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Parkinson's Disease, Headache and Pain

Marc E. Lenaerts

Abstract

Parkinson's disease (PD) is a vast and complex syndrome. Far more than a mere disorder of motor function, it encompasses autonomic, cognitive, emotional and systemic symptoms. Moreover, pain has increasingly been recognized as an associated feature. Within pain and headache, migraine can bear a unique relation with PD. We hereby review the scientific literature on the relation between PD, pain and migraine and analyze the pathophysiological underpinnings and suggest adjustments in the management to tentatively improve clinical outcomes in this setting.

Keywords: Parkinson's disease (PD), cervical dystonia, migraine, headache, pain, comorbidity, comprehensive management

1. Introduction

Parkinson's disease (PD) is a very complex condition, and increasing emphasis is given on the non-motor symptoms. Mindful of the extent of its pathology in the CNS (central nervous system) and of the complexity of its symptomatology approaching PD comprehensively including pain has vast clinical benefits. As such, the study of comorbidities in PD as well as its clinical ramifications with various pathophysiologic processes brings much benefit for the comprehensive care of this disease.

Here, we concentrate on the relations between PD on one hand, and pain and headaches on the other. At the core of PD symptomatology is hypertonia that causes abnormal musculoskeletal dynamics including among others, painful muscle contractions, acceleration of joint degeneration and encroachment of neural structures in the spine. Abnormal central pain mechanisms might also be involved. The relation with migraine is more elusive but likely relates to pathologic central pain processing and neurotransmitter shifts, particularly dopamine.

2. Epidemiology

Pain was already mentioned by James Parkinson himself in his 1817 seminal article "An essay on the shaking palsy" [1].

Pain is highly prevalent in PD, and several epidemiological studies have highlighted this issue [2–6]. It affects women disproportionately [7].

Few studies have investigated the comorbidity of migraine and PD. This merits several considerations. Both conditions are diagnosed with clinical criteria, even PD that could otherwise be diagnosed with certainty with pathology. Some of the

basic aspects that we know of some of pathogenesis of the two conditions, one with degenerating neurons in the substantia nigra and one with dysregulation on the trigemino-cervical complex, do not raise a high suspicion of comorbidity. The age of onset as well as the gender predominance is likewise pointing away from comorbidity. Thus, it seems at first glance that comorbidity would be unlikely, or even that the two conditions would partly mutually exclusive, or protective of one another.

One-year prevalence of migraine is high, about 12% population (chronic migraine about 2%); and that of PD moderate, about 0.5% population, making statistical evaluations more cumbersome by requiring relatively high numbers of observations [8–10].

In an in-depth analysis of 237 patients suffering from PD, 66 had a history of migraine, a lifetime prevalence of 28% [11]. The prevalence of current migraine was 13%. These are similar to those in the general population [12]. More interestingly, among these 66 comorbid patients, the prevalence of current migraine was significantly lower than in 66 matched non-PD controls (47% vs. 68%), suggesting a possible surprising benefit from chronic dopamine therapy or, interestingly, an ongoing protective effect of PD on migraine [11].

In a large Taiwanese, 2.5-year cohort of one group of over 40,000 of 40–90-year-old migraine sufferers and an equal same-age group of controls, the prevalence of PD in the first group was at 1.64 odds above that in the second, and the incidence rate was increased as well [13].

A survey of 223 patients with PD reported a migraine prevalence of 19% and another of 71 patients one of 11% [14, 15].

A case–control study of 109 patients with PD demonstrated no significant effect of the emergence of PD motor symptoms on the course of migraine [16].

A cross-sectional analysis of 43 patients with PD with headache (12 with migraine and 31 with tension-type headache) demonstrated no correlation between PD stages and the presence or characteristics of headache including migraine [17].

In a recent survey, the largest-to-date, of 436 patients with PD and 401 controls, PD was associated with a significantly lower rate of migraine (one-year and lifetime prevalence) by almost half, and this was not the case for headaches in general. Moreover, the onset of PD was associated with a substantial reduction in migraine symptom burden when compared with prior to onset. This was not because of age which we know reduces migraine frequency, for the decrease was far more pronounced than in migraine controls without PD [18].

