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Review Article

Role of Safinamide in controlling Pain in Parkinson's Disease

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Abstract

Pain is considered as one of the most important non-motor symptom of Parkinson's disease (PD) which is frequently overlooked in medical practice. Many patients find it more distressing as compared to the motor symptoms. It is a debilitating symptom with a high prevalence in PD population. It is often underestimated and not treated adequately by clinicians. Quality of life and activities of daily living is severely impaired. The pathomechanism of pain in PD is complex and several neurotransmission system is involved which includes glutamergic, serotonergic, noradrenergic, GABAergic, dopaminergic. The fine balance between glutamate and dopamine levels are not maintained in blood and brain in PD patients which somehow explains the neurobiology. Several pharmaceutical agents are present for treatment of pain however the greatest reductions were found with safinamide. Safinamide is now considered as an important adjunct to standard parkinsonian medication for alleviating pain in PD.

Keywords: Safinamide; Pain; Parkinsons Disease; Glutamate; Dopamine

Introduction

Parkinson's Disease (PD) is typically associated with characteristic motor symptoms (resting tremor, rigidity, bradykinesia and postural instability), caused by the degeneration of the dopaminergic nigrostriatal cells [1]. Clinical symptoms are due to dopamine (DA) depletion resulting from the significant progressive loss of dopaminergic neurons that project into striatum from the pars compacta of the substantia nigra [2,3]. It has a prevalence of 0.3% in the entire population (or 1% for people above the age of 65 years), and continues to increase at a very rapid rate with associated economic, carer, and social burden [4-6]. It is also associated with many non-motor symptoms (NMS) like mood disorders (depression, anxiety, irritability, apathy), cognitive decline, hallucination and delusions, orthostatic hypotension, sleep disorders, constipation and early satiety, fatigue, vision problems, excessive sweating, seborrheic dermatitis, urinary urgency, frequency and incontinence, anosmia, sexual problems, weight loss or weight gain, impulse control disorders and pain, which can have a strong impact on quality of life across various patient populations particularly in patients over 40 years of age [7,8]. There is also something called mixed motor and non motor symptoms which comprises of soft voice, drooling or excessive saliva due to slow swallowing, speech and swallowing problems [8].

The pathophysiology of NMS is still not clearly understood till date, and a dysfunction of both dopaminergic and non-dopaminergic systems contributes to their development. Drugs focusing only on the dopaminergic system are unable to ameliorate non-motor symptoms, while agents that interact with several neurotransmitter system might be very useful for the treatment of PD [9]. Therefore, pharmacological approaches to compensate DA deficits in the nigrostriatal dopaminergic pathways have been used for symptomatic improvement in PD patients [10]. Pain usually chronic type is an extremely common non-motor symptom that is prevalent among 68 - 95% of PD patients [11-14]. It is associated with higher scores of both depression and anxiety in these patients [15]. Despite the high rates of pain prevalence, between 25 and 50% of PD patients are receiving no treatment for their pain [11-13].

Nociceptive inputs travel to the striatum from the various pain-related cortical areas including SII, prefrontal areas, cingulate cortex, insula, and thalamic intralaminar nuclei [16]. Striatal neurons are highly sensitive and strongly respond to increase in intensity of noxious stimulus to localization of pain as compared to spatial recognition to increase in noxious input and strongly responding to this stimulus [17]. Several pain related areas in brain are also connected to basal ganglia. Amygdala, prefrontal and cingulate cortex are connected to substantia nigra efferent, responsible for motivational-affective pain dimension [18]. Pain modulation in human involves striatal dopamine D2 receptors as shown by several neuroimaging and metabolic studies [19]. Clear evidence suggest that abnormal basal ganglia function and

its connections modulates pain in PD. There is a strict regulation how patients expect, experience and interpret nociceptive signals and pain. Increase or decrease in nociceptive signal propagation, influencing cognitive and affective processes will determine the severity of pain.

Neuropathic and nociceptive pain are the two most common types of pain in PD patients. 40-90% of reported pain in movement disorder clinic or general practice are nociceptive pains [20]. Nociceptive pain is comprised mainly of visceral and musculoskeletal. Abnormal posture mainly kyphoscoliosis or camptocormia, akinesia, rigidity causes motor fluctuations, thus leading to painful early morning dystonia in about 40% of patients with PD, The main reason is because of low dopaminergic stimulation and severity of rigidity and akinesia. Foot inversion and plantar flexion are the two most common types of early morning focal dystonia. On the other hand, visceral pain frequently accompanies constipation. Autonomic failure of the enteric system causes abnormal bowel functioning in patients with PD. Painful anismus has been reported in literature due to dystonic contractions of anal sphincter [20-22]. Pain during the "OFF" periods is maximum because of low dopaminergic activity in the striatum. Furthermore, gamma-aminobutyric acid (GABA) and glutamate, may also play a relevant role in modulation of pain processing in other regions of the brain [20].

