EXPERT OPINION

Emerging analgesic drugs for Parkinson's disease

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Introduction: Pain affects between 40 and 85% of Parkinson's disease (PD) patients. It is a frequently disabling and overlooked feature, which can significantly reduce health-related quality of life. Unfortunately, there are no universally recommended treatments for this condition.
Areas covered: Evidence about the efficacy and safety of available analgesic treatments is summarized in this review. Potential targets for upcoming therapies are then discussed in light of what is currently known about the physiopathology of pain in PD. Protocols for efficacy and safety assessment of novel analgesic therapies are discussed. Finally, critical aspects of study protocol design such as patient selection or outcomes to be evaluated are discussed.
Expert opinion: Preliminary results indicate that duloxetine, cranial electrotherapy stimulation, rotigotine, subthalamic or pallidum nuclei stimulation or lesion or levodopa could be effective for treating pain in PD. Similarly, some case reports indicate that repetitive transcranial magnetic stimulation (rTMS) or apomorphine could be effective for relieving painful off-period dystonia. Clinical trials with rTMS or oxycodone/naloxone prolonged-release tablets for neuropathic pain or botulinum toxin for off-period dystonia are underway. Success of clinical trials about analgesic strategies in PD will depend on the selection of the right PD population to be treated, according to the type of pain, and the proper selection of study outcomes and follow-up of international recommendations.

Keywords: analgesic treatments, botulinum toxin, cranial electrotherapy stimulation, dopamine agonists, duloxetine, levodopa, non-motor symptoms, outcome evaluation, pain, Parkinson's disease, patient selection, repetitive transcranial magnetic stimulation, surgical treatments for PD

Expert Opin. Emerging Drugs [Early Online]

1. Background

Parkinson's disease (PD) is a progressive neurodegenerative condition [1] affecting more than 1 million people worldwide [2,3]. It is characterized by a progressive degeneration not only of the dopaminergic nigrostriatal pathway, but also of many other central and peripheral neuronal systems [4]. The involvement of such dopamine and non-dopaminergic systems is responsible for the occurrence of the motor and non-motor parkinsonian symptoms. Non-motor symptoms and their management are now recognized as an important unmet need in PD [5]. They affect the great majority of PD patients and may sometimes be more closely related to reduced quality of life than the core motor symptoms [6,7]. It has also been shown that significant health gains could be achieved if non-motor symptoms, such as pain, depression or insomnia, were treated since the onset of the disease [8].

Pain is a frequent non-motor parkinsonian symptom, contributing significantly to disability and reduced health-related quality of life in PD [9]. In the remaining portion of this section, we will briefly review its epidemiology and pathophysiology.

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1.1 Pain classification and prevalence in PD

Pain prevalence in PD, ranging from 40 to 85% according to a recent systematic review [10], is greater than that in the general population [10-19]. The variability in pain's prevalence figures in PD may be accounted for by lack of standard definition or systematic assessment of the different types of pain associated with PD [9]. In fact, no international validated classification system has yet been proposed to describe pain, which is nowadays described according to variable approaches including its relationship with dopaminergic clinical response [20], its clinical features [21] or its association with other PD features (time of onset, laterality, etc.) [17]. These different approaches illustrate the fact that pain in PD is a heterogeneous condition, with multiple origins and mechanisms. It has been suggested that PD-related pain is the pain that starts after PD diagnosis, responds to antiparkinsonian treatment, is more prominent on the side maximally affected and/or that does not have any other clear cause [13,17].

1.2 Mechanism of pain in PD

From a pathophysiological perspective, pain can be broadly divided into two main categories: 'nociceptive' and 'neuropathic' pain. Schematic representation of pain and basal ganglia circuits in normal conditions and in Parkinson's disease is offered in **Figure 1**. Nociceptive pain can be defined as pain arising from actual or potential damage to nonneural tissue and being due to the activation of nociceptors. Among such pains, we can cite dystonia-related pains located in toes, feet and more rarely in hands, occurring during off-periods such as early in the morning or biphasic beginning-of-dose or end-of-dose painful dyskinesias [20,22]. Similarly, pain symptoms arising from skeletal or articulation deformations, from parkinsonian rigidity or from postural abnormalities, can also be classified as nociceptive pain [21]. It can be supposed that such conditions could lead to an overstimulation of peripheral nociceptors and thus to the occurrence of pain. Therefore, this type of pain seems to be closely related to motor symptoms of the disease. Nonetheless, altered central processing of pain stimuli in PD could also play a role, as discussed in the following paragraphs.

The second main type of pain, corresponding to neuropathic pain, is defined as 'pain caused by a lesions of the central or peripheral somatosensory system' leading to central or peripheral neuropathic pain respectively. Pathophysiological mechanisms underlying such pains in PD are not well understood, but several pieces of evidence suggest a role of altered pain processing. For example, lowered subjective [13,23-29] and objective pain thresholds measured by recordings of the nociceptive flexion reflex [26,30,31] and pain tolerance [25,29] were found in painful and pain-free PD patients compared with healthy subjects. In addition, positron emission tomography (PET) studies, performed both in non painful patients and in patients suffering from PD-related neuropathic pain, showed abnormal hyperactivations in nociceptive brain areas underlying sensory-discriminative, affective and cognitive aspects of pain, during experimental painful stimulations [23]. Arguments supporting abnormalities of pain perception in PD are also provided by electrophysiological studies recording nociceptive laser-evoked potentials (LEPs) in PD patients [27].

Involvement of basal ganglia dysfunction following nigrostriatal denervation in the genesis of neuropathic pain in PD has been suggested by the finding that levodopa normalized pain perception abnormalities [23,27,30]. However, the finding that apomorphine did not modify pain perception [32] further suggests the potential importance of non-dopaminergic systems, such as the noradrenergic or serotoninergic ones.

A possible peripheral origin for neuropathic pain in PD has been also suggested by studies showing a decreased density of unmyelinated nerve fibers in sural nerve of PD patients [33] or a loss of epidermal nerve fibers and Meissner's corpuscles in epidermal tissue of PD patients [34].

2. Medical need

Pain is a frequently overlooked characteristic of PD, but can be severe enough to overshadow the motor symptoms of the disorder [21].

Quality of life has been shown to be reduced in PD patients with pain [35,36].

Improvement of patients' quality of life is one of the most important goals of antiparkinsonian treatment [37]. Treatment of pain has the potential to significantly improve PD patients' well-being [36]. Therefore, every effort should be placed in diagnosing and treating this condition.

