ORIGINAL ARTICLE

Current Status of Pain Management in Parkinson's Disease

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ABSTRACT: ***Background:*** Pain is a non-motor symptom in Parkinson's disease (PD) which commonly goes underreported. Adequate treatment for pain in PD remains challenging, and to date, no clear guidelines for management are available. ***Methods:*** With the goal of understanding and organizing the current status of pain management in PD, we conducted a review of pharmacological and non-pharmacological treatments for pain in patients with PD. Suitable studies cataloged in PubMed and the Cochrane database up to October 31, 2019, were included prioritizing randomized controlled trials. *Post-hoc* analyses and open-label studies were also included. ***Results:*** Treatment with levodopa increases pain thresholds in patients with PD. Apomorphine did not have similar efficacy. Duloxetine provided benefit in an open-label trial. Oxycodone-naloxone PR did not have a significant improvement in pain, but per-protocol analysis showed a reduction in pain when adherence was strong. Rotigotine patch had numerical improvement on pain scales with no statistical significance. Safinamide significantly improved the "bodily discomfort" domain in the PDQ-39 questionnaire. Botulinum toxin A had a non-significant signal toward improving dystonic limb pain in PD. DBS to the subthalamic nucleus may modulate central pain thresholds, and a pilot study of cranioelectric therapy warrants future research in the area. ***Conclusion:*** After optimizing dopaminergic therapy, understanding the type of pain a patient is experiencing is essential to optimizing pain control in PD. While recommendations can be made regarding the treatment options in each domain, evidence remains weak and future randomized controlled studies are needed.

RÉSUMÉ : La prise en charge de la douleur dans le cas de la maladie de Parkinson : un état actuel des lieux. ***Contexte*** : La douleur est un symptôme non-moteur de la maladie de Parkinson (MP) qui tend communément à être moins signalé. Plus encore, compter sur un traitement adéquat de la douleur dans le cas de la MP constitue encore un défi de nos jours. En effet, il n'existe pas de lignes directrices claires à ce jour en ce qui concerne sa prise en charge. ***Méthodes*** : Notre objectif étant de comprendre l'état actuel des lieux en matière de prise en charge de la douleur des patients atteints de la MP, nous avons passé en revue les traitements pharmacologiques et non pharmacologiques leur étant offerts. Pour ce faire, nous avons inclus des études jugées appropriées ayant été répertoriées dans les bases de données *PubMed* et *Cochrane Library* jusqu'au 31 octobre 2019. Nous avons également choisi de donner la priorité à des essais cliniques randomisés (ECR) sans négliger pour autant des analyses *a posteriori* et des études ouvertes (*open-label studies*). ***Résultats*** : Les traitements à la lévodopa ont augmenté les seuils de la douleur chez des patients atteints de la MP. L'apomorphine, elle, n'a pas eu la même efficacité. La duloxétine s'est avérée bénéfique dans le cadre d'une étude ouverte. L'association oxycodone-naloxone à libération prolongée n'a pas entraîné une amélioration notable dans le soulagement de la douleur ; cela dit, une analyse menée conformément au protocole a montré une réduction de la douleur lorsque l'adhésion était marquée. Les timbres transdermiques de rotigotine ont donné à voir une amélioration sur des échelles numériques de la douleur sans que cela ne soit significatif sur le plan statistique. Le safinamide a pu considérablement améliorer le niveau « d'inconfort corporel » mesuré par le *Parkinson's Disease Questionnaire* (PDQ-39). La capacité de la toxine botulique à soulager la douleur produite par la dystonie des membres ne s'est pas révélée significative. Il est par ailleurs possible que l'utilisation de la stimulation cérébrale profonde (SCP) dans le noyau sous-thalamique puisse moduler les seuils de douleur ressentie au niveau du système nerveux central. Enfin, une étude pilote au sujet de la stimulation crânienne par électrothérapie mérite qu'on effectue de plus amples recherches. ***Conclusion*** : Une fois optimisé un traitement médicamenteux à la dopamine, le fait de comprendre le type de douleur que ressent un patient atteint de la MP est essentiel si l'on veut en optimiser la prise en charge. Bien qu'il soit possible de faire des recommandations en matière d'options thérapeutiques pour chaque type de douleur, les preuves en la matière demeurent faibles, ce qui fait que de futurs ECR sont encore nécessaires.