In summary, there is limited literature on the comorbidity between PD, on one hand, and pain and migraine, on the other. Results of studies vary, in part due to methodology, and so far no definite conclusion can be drawn, more investigations being warranted.

3. Pathophysiology

Dopamine modulates pain and levodopa increases pain thresholds [19, 20].

Pain can relate to the motor function in PD and should always be analyzed within that mind frame. Rigidity causes pain *via* muscle hyperactivity, contractions, tendon pain and joint wear [21]. Nonetheless, there is no clear time correlation between pain levels and motor scores [3, 5].

Several anatomical targets of PD pathology (Lewy bodies, degeneration) are involved in pain, emotion and autonomic control: basal ganglia; medial

spino-reticulo-thalamic pathway, including locus coeruleus, periaqueductal gray and thalamus; lateral spino-thalamic pathway (modulated by DBS) [22–24].

The role of dopamine is most interesting. Dopamine-blocking agents help the symptoms of migraine (and not only the nausea but the pain itself), dopamine-enhancing or mimicking agents help PD and dopamine is key in placebo response.

Dopamine seems involved in behavioral and autonomic modifications during migraine attacks: appetite, vigilance, energy and blood pressure [25, 26]. Some mutations in dopamine D2 receptor (DRD2) and some in catechol-oxy-methyl-transferase link to migraine [27–29]. Central catecholamines including dopamine modulate pain, pain sensitization and other symptoms [30, 31].

Dopamine receptors are found in the nucleus tractus solitarius, dorsal vagus and area postrema, all involved in the gastro-intestinal symptoms of migraine [32]. Also, D1 receptors found in renal arteries might influence the diuresis of migraine postdromes and D2 receptors in the sympathetic ganglia contribute to migraine hypotension and syncope by reducing norepinephrine release [33, 34].

Migraine prodromes (yawning hunger, hypervigilance), accompanying symptoms (anorexia, nausea, vomiting, hypotension), are partly under dopamine control. Dopamine agonists such as apomorphine cause similar symptoms as side effects and these side effects occur. In migraine sufferers, these effects can occur at lower than average doses [35–37], and apomorphine can trigger migraine [38].

The clinical severity and responsivity to dopamine was investigated in patients with PD with or without migraine. In a trial of 18 patients with PD among whom 10 with migraine, UPDRS (Unified Parkinson's Disease Rating Scale) showed longer on-times, shorter off-times and lower levodopa requirements but no difference in hallucinations [39].

The dopamine-dependent late phase of CNV (contingent negative variation) electrophysiology test is abnormal but normalizes with migraine episode resolution and is modulated by the dopaminergic apomorphine [40, 41]. Hallucinations can be observed in both PD and migraine. In migraine, CSD (cortical spreading depression, mechanism of the aura) can cause hallucinations and seems under serotonergic and cholinergic control, themselves relevant to PD [42, 43].

Valproate and flunarizine, used in migraine prophylaxis, can induce parkinsonism [44, 45].

Dopamine-blocking agents such as promethazine and prochlorperazine are well known to help the gastro-intestinal symptoms of migraine symptoms but also reduce pain independently. Domperidone had equal effect to acetylsalicylic acid or metoclopramide or prochlorperazine alone [35, 46–49].

However, increasingly the gastro-intestinal symptoms of migraine are treated with serotonin 5 HT-3 receptor antagonists ondansetron or granisetron for tolerability reasons, and thorazine infusions for refractory status migrainosus should be avoided in PD.

The substantia nigra possesses a high concentration of serotonin 1—B, D and F—receptors that are the target of sumatriptan [50] and this could alter tolerability of sumatriptan in PD. The substantia nigra is activated after occipital aura on functional MRI (magnetic resonance imaging) [51]; therefore, PD could influence the expression of migraine auras.

Hormonal fluctuations can influence several neurologic conditions [52]. Estrogens specifically influence involves the striatum. PD tremor probably, and migraine certainly, is menstrually exacerbated [52–54]. The incidence of PD might be reduced with the implementation of hormone replacement therapy [55, 56].