3. Existing treatments

Treatment of pain in PD depends on many factors, including its cause and relationship with PD. For example, suggested treatments for musculoskeletal pain of parkinsonian origin are adjustment of dopaminergic therapy, physical therapy, exercise programs or analgesics [9,21]. Dystonic pain may be treated by adjusting dopaminergic therapy or botulinum toxin or by stimulation of pallidum or subthalamic nuclei [38]. Finally, no treatment can be recommended nowadays for neuropathic 'central' pain [21]. Nonetheless, some authors suggest that it might be dopamine-mediated and might respond to dopaminergic therapy [9].

In this section we will discuss the scientific evidence about the efficacy and safety of available treatment for pain in PD. We will discuss only 'therapeutic' trials (i.e., studies aimed at assessing the therapeutic potential of drugs or devices). A summary of most relevant studies is offered in **Table 1**.

3.1 Pharmacological treatments

3.1.1 Dopaminergic agents

As reviewed earlier, basal ganglia are related to processing of pain information [39]. Interestingly, dopamine exerted an inhibitory effect of pain-evoked stimuli in rats [39], thus supporting a possible clinical analgesic effect. Moreover, in

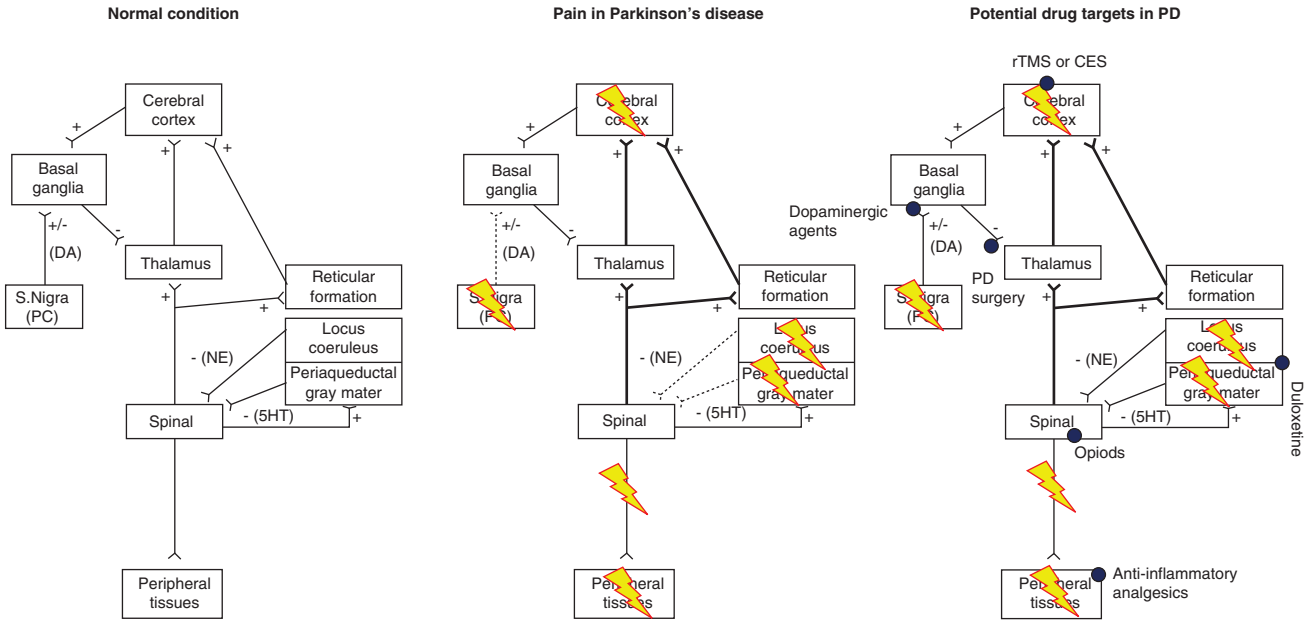

Figure 1. Schematic representation of pain or basal ganglia circuits in normal conditions and in Parkinson's disease (PD; left and central panel). Potential alterations leading to pain in PD are marked with thunders. In the right panel potential target for analgesic therapies are shown. See text for detailed discussion about pain mechanisms and potential therapeutic targets.
5HT: Serotonin; CES: Cranial electrotherapy Stimulation; DA: Dopamine; NE: Norepinephrine; PC: Pars Compacta; rTMS: Repetitive transcranial magnetic stimulation.

one study it has been shown that 45% of patients reported less pain while in on-state as compared with the off-state [40]. Nonetheless, clinical evidence about the efficacy of dopaminergic agent such as levodopa or dopamine agonists for pain treatment is scarce. In most clinical trials, back or chest pain has been nonsystematically explored as an adverse event, without significant results. Abdominal pain can also be a side effect of drugs such as entacapone [41]. Such results will not be herein reviewed. Finally, it should be also mentioned that generalized pain can also be observed as a part of a withdrawal syndrome to dopamine agonists in some PD patients [42].

Although some clinical case reports have suggested an analgesic effect of levodopa on herpetic neuropathic pain, bone pain from breast cancer or diabetic polyneuropathy [43-45] and in rat models of neuropathic pain [46], its analgesic effects have seldom been evaluated, as opposed to its motor effects [47].

Jejunal levodopa has been shown to significantly improve the 'miscellaneous' subscore from the Nonmotor Symptoms Scale [48], which includes pain among other symptoms. In the ELLDOPA study, leg pain was explored as an adverse event, but its frequency was reduced after levodopa in a dose-related fashion [49]. Pain intensity was also evaluated by means of a 10-cm visual analog scale (VAS) before and after a suprathreshold levodopa acute test in 15 PD patients without off-dystonia or restless legs syndrome [50]. VAS scores were 7.0 ± 1.2 in the off-state vs 3.4 ± 1.9 in the on-state ($p < 0.001$). Reductions in pain intensity correlated with improvements in motor function after levodopa ($p = 0.04$).

As is the case with levodopa, incident reports suggest that pramipexole, a D2 dopamine agonist, may be effective for pain treatment. Pramipexole 0.75 mg improved pain in a 68-year-old woman with burning mouth syndrome [51]. Pramipexole (up to 4.5 mg/day) has also been tested in 60 patients with fibromyalgia in a 14-week, double-blind, placebo-controlled, parallel-group trial [52]. VAS scores decreased by -2.48 ± 0.38 cm in the pramipexole group vs -0.71 ± 0.54 cm in the placebo group ($p = 0.008$). No significant differences were noted in depression scores.