Keywords: Parkinson's disease, Pain management, Clinical trials

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Introduction

Non-motor features of Parkinson's disease (PD) are often underreported, and adequate treatment for these symptoms remains challenging.[1] Pain is one such symptom and can affect up to 85% of patients with PD.[2] Despite how common pain can be in PD, it is surprisingly largely undertreated. In fact, patients with PD-related pain are less likely to be prescribed analgesic treatment than those with chronic pain-related diseases, such as osteoarthritis.[3]

Many types of pain manifest in PD, including musculoskeletal pain, dystonic pain, neuropathic pain, and central pain.[4] In most cases, pain in PD lasts or recurs for more than 3 to 6 months, fulfilling the definition of chronic pain, a condition that affects

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20% of the population worldwide.[5] In this context, differentiating PD-related pain from other causes of chronic pain can often be challenging. However, over the years, PD researchers worked in classifying the subtypes of pain specifically reported by patients with PD in order to assist the recognition and treatment of this problem in clinical practice. Musculoskeletal pain in PD is typically related to rigidity or motor fluctuations, limits range of motion, and can manifest as muscle tenderness, arthritic changes, postural abnormalities, or antalgic gait. Dystonic pain is more specifically linked to PD and can also fluctuate closely with medication dosing. It can occur both at the beginning or end-of-dose, the peak of the dose, or in the early morning and manifest as sustained twisting movements or postures with painful muscular contractions. Neuropathic pain is commonly related to neuroforaminal compression of nerve roots related to degenerative disc disease, again related to long-term limitations in range of motion secondary to disease state. Central pain is often relentless and can be strange in quality, not confined to a nerve root territory or explained by rigidity, dystonia, or a musculoskeletal or internal lesion. It presents as burning, tingling, aching, or even visceral pain. Additionally, oral and genital pain syndromes are recognized as unique pain complaints in PD.[6] As previously mentioned, given the diversity of pain types in PD, it comes as no surprise that the diagnosis remains challenging and treatment or modulation of pain can be extremely difficult.

Due to the complexity of pain in PD, there have been very few studies trying to ascertain the efficacy and tolerability of different analgesic drugs in this subset of patients. Here, we aim to summarize and organize the current status of pain management in PD, discussing the most current literature and implications for both pharmacological and non-pharmacological treatments for pain in PD. Lastly, based on current evidence, we aim to provide a proposed algorithm for the management of such a prevalent symptom.

Materials and Methods

Search Strategy and Literature Sources

We reviewed both pharmacological and non-pharmacological treatments for pain in patients with PD. We searched for studies cataloged in PubMed and the Cochrane library, to October 31, 2019. An initial search was conducted between February and June 2018. An updated search was performed in November 2019 to look for new publications. The keywords "Parkinson", "pain", and "treatment OR management" were combined with "and" to search within the title and abstract fields for each database. We also included relevant keyword derivatives, such as "Parkinson's Disease", "Parkinson's", and "PD". In addition to the title and abstract fields, we searched reference sections for all included articles.

Selection and Eligibility

All citations were independently reviewed for eligibility by the same two investigators. Initially, we had planned to include only randomized controlled trials, but due to the lack of published data, in order to produce treatment recommendations, *post-hoc* analyses of randomized controlled trials and open-label studies were included. Any disagreement regarding eligibility resulted in including the full article for review. Eligibility at the full text stage required that the article included patients with PD ages 18 years or older, to report on the efficacy of treating pain as one of the primary outcome measures, to be a randomized controlled trial with a minimum of 6 weeks follow-up (if applicable), and to be written in English or Spanish.

Data Extraction and Analyses

The following data were extracted from the selected articles: type of study, participant characteristics (gender and age), intervention type, method of diagnosis, mean disease duration, Hoehn and Yahr mean score, mean UPDRS score, and change in the primary outcome measure.

Bias Risk Assessment

We used the Cochrane Risk of Bias Tool to assess each study for risk of bias. This included assessing for random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Results

Our review included all randomized-controlled trials for the treatment of pain in PD. As previously described, there is a relative scarcity of data regarding the treatment of pain in PD. In order to provide a comprehensive understanding of the current status of studies evaluating treatments for this symptom, *post-hoc* analyses and open-label studies were also included. We did not include any case–control studies, case series, or case reports. The flow chart of studies included is shown in Figure 1. We focused largely on efficacy and side effects as well as on the design issues associated with each study. The results are divided into subsections based on pharmacologic and non-pharmacologic treatments below.

A total of 11 articles were included in this review: seven randomized controlled trials or randomized crossover studies, two *post-hoc* analyses, and two open-label studies. All studies were either North American or European, and given different study designs, the size of the samples also varied significantly. The smallest study included only six patients as it was a feasibility study, and the largest study, a *post-hoc* analysis, included 287 patients. The range of the mean age of patients included in these studies was from 59 to 74.7 years of age. Disease duration was also quite diverse, with one study enrolling patients with a mean disease duration of 5.9 years, and another one enrolling patients with a mean disease duration of 15.2 years. A complete list of all studies was included, and their main characteristics are found in Table 1.