Neuropathic pain in PD comprises of central and radicular pain. Radicular pain has a higher prevalence in patients with PD than in the general population(14-35% vs. 10%) [20,23]. Structural damage to lumbar disc due to dystonia itself or kyphosis or sometimes festination are the main reasons. Central Parkinson's pain is a relatively rare condition (4-10% of patients) [13,20]. It is mainly a burning, tingling or cramping sensation like discomfort predominantly felt on the side of motor symptoms. Central parkinson's pain is different from the classic central pain. The main reason is unaffected sensory afferent pathway [24]. Majority of researchers and investigators believe basal ganglia dysfunction directly alters the sensory processing of nociceptive input thereby causing pain [13,20], contrary to the data findings where diagnosis of neuropathic pain requires a sensory deficit.

PD-related pain is significantly more frequent in women than in men [13,25]. Many epidemiological studies till date has showed that various acute and chronic pains, such as abdominal, headache, musculoskeletal, orofacial pain are more frequent in women than in men which is thought to be important in answering why women PD patient experience more pain than men. Cognition and social factors can somewhat explain the sex related differences but pain tolerance and lower pain threshold might arise partly from the biological differences and genetic make up [26]. Clear demarcation between nociceptive and neuropathic pain is important because pathophysiologically neuropathic pain is associated with abnormal sensory thresholds and nociceptive pain is unrelated to changes in sensory thresholds [27]. Trail and colleagues, examined the relationships among activity and daily energy expenditure, NMS and body mass index (BMI), which surprisingly demonstrated that pain affects patients' daily activities more than their memory problems and depression [28]. No drugs are specifically indicated for PD pain and till date there is no pain modifying therapy, and about 50% of the patients do not receive any treatment because of the inefficacy of common analgesics like paracetamol, non steroidal anti-inflammatory drugs(NSAID) [13].

Monoamine oxidase (MAO) plays a very critical physiological role in metabolizing a number of biogenic amines in the brain and peripheral tissues [29]. Selectivity for MAO-B inhibition is one of the most important factor in minimizing side effects because MAO-A inhibition is responsible for undesirable hypertension risk from cheese reaction and central serotonin syndrome [30]. MAO-B inhibition can help maintain central dopamine (DA) levels by preventing DA metabolism in the PD patient because DA is catalyzed predominantly by MAO-B [31,32]. MAO-B is also involved in production of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) during oxidative deamination of monoamine neurotransmitters such as DA, epinephrine, norepinephrine, and serotonin [33,34]. The elevation of MAO-B levels in the brains of PD patients and in the aged population [35,36] is considered to be associated with chronic oxidative stress from overproduction of ROS, leading to neuronal dysfunction, release of neurotransmitters and degeneration [37]. Therefore, MAO-B inhibition is expected to improve behavioral symptoms and stop progression of disease in PD through increment of DA levels and prevention of progressive neuronal loss from oxidative insult in the brain [38]. Selegiline and rasagiline are available, FDA-approved, selective and irreversible MAO-B inhibitors. They show symptomatic improvement in PD patients by adjunctive treatment with a dopamine precursor, levodopa [39,40]. Efforts has been made by researchers in recent years for elucidating neuroprotective effects for selegiline and rasagiline in very large clinical studies, including cell and animal studies. However, all studies have failed to show disease modifying effects in the clinic even though some neuroprotective potential was observed in preclinical experiments [41,42].

Safinamide, (S)-(+)-2-[4-(3-fluorobenzyloxybenzylamino) propanamide] methane sulfonate (1:1 salt), is an orally available derivative of the chemical class of α -aminoamides, with multiple mechanisms of action and experimental evidence of symptomatic and neuroprotective potential. Several animal studies mostly ex vivo done in recent times has yielded very good results in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated mice and

6-hydroxydopamine-induced PD rat models in which safinamide treatment reduced the MAO-B activity to significant levels, which reversed the behavioral impairments, dopamine levels in the striatum, and neuronal loss in the substantia nigra and behavioral improvement by levodopa sparing activity. Moreover, the researchers also revealed additional benefits of safinamide for nonmotor symptoms of PD such as pain, anxiety, depression and even epilepsy in rodent models [43,44]. Safinamide strongly and selectively inhibits MAO-B activities in a dose-dependent manner with reversibility which increases dopamine levels in the striatum [45-48]. It is relatively a new compound with a dual mechanism of action (dopaminergic and nondopaminergic) which uniquely combines modulation of the dopaminergic and glutamatergic pathways. It is recently approved by the European Medicines Agency (EMA) for the treatment of mid to late-stage fluctuating PD patients as add-on therapy to levodopa (alone or in combination with other antiparkinson drugs). It has been shown to inhibit voltage gated state- and use-dependent sodium channels which modulates abnormal glutamate release [49,50] and thereby causing improvement in neuropathic pain [51,52]. Safinamide also inhibits DA reuptake, modulates calcium channels which serves to maintain cognition and provides neuroprotection [53,54]. Recently Qureshi., et al. also reported the most efficacious treatment is safinamide, followed by cannabinoids and opioids in treatment of chronic pain in PD patients which may be musculoskeletal and neuropathic in origin [55].