Notwithstanding, pramipexole's analgesic effects have been seldom explored in PD. The only available evidence comes from a study about pramipexole's antidepressant effects in which pain was a secondary outcome [53]. There were 296 PD patients in this 12-week randomized, double-blind, placebo-controlled trial. Depression scores, as assessed by Beck Depression Scale, decreased by 5.9 points in the pramipexole group and 4.0 points in the placebo group ($p = 0.01$). Pain scores, as assessed by a 0 – 10 cm VAS, decreased by 3.5 or 3.0 in pramipexole or placebo group ($p = 0.8$). Patients were not selected according to pain, so these results may not reflect the potential analgesic effect of pramipexole in PD.

Bromocriptine's analgesic effects have also been studied as a secondary outcome in a 14-year open pragmatic multicenter trial, in which 782 patients were randomized to L-dopa + decarboxylase inhibitor (DCCI), L-dopa + DDCI + selegiline

Table 1. Most representative studies about analgesic therapies in Parkinson's disease.

Author (year)	Study design	Sample size	Treatments	Outcome	Results
Pharmacological treatments					
Nebe 2009 [50]	Open-label uncontrolled	15 fluctuating PD patients with pain of any origin	Acute levodopa challenge	VAS pain score	7.0 ± 1.2 in the off-state vs 3.4 ± 1.9 in the on-state ($p < 0.001$)
Frankel 2000 [56]	Case series	50 PD patients	Apomorphine subcutaneous intermittent or continuous infusion	Descriptive	Three patients reported relief of pelvic pain and two of painful morning dystonia
Trenkwalder 2011 [57]	Randomized, double-blind, placebo-controlled	287 PD patients with morning akinesia (no reference to pain in inclusion criteria)	Rotigotine 2 – 16 mg/day	11-point Likert pain scale	Rotigotine-to-placebo baseline-to-end of treatment difference: -0.77 ($p < 0.01$)
Brefel-Courbon 2009 [58]	Drug utilization study in the French System of Health Insurance during 2005	PD = 11,466 Diabetic = 11,459 Osteoarthritic = 11,329 General population = 11,200	Analgesics according to WHO ladder classification	Total or chronic analgesic prescription	Total prescription: 82, 82, 90, 77% Chronic prescription: 33, 26, 32, 20%
Muller 2011 [36]	Observational, cross-sectional	4086 PD patients	Analgesics according to WHO ladder classification	Quality of life by EQ-5D scale	EQ-5D score was higher in subjects on pain drugs as compared with subjects not on pain drugs
Djaldetti 2007 [62]	Open-label, uncontrolled study	20 PD with pain not related to dystonia, akinesia or back pain	Duloxetine 60 mg per day during 6 weeks	VAS pain score	7.6 ± 3.2 vs 4.2 ± 2.6 (pre- vs post treatment: $p < 0.001$)
Non-Pharmacological treatments					
Oshima 2012 [68]	Open-label, uncontrolled	69 PD patients reporting pain of any origin	STN-DBS	VAS pain score	Significantly reduced at 2, 6 and 12 months (-75, -69, -80%, all p-values < 0.01).
Honey 1999 [74]	Open-label, uncontrolled	21 PD patients reporting pain of any origin	Pallidotomy	VAS pain score	Significantly reduced by 5 or 4 points after 6 or 52 weeks (all p values < 0.01)
Rintala 2010 [94]	Randomized, double-blind, placebo-controlled	13 PD patients with chronic musculoskeletal pain not necessarily related to PD.	Cranial electrotherapy stimulation 40 min per day for 6 weeks	Daily pain rating by a NRS	Change in pain scores: Active = -1.14, sham = -0.23 ($p < 0.05$)
Kodama 2011 [90]	Case report	One patient with painful off-period dystonia	0.9-Hz subthreshold rTMS sessions over contralateral primary motor area and supplementary motor area, once a week over 2 months	VAS pain score	3.5 points reduction ($p < 0.05$)

WHO ladder classification: step 1 = non-opioid drugs (e.g., paracetamol or nonsteroidal anti-inflammatory drugs), step 2 = weak opioids such as tramadol, codeine or dihydrocodeine; step 3 = strong opioid such as morphine, fentanyl, buprenorphine or oxycodone or adjuvants (e.g., antidepressants, anticonvulsants or steroids).

Only most representative studies (i.e., those with largest samples or with most robust designs) in each category are included in this table.

NRS: Numerical rating scale; PD: Parkinson's disease; rTMS: Repetitive transcranial magnetic stimulation; STN-DBS: Subthalamic nuclei deep brain stimulation; VAS: Visual analog scale.

or bromocriptine [54]. No differences were found in bodily pain scores as assessed by Quality of Life SF-36 scale.

Apomorphine was effective for the relief of otherwise intractable pain in a 68-year-old patient [55]. In this patient, severe, sharp, boring pain occurred during the off-state. Treatment with regular analgesics, nerve blockage or different regimes of antiparkinsonian drugs had no effects. On the contrary, apomorphine injections provided dramatic, immediate relief in an abortive fashion that lasted more than 3.5 years. In a case series dealing with efficacy of apomorphine for the treatment refractory off-period disabilities, three patients reported relief of pelvic pain and two of painful morning dystonia [56].

Rotigotine's analgesic effects have been studied in the RECOVER study, a double-blind, placebo-controlled trial, of 287 PD patients with unsatisfactory early-morning motor symptom control [57]. Sleep and nocturnal disability were assessed using the PDSS-2 scale as a coprimary efficacy endpoint. The PDSS-2 is a multi-item Likert-type scale, which includes some measures of pain such as painful posturing in the morning or nocturnal pain in arms or legs. Both measures were significantly improved by rotigotine as compared with placebo. Daily pain was also explored by means of an 11-point Likert pain scale. Results showed greater improvements with rotigotine than placebo from baseline to end of treatment (-0.77 points, $p < 0.008$).

3.1.2 *Analgesics consumption*

450 French PD outpatients were evaluated In the DoPaMip study [18]. Patients suffering from chronic pain related or unrelated to PD were compared. Less patients with PD-related pain took an analgesic during the previous month than patients with pain unrelated to PD or patients with chronic disorders other than PD (50.3 vs 67.6% or 70.2% $p < 0.01$). Patients with PD-related pain took significantly less non-opioid analgesics as compared with the two other groups (34.1 vs 48.6% or 61.4%, $p < 0.01$). The authors suggested that these differences might reflect the fact that patients with PD pain reported less frequently such type of pain to their physician than other types of pain unrelated to PD, such as arthritis, which might be more effectively relieved by classical analgesics.