Pharmacologic Treatment

Gerdelet-Mas et al. (2007)[7] published one of the first studies looking at controlling pain in PD by optimizing the dopaminergic treatment with levodopa. This study was based on previous findings that suggested that patients with PD had a lower subjective pain threshold than healthy subjects.[8] Despite a relatively small sample size, including 13 patients in the study arm (levodopa, "OFF" state – off levodopa for 12 hours, "ON" state – morning dose of levodopa plus an additional 100 mg), and 10 patients in the age-matched healthy control group (200 mg dose

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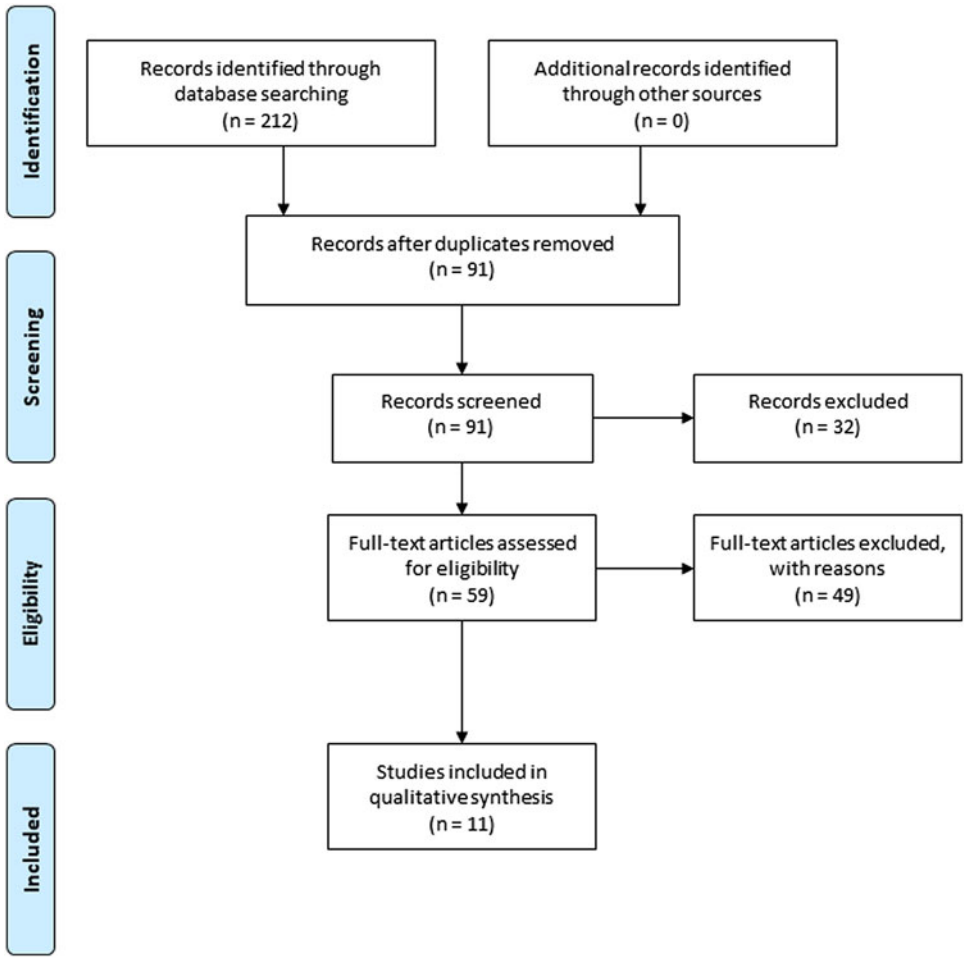

Figure 1: *PRISMA flow diagram of studies included in the review.*

of levodopa), they found that in addition to having a lower pain threshold (measured by recording the RIII nociceptive flexion reflex threshold, 6.9 (1.2) mA in the "OFF" group compared to 8 (1.05) mA in the "ON" group) than age-matched controls, patients with PD that had been treated with levodopa had a significant increase in their objective pain thresholds. However, many patients optimized on levodopa treatment still experience a significant amount of pain, and therefore, the adjustment of dopaminergic treatment alone is not always sufficient in treating this prevalent symptom.[9]

Dellapina et al. (2010)[10] performed a follow-up study assessing the effect of the dopamine agonist apomorphine on pain thresholds in patients with PD. Previously, it had been shown that other monoamine systems might be involved in central pain modulation[11], and given levodopa is also converted to other monoamines in the central nervous system, it was postulated that the effect seen on central pain thresholds may be related to monoamines other than dopamine. In this randomized-controlled crossover trial ($n = 25$), apomorphine (individualized dose based on motor improvement) given for 2 days prior to testing, compared to placebo, had no specific effect on pain threshold using the same RIII nociceptive flexion reflex (10.7 (3.6) mA in the study group and 9.4 (3.7) mA in the control group), and on pain-induced cerebral activity based on positron emission tomography scanning. There was no significant difference compared to baseline for either group, indicating that apomorphine was not non-inferior compared to placebo, but rather the treatment was ineffective. Given this study showed that a dopamine agonist is not efficacious in modulating pain thresholds, this could indicate that perhaps the increased pain threshold in PD patients is related to the conversion of levodopa to noradrenaline, or its effect as a "false transmitter" in serotonergic terminals.