Figure 1.
The multiple interrelations between PD, migraine and pain. This illustrates the complex relations between PD, pain and migraine. Abbreviations: SN: Substantia Nigra; PAG: Periaqueductal gray matter. Boxes: Red: Key conditions; black: Syndromes; purple: Pathophysiology and pathology. Orange: Treatments. Arrows: Represent influence. Blue: Clinical and physiological; dark: Strong evidence; light: Hypothetical. Red and green: Pharmacologic; red: Negative synergy; green: Positive synergy.

Post-menopausal hormone replacement therapy shows a modest benefit in PD and a more definite one in migraine [57, 58].

PD can present with cervical dystonia, which contributes to cervicogenic headaches, but also aggravates migraine. This becomes very pertinent when patients are treated with botulinum toxin for both dystonia and migraine.

The relation between microbiome and nervous system is under increasing scrutiny: The former can contribute to autoimmune conditions and alter biochemical processes affecting PD and migraine; autonomic dysfunction in these two conditions can alter the microbiome, maybe with synergy when comorbid [57].

Beta-blockers presumably affect migraine not *via* blood pressure but *via* central catecholamines (as per CNV studies) [59]. Cortical hyperexcitability in migraine depends on central catecholamine activity. Dopamine has once been coined the “migraine accelerator.” Postural stability is often affected in migraine overall, not just its vestibular form [60]. PD causes more profound postural instability.

The prevalence of depression is increased in migraine as well as in PD (Figure 1).

PD can, *via* abnormal tone and posture, cause myofascial pain and degenerative disk and joint disease, leading to pain directly and by neural compression, and cervicogenic headache. The possible degeneration and dysfunction of structures involved in pain such as thalamus, PAG, cord, contributes to pain, and that of the substantia nigra might influence migraine auras. Central sensitization in migraine can amplify systemic pains. The dopamine deficit in migraine could have a partial protective effect on migraine. PD treatment enhancing dopaminergic activity might aggravate the nausea of migraine; mirroring this, dopamine blockers, used to control migraine nausea, aggravate PD symptoms. Serotonergic agents might benefit PD. BotulinumToxinA for chronic migraine benefits cervical dystonia encountered in PD.

4. Syndromic presentations

4.1 General clinical principles

Pain syndromes in PD are attributable to either unrelated etiologies or features of the condition itself or often to a combination thereof. It is beneficial to approach pain in PD with a somewhat unifying concept [61]. It can in turn be classified within the following useful clinical frames: movement-related dystonic or akathitic, musculoskeletal, radicular or central [62] (**Table 1**). Note that choreic and athetotic movements are typically not significantly painful. Additional pain syndromes seen in PD more than the general populations but not specific to it are pain linked to constipation and the discomfort associated with orthostatic hypotension and metaphorically referred to as “coat-hanger” syndrome [63]. Aiding to classify the patient's syndrome in the aforementioned scheme (and adding a visceral pain category), the KPPS (King's PD Pain Scale) is a useful questionnaire [64].

4.2 Dystonia

Dystonia, primary or pharmacologically induced, can generate impacting painful syndromes including, if scapular, a frozen shoulder and, if cervical, cervicogenic headache [65, 66]. Dystonia is painful compared with the non-statically sustained chorea or athetosis. Akathisia is an unpleasant symptom rather than painful.

Dystonia can be present with levodopa end-of-dose fluctuation. This can be managed with extended-release levodopa or the addition of dopa metabolism to prolong the therapeutic effect, and in rare instances, even apomorphine can afford fast relief [67, 68]. A similar reasoning applies to the early AM dystonia where apomorphine might be even more necessary [62]. LCIG (levodopa/carbidopa intestinal gel) therapy can also be beneficial [69].

Dopamine agonists also show benefit in dystonia-related pain [70].

Botulinum toxin is an excellent approach for focal, such as cervical or scapular, dystonia [71].

Deep brain stimulation has shown to be effective against cervical dystonia [72].