Analgesic use information according to the WHO ladder classification was also collected in the Northumbria Healthcare NHS Trust Parkinson's Disease Service (North Tyneside, UK) in 123 PD patients [17]. Out of the 72 patients (58.5%) who were taking one or more analgesics; 12.2% took nonsteroidal anti-inflammatory drug (NSAID); 50.4% paracetamol/acetaminophen; 25.2% took weak opioids and no patients were on strong opioids. Co-analgesics such as antidepressants, antiepileptics, muscle relaxants or steroids were consumed by 8.9, 0.8, 0.8 or 0% respectively. Out of the 83.9% PD patients who had intermittent pain, 41.5% were on no analgesic. Authors suggested that analgesics were probably underused in PD.

In another study, analgesic drug prescription was compared between PD patients (n = 11466), diabetic patients (n = 11459), osteoarthritic patients (n = 11329) and the general population (n = 11200) in the database of the French Health Insurance System [58]. One or more analgesic drugs were prescribed more frequently to PD patients than to the general population (82 vs 77%, $p < 0.0001$) but less than that to patients with osteoarthritis (90%, $p < 0.0001$). Prescriptions of opiates were also more frequent in PD than in the general population but less frequent than in osteoarthritis. NSAIDs were less frequently prescribed in PD in the other groups. Other analgesics (antidepressant and antiepileptics) were significantly more commonly prescribed in PD than in the other groups.

In another study, among the 28 patients who reported pain, 78.6% used mainly NSAIDs [59]. Other analgesic medications included amitriptyline, gabapentin, carbamazepine, opioids, acupuncture and physiotherapy. Only one patient used no analgesic at all during periods of pain. In another sample of 146 painful PD patients, 50% did not receive any pain killer [11]. Non-opiods, opioids, antiepileptic/antidepressive and other co-analgesic medications were again more commonly used in patients with pain than in those without pain.

A relationship between analgesic intake and quality of life was assessed in a study conducted in more than 4000 PD patients [36]. Quality of life EQ-5D score was higher in patients who received analgesics and EQ-5D scores were directly related to the number of times per week a patient took analgesics.

Reviewed studies suggest that analgesics are used by about 50% of painful PD patients. Some authors suggested that such underuse may be related to pain underreporting, but it may also be related to analgesics' inefficacy for some type of pain, as will be discussed later. The findings that painful PD patients under analgesics show improved quality of life suggest that analgesic use in PD should be further investigated.

3.1.3 *Duloxetine*

Duloxetine is a serotonin and norepinephrine reuptake inhibitor, which possesses antidepressant and pain-relieving properties [60]. Randomized trials have documented significant analgesic effects for managing chronic pain associated with fibromyalgia and diabetic peripheral neuropathic pain [61]. In PD, the analgesic effect of 60 mg/day duloxetine has been studied for 6 weeks in an open-label fashion in 23 patients with painful phenomena described as stabbing, aching, tensioning and burning [62]. Painful PD-related conditions such as dystonia, limb rigidity, nocturnal muscle spasms and back pain were excluded as were non PD-related pain (diabetic neuropathy, post-stroke central pain and others). Patients had to be in constant pain, unresponsive to NSAIDs. Pain relief was reported by 65% of patients. McGill Pain Questionnaire, brain pain inventory or daily Likert scores were significantly lower after duloxetine

treatment (respectively, 15.1 ± 5.9 vs 9.4 ± 6.7 $p < 0.003$; 66.2 ± 21.5 vs 43.6 ± 28.5 $p < 0.0009$ or 7.6 ± 3.2 vs 4.2 ± 2.6 $p < 0.0001$). Conversely, depression as evaluated by Beck depression scale or quality of life as assessed by PDQ-39 was not significantly changed. Similarly, pain threshold was unaffected by treatment.

Given the limitations of an uncontrolled open-label study, further clinical trials are needed in order to establish the efficacy of duloxetine for this indication.

3.2 Non-pharmacological treatments

3.2.1 PD surgical treatments

Lesion or stimulation of pallidum or subthalamic nuclei has proved to be effective treatments for disabling PD [63]. These procedures dramatically improve cardinal PD symptoms, while at the same time they allow for a decrease in dopaminergic replacement therapy dose. Finally, they alleviate dyskinesias and motor fluctuations. Here we will review the analgesic efficacy of such treatments.

The effects of chronic subthalamic nucleus (STN) deep brain stimulation (DBS) on non-motor symptoms, including pain, were explored in 40 PD patients [64]. They were evaluated before and 1 year after treatment. Motor symptoms, dyskinesias and motor fluctuations were improved as expected. All domains of non-motor symptoms were also improved. Of interests, pain/sensory scores improved from 1.7 ± 0.7 before treatment to 0.3 ± 0.5 (84% of reduction, $p < 0.001$). In another study pain was assessed in 29 patients who underwent STN DBS before and 3 months after surgery [65]. Twenty-three of twenty-nine patients (79%) reported pain preoperatively. The mean pain score on the ordinal scale was 6.3 ± 2.4. At 3 months, 20 of 23 patients (87%) with the preoperative pain reported an improvement in pain. Of 18 patients with the preoperative fluctuating pain, off-period pain improved in 17 (94%) including 5 in whom the pain completely disappeared. Dystonic and central pain was resolved in 100 or 97% of patients complaining about such types of pains. On the contrary, musculoskeletal or radicular pains were less frequently resolved. Similarly, a series of 49 painful dystonia was resolved in 52% of cases after 1 year and in 38% after 5 years of surgery [66]. Pain intensity has been also found to be reduced by STN-DBS in a small group of PD patients [67].

Recently a set of 69 patients who were identified as experiencing preoperatively PD-related pain were followed up prospectively for 12 months after STN-DBS [68]. All patients described the severity of their pain according to a VAS preoperatively and at 2 weeks, 6 months and 12 months postoperatively. The overall mean VAS score was significantly decreased postoperatively by 75, 69 and 80% at 2 weeks and 6 or 12 months, respectively ($p < 0.001$). At 12 months, six patients (three with somatic back pain and three with radicular pain) required additional spinal surgery to alleviate the pain severity. In this study, patients with central pain were poor responders. This finding is not universal, since a few number of case reports suggested that PD surgery may be effective for this kind of pains [69,70]. Finally, in an unselected sample of 36 patients, UPDRS #17 (sensory complaints related to parkinsonism) score in off-state was 1.7 ± 1.0 before surgery compared with 0.3 ± 0.6 or 0.4 ± 0.6 at year 1 or 2 (both $p < 0.01$) [71].

