**Safinamide: An Additional Approach for Patients with Parkinson’s Disease**

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**ABSTRACT**

Safinamide is a neuroprotective agent that acts as a selective monoamine oxidase B (MAO-B) inhibitor and also has weak sodium and calcium channel-blocking properties. It is used as an adjunctive therapy for motor fluctuations in Parkinson's disease (PD) patients who are already taking levodopa. Safinamide has been studied for its potential neuroprotective effects and its impact on various non-motor symptoms (NMS) associated with PD. Studies have shown that safinamide can improve depressive symptoms in PD patients, reduce daytime sleepiness, and enhance overall sleep quality. It has also been found to have positive effects on cognitive function in patients with mild cognitive impairment due to PD. Additionally, safinamide has been investigated for its role in managing pain in PD patients experiencing motor fluctuations, leading to reduced pain intensity and improved quality of life. Furthermore, safinamide has shown promise in alleviating urinary symptoms in PD patients, such as urgency, frequency, and incontinence, suggesting it could be an effective treatment option for these NMS. Overall, safinamide appears to be a promising treatment option for various non-motor symptoms of PD, and its neuroprotective properties make it valuable in managing the progressive nature of the disease. However, further research is necessary to fully understand its mechanisms of action and confirm its efficacy in larger and longer-term clinical trials.

**Keywords:** Safinamide, Non-Motor symptoms, Parkinson’s disease, Neuroprotective

**I. INTRODUCTION**

Parkinson's is one of the most common motor disorders mainly affecting patients with age >65 years. The cardinal features of Parkinson’s are rigidity (stiffness), tremors, and bradykinesia with secondary manifestations like diminished facial expressivity, disturbance in balance, gait and posture, excessive salivation, and with time dementia may also accompany paradigmatic movement disorder [1]. Parkinson's disease (PD) is associated with a broad spectrum of non-motor symptoms. PD is traditionally defined as a progressive disorder characterized by the triad of rigidity, bradykinesia and tremor accompanied by several nonmotor symptoms (NMS) that show a nonlinear progression during the course of the disease These include disorders of mood and affect with apathy, anhedonia and depression, cognitive dysfunction and hallucinosis, as well as complex behavioural disorders. Sensory dysfunction with hyposmia or pain is almost universal, as are disturbances of sleep-wake cycle regulation. For treatment of these symptoms, classical treatment of levodopa and dopamine agonist was not sufficient, so the development of MAO-B inhibitor safinamide came forward [2].

1. **Epidemiology of Parkinson's Disease:** The rates of disability and mortality related to Parkinson's disease (PD) are rising at an alarming pace, surpassing the increase seen in any other neurological disorder worldwide. Over the past 25 years, the prevalence of PD has doubled. In 2019, there were more than 8.5 million individuals diagnosed with PD globally. During the same year, PD accounted for 5.8 million disability-adjusted life years, representing an 81% increase since 2000. Additionally, the disease caused 329,000 deaths, marking a surge of over 100% since 2000 [3].
2. **Pathophysiology of Parkinson's Disease:**

* The development of Parkinson's disease (PD) involves the abnormal aggregation of α-synuclein, a protein that plays a role in neurotransmitter release in the brain. This aggregation leads to the formation of Lewy bodies (LBs), which are characteristic of PD and are associated with the destruction of neurons in regions of the brain and peripheral nervous system that control autonomic function. The accumulation of α-synuclein in PD is a complex process that involves the formation of different species of the protein, such as monomers, oligomers, protofibrils, and fibrils, with varying conformations and properties. The presence of these species is associated with different stages of disease progression, with soluble oligomers of α-synuclein being more toxic than monomers and potentially contributing to the early stages of disease development. In addition to the central nervous system, the pathology of PD also affects the peripheral autonomic nervous system, including structures such as the vagus nerve, sympathetic nerve fibres, and enteric neural plexus. This system also shows signs of α-synuclein pathology, which can even precede central neuropathology (Figure 1). These findings suggest that PD is a multi-system disorder that involves dysfunction in both the central and peripheral nervous systems [4,5].

