central augmentation in some PD-related pains (i.e. dystonic nociceptive and central nociplastic pains) [37]. The beneficial effects of further increasing dopaminergic treatment doses in patients with adequate motor control remain unknown.

The treatment of PD-related pains with non-dopaminergic drugs should be the second step after the careful modification of motor and non-motor symptoms with dopaminergic drugs. Dedicated treatments are available for selected conditions such as botulinum toxin for toe dystonia and duloxetine for central neuropathic pain. The short-term use of prolonged-release oxycodone–naloxone could be useful in patients with refractory pain when side effects are carefully monitored. So far, convincing studies of THC/CBD for pain therapy in PD are lacking. NSAIDs can be used in the short term, with a high efficacy reported by the patients. Invasive therapies can be an option for refractory PD-related pain in advanced PD. DBS has been suggested to be efficacious in the treatment of pain, with its use favored in patients in whom DBS is indicated for other reasons. The responsiveness of pain to LCIG is probably lower. However, both invasive methods have many contraindications, making them less suitable in older patients. For DBS, an age > 70 years is often considered a contraindication, in addition to dementia, psychosis and depression. For LCIG application, the handling of the device by the patients or the caregivers must be respected. Finally, secondary causes of pain must be considered if pain does not respond well to any of these therapeutic measures.

8 Conclusion

We suggest approaching the treatment of pain in PD patients by performing the correct mechanistic diagnosis in the first place. In addition, motor symptoms, other NMS, frailty, concomitant diseases, and life conditions should also be taken into account. Pharmacological treatments should consider these factors as well as side effects and drug interactions.

With respect to dopaminergic medication, L-DOPA and rotigotine transdermal patch have shown some effects in open-label studies or as secondary outcomes in RCTs, and may therefore be used preferably for the treatment of pain in PD. With respect to non-dopaminergic medication, botulinum toxin can be suggested for toe dystonia, and duloxetine can be considered in central neuropathic pain. Refractory pain might respond to prolonged-release oxycodone–naloxone, when side effects are carefully monitored. Convincing studies

for THC/CBD are lacking so far. Physical therapy should not be neglected due to the reported effects on pain and positive effects on falls and frailty. Invasive therapies such as DBS and LCIG can also be an option for the treatment of pain in carefully selected patients.

The regular follow-up of the patient requires an interdisciplinary approach with regular clinical and laboratory controls as described previously [7]. Large RCTs targeting different types of PD-related pains (i.e. nociceptive, nociplastic, and neuropathic pains) are warranted in order to provide a mechanism-based treatment.

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