Our group has recently conducted a double-blind, randomized, crossover trial to investigate the potential effect of STN-DBS on pain in 16 PD patients, of whom 8 suffered from PD-related neuropathic pain. Subjective pain threshold as assessed by thermotest as well as pain-induced cerebral activity measured by PET was compared with stimulator ON or OFF (personal communication). STN-DBS significantly raised subjective pain threshold and reduced pain-induced cerebral activity in the somatosensory cortex (BA40), a brain area underlying sensory-discriminative aspects of pain in the group of PD patients with PD-related neuropathic pain but not in non-painful patients. Results will be published soon.

The effects of pallidotomy on PD pain have not been systematically explored. Kim and colleagues reported in a systematic review that pallidotomy had 'a very good effect' on one patient suffering from painful muscular spasm [72,73]. In a set of patients, UPDRS item 17 score in off-state improved at 3 and 6 months, but not at 12 months [72]. In another study, 21 patients identified as having pain related to their PD were evaluated before and after pallidotomy [74]. All patients described the severity of their pain according to an ordinal scale (0 – 10 points) preoperatively and at 6 weeks and 1 year postoperatively. Preoperative overall pain scores were significantly decreased at both 6 weeks by 5 points ($p < 0.001$) and 1 year by 4 points ($p = 0.001$) postoperatively. At year 1, 50 and 63% of patients with musculoskeletal or somatic pain related to PD reported resolution of their pain. On the contrary, no patient with dystonic or central pain reported resolution, while 50% patients with dystonic pain reported some improvement. Finally, the effects of pallidal DBS were explored in 16 patients. Pain's severity was described by the patients according to an ordinal scale ranging from 0 to 4. The rating for each off-symptom was applied to six different parts of the body (neck, trunk, upper and lower extremities at each side) resulting in a maximal total score of 24 points. Follow-up assessments were performed between 3 and 5 days postoperatively, at 3 months, and at 1 year after surgery. Pain score was 9.0 ± 5.3 at baseline, 2.4 ± 5.2 at day 5, 2.9 ± 4.3 at month 3 and 2.6 ± 2.8 at month 12. Scores were reduced by 73.3% at day 5 ($p = 0.009$), by 67.8% at month 3 ($p = 0.009$) and by 71.1% at month 12 ($p = 0.009$).

3.2.2 Transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique used for clinical and research purposes. This device modulates brain activity by applying a focal and transient magnetic field over the cerebral cortex, inducing electric currents in neuron networks (Faraday's law of induction). The efficacy of rTMS depends

on different parameters: site of stimulation, frequency, intensity and number of stimulations.

rTMS has now been used for therapeutic or research purposes in pain for more than 10 years [75-78]. In general, results indicate that a single session of high-frequency rTMS (≥ 5 Hz) applied over the primary motor cortex (M1) has an analgesic effect in patients suffering from neuropathic pain [79-82]. Multiple sessions appear to increase the amplitude and the duration of the rTMS effect [83]. The mechanism of action remains unclear, but some studies documented that rTMS applied over M1 modulated the activity of brain areas involved in pain processing such as the thalamus, the insular cortex and the anterior cingulated cortex (ACC) [84]. Analgesia seems to be produced by modulation of the pyramidal tract and the medial nociceptive pathway (ACC and prefrontal cortex) [85-87]. A recent study suggested that such effects may also involve the endogenous opioid system [88].

In PD, rTMS have been shown to reduce bradykinesia and improve gait [89]. According to a recent case report, it could also be effective for treating painful off-dystonia [90]. The patient underwent 0.9-Hz subthreshold rTMS sessions over contralateral primary motor area and supplementary motor area. rTMS over the primary motor area significantly reduced the painful dystonia and walking disturbances but repetitive transcranial magnetic stimulation over the supplementary motor area did not.

Further investigations are required to improve the therapeutic potential of rTMS in neuropathic pain, particularly by studying the best combination of stimulation parameters. rTMS appears to be a useful technique to explore the neurophysiology of pain and, consequently, to find therapeutic targets in the near future.

3.2.3 Cranial electrotherapy stimulation

Cranial electrotherapy stimulation is a noninvasive technique involving the application of a small amount of electric current through the head via ear-clip electrodes. Its analgesic effects have been shown in animal models [91] and in patients with spinal cord injury [92]. In a randomized, double-blind, placebo-controlled trial, 119 patients with chronic pain used either a cranial electrotherapy stimulation device or an active placebo device [93]. Pain level decreased significantly in the cranial electrotherapy stimulation-treated group compared with the active-placebo group 3 weeks after the end of treatment ($p = 0.0017$).

The efficacy of cranial electrotherapy stimulation was evaluated in 13 PD patients with at least one chronic musculoskeletal pain in the lower back and/or lower extremity lasting more than 6 months [94]. Pain was not necessarily PD related. Subjects were randomized to use active or sham devices for 40 min each day at home for 6 weeks. Active devices provided subsensory stimulation of 100 microamperes. Patients and investigators were blinded to study treatments. The participants were instructed to provide daily pain ratings on a 0-to-10 scale immediately before and immediately after the end of each 40-min cranial electrotherapy stimulation session during the 42-day trial. Average pre- and post-session pain ratings were calculated, which constituted the principal outcome of the study. Patients assigned to active treatment had higher Hoehn & Yahr score (43 vs 17% in stage III) and longer PD duration (15.2 vs 5.2 years). For the active group, the average daily rating was 4.89 ± 1.22 before and 3.75 ± 2.04 after the sessions yielding an average decrease of 1.14 ± 1.21 points (Wilcoxon $Z = -2.20$, $p = 0.028$). For the sham group, the average rating was 3.82 ± 1.76 before and 3.59 ± 1.75 after yielding an average decrease of 0.23 ± 0.33 (Wilcoxon $Z = -1.36$, $p = 0.173$). The average difference between the groups in change scores (1.14 versus 0.23) was significant (Mann–Whitney $U = 7.00$, $p = 0.045$), indicating that pain reduction in the active group was greater than that in the sham group. Most frequent adverse events were pulsing, tickling or tingling sensations on ears (n = 3, all in the active group). Other reports included tender ears (one case), pins-and-needles sensation near the bladder (one case), warm ears (one case) and headache after one session (one case). No serious study-related adverse events occurred during this study.