4.3 Musculoskeletal pain

Although as stated above time correlation between motor fluctuations and pain levels is not firmly established, the chronic abnormal muscle contractions, tendinous strain, abnormal posture with uneven joint wear and pressure point distribution, and most importantly limited amount and range of motion, all contribute to musculoskeletal pain. The frequency, duration, intensity and anatomical distribution are highly variable. The clinician ought to assess these multiple aspects of the syndrome to better diagnose and manage these pains, all the while addressing the specific and commonly observed contribution of the abnormal motor function. For instance, upper truncal dystonia can contribute to frozen shoulder, cervicalgia, cervicogenic headache and camptocormia, which can induce spine pain at any level. NSAIDs, muscle relaxants, physical therapy and, at times, surgery, are all part of the therapeutic armamentarium. Cannabinoids are increasingly considered but there is no consensus recommendation yet [73]. Additional beneficial aspects of therapy at large encompass the elements of social and artistic activity, such as painting, music and dancing [74]. Treating associated depression and anxiety is inherently beneficial. Choosing a pharmacologic agent that enhances dopaminergic activity is worthwhile, such as citalopram, nortriptyline or venlafaxine [75–77].

Pain syndrome	Dystonia	Akathisia	Musculoskeletal	Radiculopathic	Central
Pathophysiology	Dopaminergic deficit Excessive contractions from early AM akinesia or mid-day off phenomenon	Dopaminergic deficit	Abnormal postures Muscle and tendon contractures Abnormal joint wear	Spine degenerative disease, precipitated by abnormal posture	Unclear, possible dopaminergic deficit
Symptomatology	Posture-related nociceptive pain Any area of body Common in cervico-scapular area Can lead to cervicogenic headache and frozen shoulder syndrome	More discomfort than severe pain Restlessness Include restless legs syndrome	Pain in muscle, tendons, fascias and joint Nociceptive mechanical pain exacerbated by excessive (in) activity	Lancinating pain radiating in radicular territory	Highly variable locations and types and intensity Can be holosomatic, truncular, prosopalgic Often complex and atypical in description

Five main pain syndromes in PD with their pathophysiologic and clinical characteristics.

Table 1.
Classification of pain syndromes in PD (modified from Ford) [18].

4.4 Radiculalgia

Nerve root pain is not uncommon in PD with a survey estimating the prevalence between 10 and 29% [78]. Camptocormia can undoubtedly contribute to spine degeneration and foraminal stenoses. Tricyclic antidepressants, SNRI (serotonin-norepinephrine-reuptake inhibitors) and anticonvulsant neuromodulating drugs are part of a wide choice of pharmacologic agents to choose from in helping neuropathic pain. Gabapentin has shown to potentially have additional motor benefit in PD pain [79].

4.5 Central pain

Central pain syndromes are highly variable, protean, at times outright atypical. Pain can be diffuse, more focused on truncal or perineal areas. Prosopalgia can be observed. Often it is accompanied by numbness, paresthesia and/or allodynia. These are typically unrelated to the level of motor function. They are typically dismissed for long by providers and generate understandable accrued frustration in patients. Their etiology remains elusive and abnormal central catecholaminergic activity, including dopamine, remains likely. Cautious history and *ad hoc* ancillary investigations are warranted to ensure the more common and/or concerning nociceptive etiologies are ruled out. Cautious assessment of psychotherapeutic support is advised. Management includes neuromodulatory drugs such as gabapentin, pregabalin, duloxetine [79, 80]. Biofeedback and cognitive-behavioral therapy and supportive psychotherapy should be discussed [62, 81]. NSAIDs (Non-Steroid Anti-Inflammatory Drugs) and regular or opioid analgesics are neither typically helpful nor recommended.

4.6 Akathisia

Albeit not typically painful *per se*, akathisia is uncomfortable and merits attention and care. Related to ventral tegmental dopaminergic insufficiency, it can be diffused and occur anytime, and it can also be more focal in time and distribution such as in the case of restless leg syndrome. Management options include dopaminergic drugs such as ropinirole, levodopa especially extended-release or other avenues increasing dopaminergic activity in the brain stem [82].

5. Practice guidelines

Like cognitive, affective and autonomic symptoms, pain is an additional non-motor sphere of symptoms that can also fluctuate. It significantly impacts quality of life in PD too. Screening for depression in patients with migraine, PD and even more so both is paramount.