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| α-synuclein aggregation |  | Dysfunction of mitochondria |  | Lysosomes or vesicle transport |  | Dysfunctional protein clearance systems |  | Neuroinflammation |

|  |
| --- |
| Accelerated neuronal death of primarily dopaminergic neurons (Neurodegeneration) |

Parkinson’s Disease

**Figure 1: Pathophysiology Progression in Parkinson’s Disease [4,5]**

* Mitochondrial dysfunction plays an important role in Parkinson's disease (PD). Studies have shown that the mitochondrial complex-I, which is a vital component of the electron transport chain, is deficient in the substantia nigra pars compacta (SNpc) of PD brains. Complex-I deficiency has also been found in skeletal muscle and platelets of PD patients, compared to healthy subjects. Toxins such as MPTP, rotenone, and paraquat can impair complex-I activity and cause a Parkinsonian phenotype and dopamine cell loss in animals and potentially humans. Additionally, many genes associated with familial PD play a role in mitochondrial homeostasis, including PINK1 and parkin. Furthermore, α-synuclein can interfere with mitochondrial function by accumulating inside the organelles, leading to damage to complex-I activity and increased oxidative stress [6]. The clearance of monomeric α-synuclein involves both the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway (ALP). Dysfunctions in these pathways can contribute to the accumulation of defective proteins, including misfolded α-synuclein, and are implicated in the pathogenesis of PD [7].
* Studies of PD brains have shown increased levels of the autophagosome marker LC3-II, suggesting an accumulation of autophagic vacuoles in nigral neurons. On the other hand, essential proteins of lysosomal membranes, including LAMP1 and LAMP2A, and molecular chaperones from the heat-shock protein family, such as hsc70 and hsp35, were found to be decreased. Mutations in PARK genes, including parkin (PARK2) and PINK1 (PARK6), which are involved in the autophagic turnover of mitochondria, impair their function. Furthermore, the emergence of GBA1 mutations as a strong genetic risk factor for PD suggests that dysfunction in the lysosome-autophagy system is important in the development of PD [8].
* In PD patients, studies have shown increased inflammation in the SNpc and striatum, including activation of microglia, T-lymphocyte infiltration, and elevated levels of pro-inflammatory cytokines. This inflammatory response was initially thought to be secondary, but evidence now suggests that it can contribute to disease pathogenesis. In rodent models of PD, inhibition of microglial activation with minocycline resulted in reduced DA cell death, indicating that microglia-induced inflammation may contribute to degeneration. Alpha-synuclein can also directly trigger microglial activation and initiate inflammatory processes, suggesting that the immune system's engagement can exacerbate neuronal dysfunction [9].

1. **Treatment of Parkinson's Disease:** There is currently no cure for PD, various medications can help manage symptoms and potentially slow disease progression. Further, we will discuss the different classes of drugs used to treat PD and their doses:

* Levodopa: Levodopa is a dopamine precursor that is converted to dopamine in the brain. It is considered the most effective treatment for PD, and its use is supported by numerous clinical trials. The standard dose of levodopa is 100/25 mg taken three times daily, but the dose can be adjusted based on individual response and tolerance [10].
* Dopamine Agonists: Dopamine agonists are drugs that mimic the effects of dopamine by activating dopamine receptors in the brain. They are often used as an alternative to levodopa in the early stages of PD to delay the onset of levodopa-related motor complications. The commonly used dopamine agonists include Pramipexole, Ropinirole, and Rotigotine. The recommended starting dose of pramipexole is 0.125 mg three times daily, whereas for ropinirole it is 0.25 mg three times daily. Rotigotine is available in a transdermal patch, with the recommended starting dose of 2 mg per 24 hours [11].
* Monoamine Oxidase Inhibitors (MAOIs): MAOIs inhibit the activity of monoamine oxidase, an enzyme that breaks down dopamine and other neurotransmitters. Selegiline and Rasagiline are two MAOIs used to treat PD. Selegiline is available in two forms, oral and transdermal, with the recommended dose of 5 mg twice daily for the oral form and 6 mg per 24 hours for the transdermal form. Rasagiline is available in a 0.5 mg once-daily tablet. A newer MAOIs named as safinamide has been introduced as add on therapy which has additional effects of correcting non motor symptoms of Parkinson as well as motor symptoms [12].
* Catechol-O-Methyl Transferase (COMT) Inhibitors: COMT inhibitors are drugs that block the activity of the COMT enzyme, which breaks down levodopa. This results in increased levels of levodopa in the brain, thereby prolonging its duration of action. Entacapone and tolcapone are two COMT inhibitors used to treat PD. The recommended dose of entacapone is 200 mg with each levodopa dose, up to a maximum of 8 doses per day. Tolcapone is dosed at 100-200 mg three times daily but requires monitoring for liver function due to the risk of liver toxicity [13].
* Anticholinergics: Anticholinergics block the action of acetylcholine, a neurotransmitter that is overactive in the brains of people with PD. These drugs are used to treat the tremors and rigidity associated with PD. Trihexyphenidyl and benztropine are two commonly used anticholinergics. The starting dose of trihexyphenidyl is 1 mg twice daily, whereas benztropine is usually started at 0.5 mg once daily [14].