4. Market review

General population estimates of incidence for PD range from 1.5 to 26 per 100,000 person-years [95,96]. Worldwide estimates of PD are projected to increase to 8.67 million by 2030 [97]. Between 40 and 85% of PD patients suffer from pain. As commented earlier, it has been suggested that analgesics are underused in PD [17]. These data suggest that an important and growing number of PD patients who should be on an effective analgesic treatment remain untreated. Such number may be as high as 3.69 million patients by 2030, based on previously mentioned data and assuming that 85% of PD patients will suffer from pain, 50% of whom will be untreated.

5. Current research goals

Nowadays the most important research goals seem to be related to the correct selection of treatments according to patients' characteristics, as well as the effect of analgesic treatment over quality of life in painful PD patients. We will review the most important aspects of these basic questions.

5.1 Which treatment for which patient?

As commented earlier, pain in PD has many origins. Generally, they can be classified as pains of nociceptive or neuropathic origins [21]. Moreover, patients may be affected by pains of different origin at the same time [18]. Therefore, it seems important to correctly identify the cause of each pain before treatment initiation. Firstly, pains unrelated to PD should be promptly identified and treated accordingly. For example, osteoarthritic pains can be efficaciously

treated by NSAIDs, whereas surgery may be indicated for radicular pains.

Regarding PD-related pains, effective analgesic treatments should be selected based on the presumed origin of pain. This is a crucial issue since treatments may not be equally effective for all types of pains. For example, apomorphine appears to be ineffective for increasing pain thresholds in patients with neuropathic pain [32], but was suggested as an effective treatment for painful dystonia [56].

Identification of the relationship between pain and dopaminergic drugs appears to be equally important. For example, off-related pain of nociceptive origin may be effectively treated by modification of dopaminergic therapy, which at the same time can worsen pain during on-state.

Finally, safety is always a critical issue in pharmacotherapy. As usual, risk/benefit ratio for each patient should be evaluated before initiating any analgesic treatment in PD. For example, opiates should be used with caution as they may worsen parkinsonism according to primate studies [98] and to some case reports [99-101].

5.2 Does pain treatment improve quality of life in PD?

Chronic pain is a significant health issue often associated with negative physical, psychological and social sequelae, which often lead to reduced health-related quality of life [102]. Similarly, pain is related to reduced quality of life in PD [35,36], as mentioned earlier. Thus, effective analgesic treatment should not only reduce pain intensity in the short term, but also significantly improve quality of life.

Analgesic treatment of patient with neuropathic pain has been shown to improve quality of life [103]. In PD, subjects on analgesics reported higher quality of life [36]. Nonetheless, quality-of-life improvement after analgesic treatment may not always depend on pain intensity reduction [104]. For example, we observed that pregabalin's sleep-promoting effects were more closely related to improved quality of life as compared with its analgesic effects in a group of patients with neuropathic pain [105]. These results suggest that drugs with pleiotropic effects may have greater chances of improving life quality than analgesics devoid of other actions. Quality of life should be systematically explored in studies about pain in PD.

6. Scientific rationale

In this section we will review the potential sites of action for main types of pain in PD. Schematic representation of principal alteration leading to pain in PD is offered in **Figure 1**.

6.1 Nociceptive pain

As discussed earlier, nociceptive pain can be defined as pain arising from actual or potential damage to nonneural tissue and being due to the activation of nociceptors. In PD they appear to be related to rigidity, akinesia or dystonia [21], resulting in muscle or joint persisting stretching, which in turn may result in inflammatory lesions. Therefore, anti-inflammatory agents, such as NSAIDs, might be effective for this kind of pain [106]. Drugs enhancing inhibitory descending analgesic pathways, such as opioids or sertonergic or noradrenergic antidepressants should also be effective [107]. Similarly, therapies affecting central processing of pain stimuli, such as cranial electrotherapy stimulation or transcranial magnetic stimulation, could be effective as well. Finally, all agents relieving akinesia and/or dystonia, such as levodopa or dopamine agonists [108], may also constitute effective treatments.

6.2 Neuropathic pain

As discussed earlier, basal ganglia dysfunction resulting from dopaminergic denervation appears to be involved in the pathophysiology of neuropathic pain in PD, among other mechanisms. Thus, it can be suggested that dopaminergic replacement therapy might be effective for treating this kind of pain. If this would be true, then pain threshold should be raised by such treatments. Interestingly, while levodopa was effective for increasing them [23], apomorphine was not [32], thus pointing out the probable relevance of non-dopaminergic mechanisms. Therefore, modification of norepinephrine or serotononinergic central pathways may represent an interesting target for treating these kinds of pain. On the other hand, anti-inflammatory therapy may not be effective for neuropathic pain, while opioids may still be efficacious, based on its effects over descending inhibitory pain pathways [107].

7. Competitive environment

Scientific evidence about the efficacy and safety of current treatments for pain is weak in the majority of cases. For example, dopamine agonists represent promising options, but their analgesic effects have not been studied by specific randomized controlled clinical trials. This is the case of rotigotine, for which an analgesic effect was detected, but as a secondary outcome. Similarly, promising analgesic effects of duloxetine have been observed in an uncontrolled open-label study, but not further studied. These drugs are currently available in the market and are indicated for the treatment of PD-related conditions, which makes it easy to further study their effects in patients. Documentation of analgesic effects may provide some marketing advantages vis-à-vis to other drugs in the same market. This might be significant for 'saturated' markets, such as those of dopamine agonist or antidepressants.

On the other hand, new treatments are also welcomed, as available treatments may not be effective for all kind of pains or might not be well tolerated by all patients. A search in clinicaltrials.gov and Pharmaprojects (copyright to Citeline Drug Intelligence, an informa business) databases about new treatments for pain in PD was conducted. We will discuss

Table 2. Clinical trials of upcoming analgesic therapies in Parkinson's disease.

Trail ID	Study design	Sample size	Treatments	Primary outcome	Secondary outcome
NCT01439100 (sponsor: Mundipharma)	Randomized, double-blind, parallel, placebo-controlled	172 PD patients with pain of any origin	Oxycodone/naloxone prolonged-release tablets or placebo (dose undisclosed)	7 days averaged 24-pain NRS scores	Quality of life
NCT01504178 (Sponsor: Toulouse University Hospital)	Randomized, double-blind, parallel, placebo-controlled	36 non-painful PD patients	Duloxetine 60 mg/day for 28 days. A single dose of duloxetine, levodopa or placebo before the second evaluation	Subjective and objective pain threshold	-
NCT00909883 (sponsor: Clermont-Ferrand University hospital)	Randomized, double-blind, parallel, placebo-controlled	45 patients with PD and foot dystonia	Botulinum toxin in the extrinsic or intrinsic feet muscles or placebo	VAS pain score	Dystonia by Burke scale, clinical improvement by CGI scale and quality of life by PDQ-39 scale
NCT01275573 (Sponsor: Toulouse University Hospital)	Randomized, double blind, cross-over, placebo-controlled	19 PD patients (10 pain-free and 9 painful)	20 Hz rTMS or placebo	pain thresholds by Thermotest®	VAS clinical pain, UPDRS III motor state, VAS mood scale

NRS: Numerical rating scale; VAS: Visual analog scale.

the results of such search in this section. Principal characteristics of clinical trials retrieved in these databases are depicted in **Table 2**. Principal targets and action mechanisms of drugs are shown in **Figure 1**.