Patients with PD will consult for their pain either to their movement disorder specialist or to general neurologist or other providers. It is important for the former to be involved in case the specific management of the parkinsonian syndrome needs to be managed in depth, as discussed below. Indeed, often, dopaminergic adjustment is beneficial to pain in PD. This is particularly relevant given the propensity for pain to be at times the presenting symptom of PD [5, 83, 84].

Pain in PD is complex, often multifactorial, and the relationship with PD itself is far more complex than might initially appear and requires a thorough and cautious approach. After a comprehensive history and physical exam,

judicious use of ancillary investigation might be warranted. Multifaceted therapy is typically necessary and pharmacotherapy, and physical and occupational therapies, psychotherapeutic measures, social interventions, procedures and surgery might be indicated. Moreover, physical therapy can be considered in the broader sense and encompass, if supported by evidence, thermotherapy, osteopathic and chiropractic measures, water exercise, (electro-)acupuncture, etc. As an example, acupuncture shows benefit in PD pain [85]. Patient education is not least crucial, for patient's emotional comfort as well as active participation to treatment. Special attention is recommended for the most at-risk and vulnerable patients. Ensuring patients remain engaged in family, social and, if applied, work activities is paramount. Additional attention to balance is advised in patients with PD suffering from migraine. Dysautonomia being common in PD and migraine, great caution is required using medications affecting blood pressure in comorbid patients. Orthostatic blood pressure assessments are essential.

A summary of management of pain syndromes in PD is outlined in **Table 2**.

The care of migraine rests on four pillars (**Figure 2**):

1. Lifestyle modification: proper sleep hygiene, quality diet with regular meals and limited artificial and fermented foods and drinks, regular exercise and stress management;
2. Abortive treatment: acute relief of the migraine attack symptoms: pain, gastrointestinal symptoms such as nausea and vomiting, sensoriphobia (photophobia, phonophobia, kinesiophobia, etc.) and others; insurance patient can return to a functional and productive state;
3. Rescue therapy: measures to help patient who remains severely symptomatic of the attack after abortive treatment;
4. Prophylactic treatment: applies if attacks are weekly or more frequent, if the abortive treatment is insufficient (along with rescue measures) or contraindicated; this part of therapy aims at reducing the burden of migraine overall: attack frequency, duration, intensity, impact; and doing so in respect of patient's ability to function and be productive.

Lifestyle modification has substantial overlap with PD, including stress management and relaxation therapy, regular sleep, regular physical activity.

Abortive treatments include the following:

Non-specific agents such as acetaminophen, non-steroid anti-inflammatory drugs and combination medications (e.g., acetaminophen and caffeine) as well as, albeit rarely advised, opioids. These have no specific impact on, nor are to be modified in, PD.

Specific agents include ergot-derivatives, which activate the 5 HT receptor as well as the dopamine receptor, thus often requiring a dopamine blocker toward off gastrointestinal symptoms, which can negatively impact PD; triptans (5 HT 1 B/D agonists); gepants (CGRP receptor blockers) and a ditan (like triptans, a 5 HT agonists but on a separate receptor subtype (F) without vasoconstrictive effect). Thus, mainly the dihydroergotamine must be the subject of particular caution in PD.

Prophylactic treatments include the following:

Antidepressants: tricyclic such as SNRI (serotonin-norepinephrine reuptake inhibitors); some with enhancing effect on dopamine (see section on pain).

Pain Syndrome	Dystonia	Akathisia	Musculoskeletal	Radiculopathic	Central
	Levodopa (extended release) Dopaminergic agents MAO-i, COMT-i DBS (seep brain stimulation) Apomorphine	Amantadine Beta-blockers Benzodiazepines, Mirtazapine Vit B6	NSAIDs Muscle relaxants Physical therapy Pain management procedures Surgery	Neuropathic pain medication such as amitriptyline, gabapentin or pregabalin Physical therapy Pain management procedures Surgery	Neuromodulating agents such as gabapentin, pregabalin, duloxetine or amitriptyline Biofeedback and CBT (cognitive-behavioral therapy)

Table 2.
Management of pain syndromes in PD (modified from Ford) [18].

Figure 2. The four pillars of migraine treatment. Migraine is best managed comprehensively with a plan for healthy lifestyle adjustment, abortive treatment to stop the ongoing symptoms, rescue treatment if the latter fails, and preventive (prophylactic) care to reduce burden over time and decrease the need for abortive and rescue interventions.