Based on this theory that norepinephrine and serotonin may regulate central pain, Djaldetti et al. (2007)[12] performed an open-label study assessing the effect of duloxetine on central pain symptoms in patients with PD. They enrolled 23 consecutive PD patients complaining of any type of pain and treated with 60 mg of duloxetine for 6 weeks. Given the open-label nature of the study, there was no control group. There was a significant reduction in pain on an 11-point Likert visual analog scale after 6 weeks of treatment (7.6 (3.2) pre treatment compared to 4.2 (2.6) after treatment). The antidepressant activity of duloxetine may have played a role in these results. However, Beck Depression Inventory scores were not significantly different between the two groups at the end of the treatment period, and patients with significant depression were excluded from the study altogether. Three patients had to withdraw from the study, and three had to reduce the dose to 30 mg due to medication side effects including nausea and vomiting, vertigo, sleepiness, insomnia, diarrhea, and aggravations of tremor. Given the open-label nature of the study, the potential for

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Table 1: Studies included in the systematic review, including type of study, intervention, type of pain studied, number of patients, mean age, mean disease duration, and primary outcome measure

Author (Year)	Type of Study	Intervention	Type of Pain	Number of Patients	Age, average in years (SD)	Mean Disease Duration, years (SD)	Duration of Study	Primary Outcome
Gerdelet-Mas et al. (2007)	RCT	Levodopa	No pain – decreased pain threshold	13	NR	NR	Nociceptive reflex measured during "ON" phase, determined by >50% improvement in UPDRS	Lower pain threshold based on the RIII nociceptive flexion reflex threshold
Bruno et al. (2017)	RCCT	Botulinum toxin A	Musculoskeletal and dystonic	12	65.8 (9.9)	14.8 (6.4)	12 weeks	Decreased subjective pain on visual analog and numeric scale
Marques et al. (2013)	RCCT	DBS	Central pain	19	62.3 (5.7)	13.2 (2.8)	Evaluated thresholds with stimulator on and off immediately after activating device	Increase of pain and tolerance mechanical thresholds
Dellapina et al. (2011)	RCCT	Apomorphine	Neuropathic pain	25 (12 with pain)	63 (6.2)	8.4 (2.7)	Two days of treatment, thresholds tested during "ON" phase	Subjective pain threshold based on Peltier-based contact temperature stimulation
Rascol et al. (2016)	RCT Pilot Study	Rotigotine patch	All cause moderate PD pain	35	66.5 (11.9)	5.9 (3.5)	12 weeks	Decrease in subjective pain on Likert scale
Trenkwalder et al. (2015)	RCT, open-label crossover	Oxycodone-Naloxone	All cause – central, peripheral, neuropathic	88	66.7 (8.9)	6.9 (5.2)	16 weeks	Decreased subjective pain on Likert scale
Rintala et al. (2010)	RCT pilot study	Cranial electrotherapy	Lower body pain, musculoskeletal or all cause	6	74.7 (7.8)	15.2 (12.9)	40 minutes per day for 6 weeks	Decreased subjective pain on Likert scale
Cattaneo et al. (2017) – 1*	*Post-hoc* analysis	Safinamide	All cause – "bodily discomfort"	224	60.1 (9.2)	8.2 (3.8)	6 months	Improved bodily discomfort on PDQ-39 scale
Cattaneo et al. (2017) – 2*	*Post-hoc* analysis	Safinamide	All cause – "bodily discomfort"	274	61.7 (9)	8.9 (4.3)	6 months	Improved bodily discomfort on PDQ-39 scale
Kassubek et al. (2014)	*Post-hoc* analysis	Rotigotine patch	All cause	287	64.8 (9.3)	4.6 (4.2)	4 weeks	Decreased subjective pain on Likert scale
Djaldetti et al. (2007)	Open-label	Duloxetine	Central pain, excluding dystonia, back pain, limb rigidity and nocturnal spasms	23	59 (7.9)	7.2 (4.4)	6 weeks	Decreased pain on SF-MPQ and BPI
Madeo et al. (2015)	Open-label	Oxycodone-Naloxone	Chronic pain, all cause	16	71.6 (8.9)	NR	8 weeks	Decreased subjective pain on numeric rating scale

SD = standard deviation; RCT = randomized controlled trial; RCCT = randomized controlled crossover trial; DBS = deep brain stimulation; PD = Parkinson's Disease; PDQ-39 = Parkinson's Disease Questionnaire; SF-MPQ = Short-form McGill Pain Questionnaire; BPI = Brief Pain Inventory.