7.1 Pharmacological treatments

7.1.1 Oxycodone/naloxone prolonged-release tablets

Oxycodone/naloxone prolonged-release tablet (OXN PR) is a prolonged release tablet consisting of oxycodone and naloxone in a 2:1 ratio. Due to the local competitive antagonism of the opioid receptor-mediated oxycodone effect by naloxone in the gut, naloxone reduces opioid-associated bowel dysfunction. If effective pain relief can be achieved with an analgesic without such side effects, this could reduce the need to increase the dose of dopaminergic medications to manage pain, and, therefore, reduce the negative side effects of dopaminergic therapy described above. Given the prevalence of constipation in this patient population, the bowel sparing effects of the OXN PR combination treatment may provide an ethical rationale for its use over that of other opioids.

The objective of this study is to demonstrate superiority of OXN PR compared with placebo with respect to analgesic efficacy in subjects with chronic severe pain associated with PD, as assessed by averaged 24-h pain scores collected for 7 days prior to the clinic visits. A secondary objective is to examine whether OXN PR may offer any additional benefits to the patients' quality of life or symptoms of PD. CT identifier is NCT01439100 and the sponsor is Mundipharma Research GmbH & Co KG. For this study, 172 PD patients with an average pain score of 6 or above on an 11-point numerical rating scale (NRS), over the previous 7 days, and who are likely to benefit from WHO step III opioid therapy will be recruited.

7.1.2 Duloxetine

A double-blind, randomized, placebo-controlled study is currently being conducted by our group in order to investigate the duloxetine's effects on pain thresholds (Identifier: NCT01504178, Sponsor: Toulouse University Hospital). Thirty-six non-painful PD patients will follow a 28-day treatment course with duloxetine 60 mg/day. Subjective and objective pain thresholds will be evaluated before and after such treatment period. Patients will be randomly divided into three groups according to which treatment they will receive immediately before the second pain threshold evaluation. The first group will receive a single dose of duloxetine, the second one a single dose of levodopa and the third one placebo.

This trial has been set up in order to further explore the involvement of noradrenergic and serotoninergic systems in pain perception abnormalities.

7.1.3 Botulinum toxin injection for foot dystonia

Foot dystonia is frequently observed in patients suffering from PD. It is characterized by an abnormal involuntary

movement, which is very uncomfortable (difficult to walk) and painful for the patient. Botulinum toxin injections seem to be efficient to treat this dystonia. However, studies on this topic are few and very imprecise. Therefore, this controlled, double-blind, randomized study was envisaged to show that intramuscular injections of botulinum toxin are beneficial to reduced dystonia and associated pain in patient with foot dystonia as compared with placebo injections (NCT00909883, sponsored by University Hospital, Clermont-Ferrand in collaboration with Merz Pharma France). In this study, 45 patients with PD and foot dystonia will be assigned to receive placebo or toxin injection in the extrinsic or intrinsic feet muscles. Before and 1 month after injections, pain will be evaluated by VAS scales, dystonia by Burke scale, clinical improvement by CGI scale and quality of life by PDQ-39 scale.

7.2 Non-pharmacological treatments

7.2.1 Repetitive transcranial magnetic stimulation

A prospective, comparative, randomized, double blind, cross-over study is being conducted by our group aiming at evaluating the effect of a high-frequency rTMS session, compared with a sham stimulation, applied over the primary motor cortex, on the heat pain threshold in PD (Identifier: NCT01275573, Sponsor: University Hospital, Toulouse). The research hypothesis is that a 20 Hz rTMS session could modify the nociceptive threshold perception in PD by modulating nociceptive cortical area activity.

In this study, 19 PD patients (10 pain-free and 9 painful) will be included. Pain threshold using thermotest, clinical pain (VAS), depression and motor state (UPDRS III OFF) will be assessed before, 10 and 40 min after rTMS session, applied over the primary motor cortex. The procedure will be repeated 1 week later under the other rTMS conditions (i.e., either real or sham rTMS). The rTMS parameters were a frequency of 20 Hz, a duration of 26 min and an infra-threshold intensity (95% of the motor threshold).

8. Potential development issues

As has been discussed in earlier sections, there are few studies about safety and efficacy of intervention for pain in PD. On the other hand, there are several treatments options in the 'pipeline' and many more will surely come. The success of such studies will depend on their capacity to match the right treatments for the right patients and on their methodological design. In this section, we will discuss these issues.

8.1 Patient selection

As discussed earlier, all treatments are not probably equally effective for all types of pains. Therefore, selection of the right patient group according to the mechanism of action of the investigational product is a crucial issue. In PD, pain can be classified according to their physiopathology or according to their relationship with PD [17,21,38]. Such classifications can be seen as complementary pieces of information that needs to be combined in order to assure the recruitment of the targeted patients. For example, there is no use in recruiting patients with musculoskeletal pain, except if they are related to PD. Similarly, patients with neuropathic pain should not be targeted in a study about the efficacy of an anti-inflammatory analgesic.

In order to achieve a good matching between the investigational product and the targeted PD group, efforts will be necessary from scientists and from the medical community. The formers will have to ensure that the right PD group is targeted by thoughtfully analyzing action mechanism of the investigational product. On the other hand, medical community needs to work on improved pain classification in PD as it is essential that it accurately reflects pain's physiopathology.

8.2 Outcomes

To facilitate the execution and interpretation of clinical trials of chronic pain treatments, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended a set of core outcome domains and measures [109].

They recommended that six core outcome domains should be considered when designing chronic pain clinical trials. The five single most important core outcome domains are i) pain; ii) physical functioning; iii) emotional functioning; iv) participant ratings of improvement and satisfaction with treatment and v) symptoms and adverse events [110]. The sixth domain refers to patient disposition through the trials (i.e., how many patients were recruited, randomized and followed until study end) as recommended by CONSORT statement [111]. All other outcomes should be evaluated only by validated tools. **Table 3** summarizes proposed measures for each outcome.