Anticonvulsants: Topiramate is neutral on PD but can add its cognitive side effects to the potential existing PD-related dysfunction; valproate has been shown to cause tremor and maybe secondary parkinsonism, while gabapentin, albeit a weak agent, seems to be beneficial on PD motor symptoms (see section on pain).

Antihypertensives: Beta-blockers can be beneficial in akathisia; angiotensin conversion enzyme inhibitors and angiotensin receptor blockers are neutral in PD and so are calcium channel blockers; hypotension can in any case, however, have more likely side effect in patients with PD who have orthostatic hypotension.

Botulinum Toxin A injections can most definitely benefit PD-related cervical dystonia (see section on pain).

Other medications such as Memantine can also be considered.

An increasing number of FDA-approved options are at the disposal of the clinician for the non-pharmacologic management of headache, which is attractive in the pharmaco-therapeutically loaded regimen of PD management. These include the following:

- Trigeminal nerve stimulator.
- Peripheral remote neuromodulating stimulator.
- Transcranial magnetic simulator.

A number of procedures are also now available, often, however, off-label, and include the following:

- Anesthetic blocks:
 - Occipital nerve injections (greater, lesser, third or all occipital nerves) with local anesthetic.
 - Supra-orbital nerve anesthetic blocks.
 - Spheno-palatine ganglion anesthetic block.

- Other:
 - Trigger point injections.
 - Lidocaine IV infusion.
 - Ketamine IV infusion.
 - Thorazine infusion (not recommended in PD).

As much as the role of physical therapy is known to benefit pain, relative immobility has the inverse effect.

Table 3 relates the main pharmacotherapies for migraine to their potential impact, positive and negative, on PD symptoms and treatment.

CATEGORY	Name(s)	Indication	Side effects relevant to PD	Positive synergy	Negative synergy	Caveats/ other
Beta-blockers	Propranolol, metoprolol	Prophylaxis	Orthostatic hypotension Fatigue Impotence	Can help if associated essential tremor	—	—
Angiotensin conversion enzyme inhibitors	Lisinopril	Prophylaxis	Hypotension	—	—	—
Angiotensin receptor blockers	Candesartan	Prophylaxis	Hypotension	—	—	—
Calcium channel blocker	Verapamil	Prophylaxis	Hypotension, arrhythmia	—	—	Avoid with clozapine
Calcium channel blocker	Flunarizine	Prophylaxis	Sedation; depression; hyperphagia; tremor	—	Can aggravate parkinsonism	Avoid in PD; QT prolongation
Tricyclic antidepressants	Amitriptyline, nortriptyline	Prophylaxis	Anticholinergic Alpha-adrenergic (tachyarrhythmias)	Mood improvement Xerostomia might help sialorrhea	Constipation Confusion	Avoid in elderly especially if cognitive concerns
SNRIs (serotonin-norepinephrine reuptake inhibitors)	Venlafaxine	Prophylaxis	Abnormal dreams; sexual dysfunction	Mood improvement	Affected dreams if already having RBD (REM-sleep behavior disorder)	—
Anticonvulsant	Topiramate	Prophylaxis	Cognitive (language) slowing; paresthesia; dysgeusia; anorexia; cramps	Can help if associated essential tremor	Cognitive slowing; muscle cramps	Avoid if cognitive concerns
Anticonvulsant	Divalproex	Prophylaxis	Tremor (even at rest); hyperphagia;	Mood stabilization	Added tremor	Possible liver toxicity
Anti-CGRP monoclonal antibodies	Eptinezumab, erenumab, fremanezumab, galcanezumab	Prophylaxis	Local injection site reaction	—	—	—