*Cattaneo et al. (2017) was a *post-hoc* analysis of two studies. For the analysis, only the 100 mg dose was used due to differing protocols in the two trials.

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placebo response is high and a randomized-controlled trial is required to measure clinically significant efficacy.

The first randomized controlled trial specifically designed to investigate the pharmacologic treatment of PD-related pain came from Trenkwalder et al. in 2015.[13] This was a phase 2 study in which OXN PR, a combination of oxycodone and naloxone (thought to reduce gastrointestinal side effects of opioid medication), was used in patients with scores of at least 6 on an 11-point pain scale, in comparison to placebo. While safe, OXN PR did not have a significant effect on the primary endpoint of improved average 24-h pain score at 16 weeks on the same Likert scale. Per-protocol analysis, however, showed that adherence to protocol resulted in significantly improved pain scores compared to placebo (least-squares mean difference of −0.9 (0.8) on the likert scale). Possibly, the heterogeneity of PD pain types may have contributed to the negative trial, as OXN PR has been shown to improve severe musculoskeletal pain and severe nocturnal pain, but not necessarily central or neuropathic pain. The dropout rate was also high, and understandably so, as many patients are unlikely to tolerate severe PD-related pain for 16 weeks, which was an inclusion criterion. This study was released shortly following a Madeo et al. (2015)[14] study which assessed the efficacy and safety profile of OXN PR in the PD population. Despite negative results from the Trenkwalder et al. study, Madeo et al. did describe a significant reduction in global pain on a numeric rating scale, as well as pain intensity over 8 weeks in their small, prospective, open-label study (−2.31 (0.52) reduction on the numeric rating scale, from 0 to 10). Once again, the open-label nature of the Madeo study means that there may be a strong placebo effect on the results.

Following the OXN PR studies, Rascol et al. (2016)[15] performed a randomized-controlled pilot study looking at the efficacy of the transdermal rotigotine patch in treating chronic PD-related pain. Based on the RECOVER study which suggested that rotigotine may help improve PD-related pain compared to placebo, the Rascol trial was intended to be a large-scale study as assessed on an 11-point Likert scale after 4 weeks of treatment.[16] A *post-hoc* analysis of the RECOVER study by Kassubek et al. (2014)[17] indicated a statistically significant improvement in the Likert scale in PD patients with "any pain" (least square mean difference of −0.88) or "moderate-to-severe pain" (least square mean difference of −1.31), but not in those with "mild pain". With these *post-hoc* results, it is important to keep in mind that because patients were not selected for the original study based on symptoms of pain, *post-hoc* selection using subjective pain scales may bias results. These patients were also categorized into arbitrary subgroups of "mild pain" and "moderate-to-severe pain" on the Likert scale.[18] That being said, the results showed promise and certainly warranted an investigation into the potential improvements in pain seen with the rotigotine transdermal patch.

Unfortunately, a subsequent trial investigating non-motor symptoms in PD did not demonstrate a statistically significant difference between rotigotine and placebo in the individual item of the Non-Motor Symptoms Scale that assessed pain.[18] Therefore, a smaller number of patients than initially planned were enrolled into the 2016 Rascol trial[15] – with 33 randomized to the placebo arm and 35 to the rotigotine arm. The goal of the study was to collect preliminary information on the potential efficacy of rotigotine on PD-associated chronic pain, and to assess the feasibility of conducting a larger trial. Given the small sample size, the study was heavily underpowered and although no statistically significant improvements were seen over the 12-week trial period, numerical improvements in the primary outcome, the severity of PD-associated pain experienced in the last 7 days of the trial, as assessed by an 11-point Likert pain scale, were seen (least square mean difference of −0.76, $p = 0.172$). Importantly, the percentage of patients who responded to treatment as assessed by a ≥2-point improvement on the Likert scale was numerically higher in the rotigotine group (60%) compared to the placebo group (47%). While a nearly 50% placebo response should be noted, a 2-point change on an 11-point Likert scale is generally considered to be a clinically important difference, and therefore with an adequately powered study, a statistically significant difference may be seen.