Discussion

The correlation between pain and PD was first described in literature by James Parkinson as ‘‘rheumatic pain extending from the arms to the fingers”[56]. Chronic pain is one the most important debilitating nonmotor symptoms of PD and is present in majority of patients. Consensus say it occurs two to three times more frequently in PD patients than in the age matched healthy population [57]. It is classically classified into nociceptive pain (musculoskeletal, dystonic and visceral) and neuropathic pain (radicular-peripheral and central).Surprisingly, musculoskeletal and central neuropathic pains are the most prevalent ones [58]. Chronic pain is associated with worsening of quality of life greater than the motor symptoms and thereby influence patients daily activities more than memory problems and depression, with a significant economic burden [59]. Chronic analgesic prescription is significantly higher in PD patients (33%) than in the general population (20%) and diabetic patients (26%) with an abuse of nonsteroidal anti-inflammatory drugs [60].

The basal ganglia circuit are involved not only in movements, but also important is processing of nociceptive inputs through two main dopaminergic pathways: the striatonigral pathway, which is directly involved in the deterioration of motor system either as hyperkinetic, hypokinetic or akinetic symptoms, and the mesolimbic pathway, which is related to the reward system and central pain modulation. Therefore, there is a characteristic overlap between the dopaminergic system and specific brain regions implicated in processing of pain. Any changes in dopaminergic neurotransmission in these areas could lead to both motor and sensory abnormalities [61]. Moreover, a small fiber pathology occurs in the early stage of PD which causes damage to the peripheral nerves predominantly the small myelinated (Aδ) fibers or unmyelinated C fibers and may contribute to some non-motor symptoms including pain [62]. Pain in PD is often associated with motor fluctuations and wearing-off, and its intensity may also fluctuate during the day [63].

It’s a well established fact that modulation of central pain is dependent on dopamine and its pathways, however glutamate as an excitatory neurotransmitter, play an important role in transmission of pain signals, as suggested by the poor response of non-dystonic pain to levodopa [64]. Recent studies have shown increased glutaminergic activity in neuropathic pain. Any imbalance between dopaminergic and non-dopaminergic systems might contribute to chronic pain in PD [65]. The add-on of safinamide 100 mg/day to a stable dose of levodopa (alone or in combination with other dopaminergic treatments) was associated with a reduction of the number of concomitant pain treatments of about 26% and a significant improvement in the Parkinson's Disease Questionnaire -39(PDQ-39) ‘‘Bodily discomfort’’ domain and in the two items related to musculoskeletal and neuropathic pain [50]. The results showed by Cattaneo., et al. may be explained by dual mechanism of action of safinamide on dopaminergic and nondopaminergic pathway. Safinamide, in fact, is not just another MAO-B inhibitor, but also modulates the glutamatergic hyperactivity through the state and use dependent inhibition of sodium channels [50,66].

In fact, a significant correlation exists between motor complications (fluctuations and dyskinesia) and chronic pain, and they may share the same pathophysiologic mechanisms. The nondopaminergic neurotransmitter systems (including glutamate) may contribute to both motor complications and chronic pain [63]. It is a well known fact that sodium channel blockers have great efficacy against neuropathic pain [67,68].

Conclusion

Pain is highly prevalent in PD and, while often overlooked, represents a substantial cause of morbidity and disability, negatively impacting sleep, mood, daily activities. The under recognition of pain in PD by clinicians has amounted to inadequate treatment in clinical practice. Categorizing painful symptoms based on the clinical descriptions of musculoskeletal, dystonic, radicular-peripheral neuropathic and central pain provides a useful framework for diagnostic evaluation and management. Importantly, painful symptoms should be evaluated in relation to dopaminergic therapy. The loss of dopaminergic neurons causes glutamatergic hyperactivity, the selective inhibition of which is considered as an effective strategy for the treatment of

pain in PD in addition to other multidisciplinary approaches and pharmacotherapy. Safinamide is one novel reversible MAO-B inhibitor which has shown maximum benefit in controlling chronic pain as compared to other agents. However, further investigation in the form of large-scale randomized controlled trials is needed to fully evaluate the efficacy of safinamide on PD chronic pain.

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Search Strategy

We identified relevant full articles in English by searching PubMed with no language restrictions for articles published till November 2019 and reference lists from relevant articles. We used the search terms: "pain", "safinamide", "neurology", "glutamate", "Parkinson's disease", "Akinetic rigid syndrome", dopamine"," basal ganglia" for this article. We included only references published related to the topic plus few hand searched articles from other databases as accepted manuscripts. The final reference list was made on the basis of relevance to the theme of this review.

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