In the majority of cases, pain intensity will constitute the principal outcome. It can be evaluated either by VAS, NRS and verbal rating scales (VRS) [110]. The committee recommended an 11-point (i.e., 0 – 10) NRS measure of pain intensity as a core outcome measure in clinical trials of chronic pain treatments. Pain should be ordinarily assessed by means of this scale during the 24-h time span preceding the visit, but pain during the past week or pain 'at its worst' or pain 'at its least' can also be used. In patients with cognitive impairment, NRS can be replaced by a VRS. Values of these scales should be analyzed not only as absolute changes in pain intensity but also as the percentages of patients obtaining reductions in pain intensity from baseline of at least 30% (i.e., a responder analysis). In PD, more than one type of pain may coexist in the same patient [18]. These patients should probably be instructed to rate the intensity of targeted pain, thus not taking into account other pains.

Physical functioning or, more generally speaking, health-related quality of life should also be analyzed in chronic pain trials [110]. They can be either generic or specific for PD. Among the specific ones, the use of the Parkinson's

Table 3. Recommended core outcome measures for clinical trials of chronic pain treatment efficacy in Parkinson's disease.

Domain	Measure
Pain intensity [110]	11-point (0 – 10) numerical rating scale of pain intensity Categorical rating of pain intensity (none, mild, moderate, severe) in circumstances in which numerical ratings may be problematic
Physical functioning and health-related quality of life [112]	Parkinson's Disease Questionnaire (PDQ-39 or PDQ-8) Parkinson's Disease Quality of Life Questionnaire (PDQL) Parkinson's Impact Scale (PIMS)
Emotional functioning [115]	Hamilton Depression Rating Scale Montgomery–Asberg Depression Rating scale Beck Depression Inventory Geriatric Depression Scale
Participants' overall evaluation of their treatment [110]	Patient Global Impression of Change scale (PGIC)
Safety [110]	Passive capture of spontaneously reported adverse events Unified PD rating scale

Disease Questionnaire (PDQ-39), the PDQ-8 which is a short form of the preceding one, the Parkinson's Disease Quality of Life Questionnaire scale or Parkinson's Impact Scale, has been recently recommended [112]. The Parkinson's Disease Questionnaire (PDQ-39), which has been developed to allow a meaningful evaluation of quality of life in PD [113], is probably the most frequently used one [112]. Among the 39 questions, 2 refer to painful cramps or spasms or aches and pain in joints of body. Generic quality-of-life scale such as the EQ-5D or SF-36 may also be used [112].

Evaluation of emotional status is particularly important in PD, as this is a usual symptom of the disease [114]. Patients suffering from pain have been shown to be more severely depressed than their counterparts [18]. There are several scales that can be used in PD, such as the Hamilton Depression Rating Scale, the Montgomery–Asberg Depression Rating scale or the Beck Depression Inventory [115]. They appear to be similar in terms of validity, reliability and limitations.

For the evaluation of participants' overall evaluation of their treatment, the Patient Global Impression of Change scale has been recommended [110]. This measure is a single-item rating by participants of their improvement with treatment during a clinical trial on a 7-point scale that ranges from 'very much improved' to 'very much worse' with 'no change' as the midpoint.

Safety is usually evaluated in clinical trials by recording the occurrence of spontaneously disclosed adverse events or adverse drug reactions. In PD it is also important to evaluate disease severity by the Unified PD rating scale, to exclude any untoward effect in this domain. This, for example, may be the case with opioids, as was discussed earlier.

9. Conclusion

Pain is a frequent and disabling feature of PD for which there are no current universally recommended treatments. The first therapeutic strategy might probably be dopaminergic therapy optimization. Preliminary results indicate that duloxetine, a norepinephrine and serotonin reuptake blocker, cranial electrotherapy stimulation, rotigotine, a dopamine agonist, subthalamic or pallidum nuclei stimulation or lesion or levodopa could be effective treatments for pain in PD. Similarly, some case reports indicate that repetitive transcranial magnetic stimulation or apomorphine could be effective for relieving painful off-period dystonia. On the other hand, analgesics such as NSAIDs, which should be effective for treating PD-related pain of nociceptive origin, such as musculoskeletal or dystonia-related pain, are underused in PD.

The need of effective treatments has prompted the evaluation of new analgesic therapies in PD. Our group has recently finished a study about rTMS efficacy for neuropathic pain and results analysis is ongoing. Trials of OXN PR or of botulinum toxin for painful off-period dystonia are also underway.

10. Expert opinion

It is estimated that about 3 million PD patients will suffer from pain by 2030, of whom 50% will be untreated. Pain usually leads to reduced quality of life. Thus, pain treatment is not only an unmet medical need but also an interesting market.

PD-related nociceptive pain can probably be effectively treated by anti-inflammatory analgesics, such as NSAIDs, or by dopaminergic agents, such as levodopa or dopamine agonists. Nonetheless, further studies are needed in order to formally prove these hypotheses. It is possible that publication of such studies will boost the utilization of such drugs and thus enhance pain treatment in PD.

On the other hand, NSAIDs or dopamine agonists are not likely to be effective for neuropathic pain. Conversely, levodopa or drugs enhancing non-dopaminergic neurotransmission, such as duloxetine, may offer relief for this kind of pain. Similarly,

modification of central pain stimuli processing by rTMS, cranial electrotherapy or DBS may also represent interesting alternatives, as they may treat pain while avoiding further increasing 'pill burden,' which exposes patients to higher drug–drug interaction risk and thus to adverse drug reactions.

Follow-up of international recommendations is a key issue for the success of such trials. Pain intensity should be evaluated by NRS or by VRS if cognitively impaired patients are targeted. If patients suffer from more than one type of pain, all of them should be evaluated, while probably only the most important should be targeted. Evaluation of quality of life or patients' impression is also important. Effects of analgesics over quality of life need to be carefully documented. Safety assessment should always include PD severity evaluation, as some treatments, such as opioids, may worsen parkinsonism. Last but not least, patient selection for such trials will remain problematic as long as a validated pain classification system is not developed.

Declaration of interest

C Brefel-Courbon serves on a scientific advisory board for Medtronic, Inc., Boehringer Ingelheim and GlaxoSmith-Kline. O Rascol has acted as an advisor for most drug companies developing antiparkinsonian medications. The other authors declare no conflicts of interest.

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