One of the more recent studies assessing pharmacologic treatment for PD-related pain was the Cattaneo et al. (2017)[19] *post-hoc* analysis of two studies assessing the efficacy and safety of safinamide, an orally active, selective, reversible monoamine oxidase-B inhibitor with both dopaminergic and glutamatergic properties, compared to placebo as an adjunct medication to stable doses of levodopa. These trials were conducted in patients with mid- to late-stage PD and motor fluctuations. At 24 weeks, safinamide (at a dose of 100 mg) significantly improved scores on the "bodily discomfort" domain of the PDQ-39 questionnaire, which addresses musculoskeletal and neuropathic pain (−5.28 (−3.79 to −6.78) numerical reduction in "bodily discomfort" domain score compared to −1.59 (−1.10 to −3.09) in the placebo group). In addition, significantly more patients were free of pain medications as compared with the placebo group, and there was a 34% reduction in the number of concomitant pain treatments. Again, given the original trials were not designed to investigate pain as a primary endpoint, only indirect measures could be used to evaluate pain. As such, these results should also be considered exploratory, and their clinical relevance must be confirmed in larger trials with pain as a primary endpoint.

Botulinum toxin is frequently used in PD patients to treat dystonia and rigidity, most commonly in patients with advanced disease.[20] Based on results from a retrospective study and clinical experience with patients that received injections and had subjective improvements in pain,[21] Bruno et al. (2017)[22] performed a prospective randomized placebo-controlled crossover trial using botulinum toxin type A (BTXA) to treat limb pain in advanced PD. Fourteen patients were enrolled and twelve finished the trial. Half of the patients had dystonic pain and half musculoskeletal pain defined using the Ford's clinical classification of pain.[23] Pain was assessed using both a numeric rating scale and a visual analog scale. Overall, the study showed a mild, non-significant reduction in pain after 4 weeks (peak effect) compared to placebo (reduction in 1.75 points on the numeric rating scale compared to 1.16 in the placebo group), and subgroup analysis showed that those with dystonic pain had an even greater, yet still non-significant, reduction in pain (2.66 points reduction compared to 0.75 in the placebo group). There were no changes seen at the conclusion of the 12-week study. This subgroup analysis was insufficiently powered, and a clinically meaningful benefit from BTXA injections is usually seen after multiple treatments, rather than just after one injection as per this study's protocol. Certainly, the results showed that BTXA is safe in patients with limb pain and further studies may focus on evaluating long-term effects of BTXA in patients with dystonic pain, as they seemed to show the most benefit.

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Non-Pharmacologic Treatment

Deep brain stimulation (DBS) is a well-documented treatment for severely disabled PD patients with motor fluctuations, and interestingly, previous studies have shown clinical pain relief after bilateral DBS of the subthalamic nuclei (STN).[24] However, it was unclear as to whether this improvement was based on a central or nociceptive mechanism. Marques et al. (2013)[25] aimed to investigate the effect of DBS to the STN and levodopa administration on pain and pain tolerance thresholds. Three groups were included in the study: stimulation on with levodopa off, stimulation off without levodopa on, and stimulation off with levodopa off. They used Thermotest and Algometer devices to measure thresholds for thermal pain and mechanical pain, respectively. Following acute DBS surgery to the STN, there was a significant increase in both thermal and mechanical pain thresholds, and with acute stimulation, there was an increase in mechanical pain threshold.

Finally, Rintala et al. (2010)[26] explored the use of cranial electrotherapy stimulation (CES), a non-invasive technique which applies a small amount of current through the head via ear-clip electrodes, to treat pain in PD. A review of the use of CES in chronic pain concluded that CES has been found to be effective in reducing both headache and spinal pain, amongst others.[27] Therefore, Rintala et al. performed a small feasibility randomized-controlled trial assessing the efficacy of CES in lower body pain only. They limited the study to patients with lower body pain to ensure a more homogenous sample, and because lower body pain typically contributes to limitations in mobility. Even in this small sample size with the application of CES for 40 minutes/d for 6 weeks, there was a significant pain reduction in the active treatment group compared to the sham group, based on a 10-point Likert scale. With only 13 participants reporting data, it is very difficult to generalize the results, but this study provides the basis for future trials investigating non-invasive, non-pharmacologic treatments for PD-related pain.

Discussion

Pain in PD was an under-recognized problem until recent years. Due to the diversity of presenting symptoms and similarities between PD-related pain and other chronic pain conditions, diagnosis remains challenging. Different classifications were proposed for this symptom,[23,28] and until the publication of the Kings Parkinson Pain Scale, there were no validated instruments to document and measure pain in this population. These factors limited the design and development of high-quality clinical trials for treatment. The lack of evidence for the treatment of pain became evident during the systematic search performed for this review.