CATEGORY	Name(s)	Indication	Side effects relevant to PD	Positive synergy	Negative synergy	Caveats/ other
NMDA-receptor antagonist	Memantine	Prophylaxis	Nausea, dizziness, paradoxical confusion	Cognitive improvement	—	—
Chemodenervation	OnabotulinumToxinA	Prophylaxis	Weakness facial and neck muscles	Benefit for dystonia and sialorrhea	Can aggravate camptocormia	—
Natural supplements	Riboflavin; Coenzyme Q 10; magnesium	Prophylaxis	—	Might benefit when nutrition is challenged; decreased muscle contractions	—	No concern re: interaction
Neurostimulators	Electric: trigeminal, armband; vagal; magnetic: transcranial	Prophylactic and abortive	Discomfort	—	—	No concern re: interaction
Analgesic	Acetaminophen	Abortive	—	Helps other PD-related pains	—	Liver malfunction
NSAIDs	Ibuprofen, naproxen	Abortive	Gastralgia, GI bleed	Helps other PD-related pains	—	Avoid in GI disease and in coronary artery disease
Triptans	Sumatriptan and six other triptans	Abortive	Chest pressure; palpitations; sedation	—	—	Avoid in active atherosclerosis
Ergot derivative	Dihydroergotamine	Abortive or rescue	Chest pressure; palpitations; sedation			Avoid in active atherosclerosis Requires anti-emetic and thus prefers serotonin-3 receptor antagonist
Ditan	Lasmiditan	Abortive	Nausea; sedation	—	—	—

CATEGORY	Name(s)	Indication	Side effects relevant to PD	Positive synergy	Negative synergy	Caveats/ other
Gepants	Ubrogепant; rimegepant; atogepant	Abortive (ubrogепant and rimegepant) and prophylactic (rimegepant and atogepant)	Nausea	—	—	—
Anti-emetics: antidopaminergic	Oral: domperidone Oral or injectable: promethazine, prochlorperazine	Adjuvant	Sedation oculogyric crisis	Help nausea associated with PD meds	Can aggravate PD symptoms	Avoid in PD
Neuroleptic	Injectable thorazine	Thorazine	Sedation, oculogyric crisis	—	Can aggravate PD symptoms	Avoid in PD; QT prolongation
Anti-emetics: anti-serotonergic type 3	Ondansetron, granisetron	Adjuvant	Confusion	Help nausea associated with PD meds	—	No aggravation of PD symptoms
Peripheral nerve blocks	Lidocaine, bupivacaine	Rescue	Procedure-related	Can help other PD-related pains including musculoskeletal	—	—

Pharmacotherapy for migraine by category, indication (prophylactic, abortive, rescue), with emphasis on side effects relevant to PD, and positive and negative synergies for PD and other caveats re: PD.

Table 3.
Medications for migraine and potential impact on PD.

6. Discussion

As we universally understand diseases better, we humbly reminded of their complexities and ramifications. Initially and for a long time considered a condition of primarily motor dysfunction, which it does remain, PD is now considered a multifaceted condition and pain and headaches are integral to the syndrome. Much remains to be studied to understand the complex epidemiology linking PD to the painful conditions. In PD as well as migraine, the natural evolution over the decades calls for a cautious interpretation of data and further refined studies, to understand the potential influencing role of one onto the other. Migraine manifests most of its symptoms in the early and middle part of life but singular presentations occur later, including silent auras and white matter hyperintensities that could have more impact on PD, a condition affecting mostly middle and later life. Chronic migraine has profound influence on the brain ability to process pain, likely beyond head pain, and even structural changes in the pain matrix are observed [86]. This could in turn be relevant to the other pain syndromes associated with PD.

From a clinical practice standpoint, the multitude of available treatments for PD, pain and headaches makes co-management complex and one can anticipate future discoveries on interactions, contraindications and synergies, leading to additional guidelines.

7. Conclusions

Scientific literature calls for increased awareness of the relation between PD, headache and pain syndromes. Comorbidity is subtle, clinical presentations varied and co-management delicate. More epidemiologic studies with wider population and sharp diagnostic accuracy, more understanding of the pathophysiology of each conditions, are warranted. Genetic investigations including areas relevant dopamine regulation might shed additional light on comorbidity. Increasing awareness includes better education and clinical guidelines.

It is suggested to integrate the assessment of pain and headaches in every patient suffering from PD.

From the standpoint of what physicians stand for, we can use these data to improve the quality of the care we deliver to patients with these comorbidities but also apply similar reasoning and principles to all comorbidities. It is about just doing best state-of-the art healthcare. At the core is the principle of holistic medicine to its true acceptance.

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