A critical step before designing suitable trials for pain in PD is understanding the pathophysiology of pain in this condition, as this differentiates PD-related pain from other chronic pain conditions. Current knowledge in the field supports the role of the sensory function of the basal ganglia through the modulation of information from other brain areas such as the cortex, the thalamus, and the substantia nigra as a possible mechanism to explain why patients with PD have pain. It is known that in PD, the reduction of dopaminergic input to the basal ganglia changes sensory perception and modifies pain thresholds.[29] Moreover, dopamine can modulate pain in regions outside of the basal ganglia, such as the spinal cord, the thalamus, the periaqueductal gray, and the cingulate cortex,[30] and evidence shows that dopaminergic function may modulate sensory perception.[7] In clinical practice, however, dopaminergic medication is not usually sufficient to eradicate pain in PD suggesting that additional non-dopaminergic mechanisms must be related to this symptom. Serotonergic and noradrenergic pathways are affected by pathological changes in PD, and both have a role in pain control.[31] Hence, multiple neurotransmitter pathways may be responsible for the symptom of pain in PD, and currently, it is still challenging to deliver specific treatments targeting the pathophysiology of the pain.

Due to the dearth of evidence for treatment of pain in PD, it is difficult to establish firm guidelines or recommendations. We reviewed findings from randomized controlled trials, *post-hoc* analyses, and even open-label studies, but several gaps in the literature are prominent. Small sample sizes, short-term duration of studies, vast differences in baseline characteristics, variability in pain assessments and diagnosis, and of course, differences in pain type all make it difficult to analyze a compiled set of results. In addition, randomized controlled trials in the field of pain are inherently flawed due to the high placebo effect, and as such, results from these studies always need to be interpreted with caution. Therefore, we propose a treatment algorithm and guideline with the caveat that far more research is required in this field to establish more robust recommendations.

Current knowledge suggests that identifying the type of pain a patient is experiencing is vital, as neuropathic, somatic or musculoskeletal, dystonic, and central pain can all respond to different treatments. Assessing the type of pain can help the clinician exclude other possible sources of pain unrelated to PD. Optimization of dopaminergic therapy is essential given the reductions in central pain thresholds in PD.[7] Once dopaminergic therapy is optimized, the type of pain should then determine which treatment modality is subsequently used.

Naturally, studies looking at pain in PD are heavily weighted toward pharmacologic therapy. However, most successful models of pain treatment employ a multidisciplinary approach involving both non-pharmacologic and pharmacologic therapy. Unfortunately, in an area where literature is already sparse, evidence for treatments such as exercise, cognitive behavioral therapy, physiotherapy, and massage therapy is quite thin. Petzinger et al. (2013)[32] suggested that exercise may promote neuroplasticity and improve processing of nociceptive signals in both PD patients and healthy controls, and this finding has been supported by various neuroimaging techniques.[33,34] In addition, there is a small amount of evidence which suggests that exercise may actually slow progression of PD in humans, this improving mobility and reducing motor impairment.[35–37] It could be inferred that these changes may the burden of pain in the PD population. However, the only randomized controlled trial for exercise compared aquatic therapy to dry land therapy to assess benefits on pain perception. Both arms showed improvements in pain perception, with aquatic exercise showing significant benefit compared to dry land therapy as well.[38] Clearly, there is a paucity of data in this area, and randomized trials comparing any intervention such as physiotherapy, exercise, or massage therapy to placebo are needed.

In terms of pharmacologic treatment for neuropathic pain, duloxetine may be helpful given its use as a first line agent in

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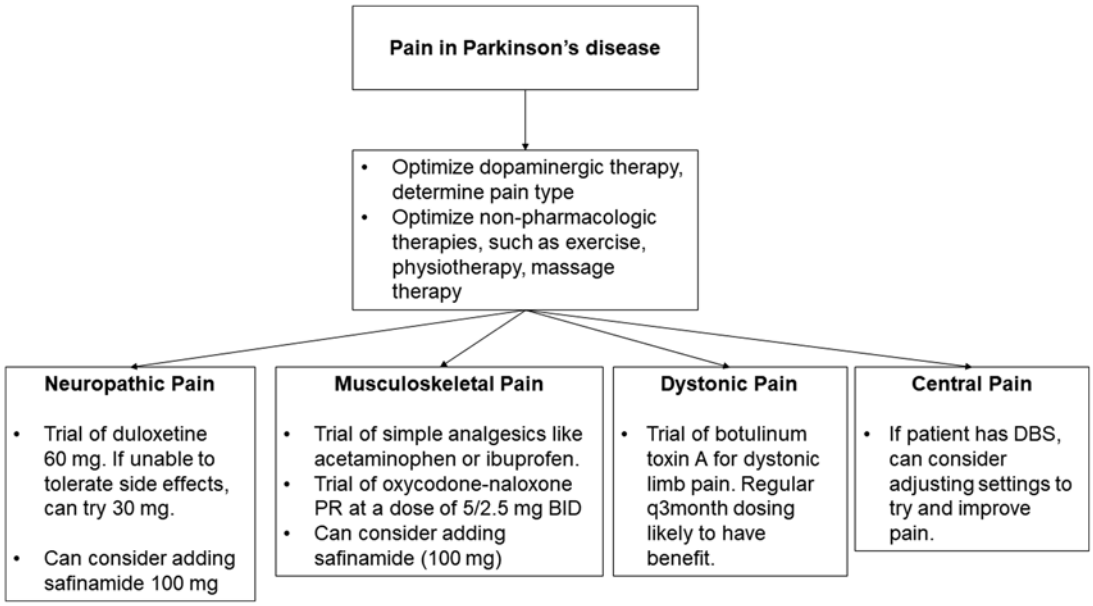

Figure 2: *Possible strategies for the treatment of pain in Parkinson's disease based on current evidence.*

conditions other than PD.[39] However, in the only preliminary open-label study which was conducted, all-cause and not specifically neuropathic pain was assessed.[12] Safinamide may also be helpful in this regard, but again, neuropathic pain as an isolated symptom was not assessed. Instead, it was tested as a domain in the PDQ-39 questionnaire as a part of "bodily discomfort", which also includes musculoskeletal pain.[19] Given the strong evidence behind duloxetine as a neuropathic pain agent in non-PD populations, it seems acceptable to encourage its use in patients with PD who are experiencing this form of pain. However, more evidence is needed to support the use of safinamide.

For musculoskeletal pain, despite a study with no statistical significance, a trial of oxycodone-naloxone should be considered following a trial of simple analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs. As mentioned, we postulate that the lack of statistical significance between the treatment and placebo groups is related to both the heterogeneity of PD pain types, as well as the lack of power in the study, but the contribution of a substantial placebo effect cannot be excluded. Since oxycodone-naloxone is known to have strong efficacy for musculoskeletal type pain[40], it may be used with relative confidence in this subset of the PD population. However, a study with musculoskeletal pain evaluation as its primary endpoint is necessary before robust endorsement can be given, and prescribers should be cautious of the sedating and confusion-related side effects of opioid medications in the PD population. Again, safinamide can be considered, but the evidence is far less compelling.

There appears to be a signal which points to BTXA being amenable to treating dystonic pain in PD. Bruno et al. (2017)[22] found a non-significant signal at 4 weeks following administration of BTXA to patients with pain in PD, and subgroup analysis showed that those with dystonic pain specifically had a stronger, yet still non-significant response to treatment. This study was only completed by 12 participants, and as such was heavily underpowered, particularly the subgroup analysis. However, it does provide compelling data for future studies, and given the safety profile of BTXA, a trial of this agent in patients with dystonic pain in the limbs associated with PD might be considered.

Central pain can be difficult to characterize for PD patients. Many describe it as a diffuse aching, burning, or cramping, and it is not caused by any lesion in the peripheral nervous system. Marques et al. (2013)[25] found that clinical pain alleviation after acute DBS to the STN was not associated with UPDRS-III improvement, nor was it associated with improvement in motor complications assessed by the UPDRS-IV after chronic STN-DBS. Therefore, they postulate that improvements in pain thresholds could be attributable to a direct central modulation of pain perception as a result of the surgery itself. Significantly more data are required regarding the effects of DBS on non-motor symptoms of PD, and excessive central pain itself certainly is not an indication to proceed with DBS surgery. However, in patients with DBS surgery already performed, slight adjustments of settings may be beneficial in modulating central mechanical pain and tolerance thresholds.

Regarding future trials, a new study is presently recruiting patients for the treatment of neuropathic pain in PD using oxycodone and levodopa versus placebo (NCT02601586) and another trial will be recruiting patients to evaluate the effect of cannabis oil on pain in PD (NCT03639064).

Again, the lack of evidence for the management of pain in PD became evident over the course of this review. While some data exist, there is no robust evidence to truly delineate guidelines for the management of this prevalent symptom. However, principles used in other chronic pain conditions can be employed, such as the initiation of physiotherapy and exercise, and are outlined on our proposed treatment algorithm (Figure 2). The need for well-designed trials for the use of non-pharmacological treatments in this population deserves special mention, as they may be a safe and useful alternative, considering their use in non-PD pain. In PD specifically, transcranial magnetic stimulation is being tried (NCT03504748) and the role of DBS should be evaluated in detail for different types of pain in future prospective studies.

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The fact that there is a validated scale for the measurement of pain in PD, the King's Parkinson's Pain Scale (a user friendly, 14 item questionnaire), and that studies are being carried out to evaluate pharmacological and non-pharmacological treatments for this symptom suggest that the outlook will be more favorable in future years. If this trend continues and existing results can be reinforced through the performance of high-quality clinical trials, we will hopefully have evidence-based treatments to offer our patients with PD suffering from chronic pain.

Conflicts of Interest

The authors have no conflicts of interest to report.

Statement of Authorship

VK: research project organization and execution, manuscript preparation, and writing of first draft; NF: research project execution; CZ: research project execution; and VB: research project conception and organization, manuscript preparation, and review and critique.

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