Overall, PD is a complex disease that requires individualized treatment plans. The drugs mentioned above are effective in managing the symptoms of PD and improving patients' quality of life. It is essential to note that the doses mentioned above are not fixed and may vary based on individual responses and tolerances. Hence, close monitoring and follow-up with a neurologist are essential for optimal treatment outcomes.

**II. SAFINAMIDE**

The chemical name of safinamide is (+)-(S)-2-[[p-(mfluorobenzyl)oxy]benzyl]amino] propionamide monomethanesulfonate and it is a chiral compound with a single stereogenic center. Safinamide is a small, water-soluble molecule, which is chemically and metabolically stable [15]. Safinamide is a selective monoamine oxidase B (MAO-B) inhibitor that also has weak sodium channel-blocking and calcium channel-blocking properties. It is approved by the FDA as an adjunctive therapy for motor fluctuations in patients with PD who are already taking levodopa. Several clinical trials have investigated the use of safinamide for the treatment of NMS in PD patients [13]. The SAFINONMOTOR study was conducted to investigate the effects of Safinamide on sleep and daytime sleepiness in patients with Parkinson's disease. The conclusion of the study was that Safinamide could be a promising treatment for individuals with Parkinson's disease who struggle with sleep quality and daytime sleepiness [16].

Safinamide is claimed to act through a multimodal mechanism of action by preventing the breakdown of both endogenous and exogenous DA in the brain; binding, at higher doses, to monoamine transporters, such as dopamine transporter, serotonin reuptake transporter, norepinephrine transporter (NET). Another study is a randomized, double-blind, placebo-controlled study evaluated the efficacy of safinamide in reducing depressive symptoms in PD patients. The study enrolled 123 patients with PD and comorbid depression who were already taking stable doses of dopamine agonists or levodopa. Participants were randomized to receive either safinamide or placebo in addition to their current therapy for 24 weeks. The study found that safinamide significantly reduced depressive symptoms compared to placebo, with a greater proportion of patients achieving a clinically significant improvement in depression scores. Following this a study was conducted for inspection of cognitive effects of safinamide which was one randomized, double-blind, placebo-controlled trial investigated the efficacy of safinamide in improving cognitive function in patients with mild cognitive impairment (MCI) due to PD. In addition to its effects on NMS, safinamide has also been shown to improve motor symptoms in PD patients. One randomized, double-blind, placebo-controlled trial investigated the efficacy of safinamide in reducing "off" time in PD patients with motor fluctuations. The study found that safinamide significantly reduced "off" time and increased "on" time without troublesome dyskinesia compared to placebo [6,17].

1. **Preclinical Data of Safinamide:**

Rat brain and liver tissues as well as human brain, liver, and platelet tissues were used in in vitro preclinical pharmacokinetic research. Safinamide has been demonstrated in in vitro studies to inhibit the dopamine transporter sites that showed no affinities for the various isoforms of D1, D2, D3, D4, and D5 DA receptor subtypes, to inhibit the uptake of [3H] DA and [3H]5-HT at relatively low concentrations, and to be a reversible MAO-B inhibitor in the rat and human brain. Ex vivo tests on cynomolgus monkeys showed that safinamide elevates DA levels in particular regions of the putamen without changing serotonin levels. Safinamide levels in the brain are consistently greater than comparable plasma levels, with a ratio of 16, 16, and 9 in mice, rats and monkeys, respectively. In vitro studies have also shown that safinamide does not affect either central or peripheral effect of aromatic L-amino-acid decarboxylase (AADC) nor COMT activity [18].

1. **Pharmacokinetics of Safinamide:**

Safinamide absorbs well and quickly via the gastrointestinal tract. Within two to four hours, the maximum concentration was seen. 95% of the bioavailability was absolute. A week was needed to obtain steady-state concentrations. With a volume distribution of around 165 L, which is equivalent to 2.5 times the body volume, plasma protein binding was within an 88% to 90% range. The safinamide was widely distributed extravascularly. The terminal half-life was 20 to 30 hours, or around 22 hours. 4.6 L/hour was the total clearance [19].

1. **Pharmacodynamics of Safinamide:**

In general, major adverse events could happen when pethidine or dextromethorphan are used with MAO inhibitors. Additionally, it is advised to use caution while combining MAO inhibitors with sympathomimetic medications. Safinamide use should not be combined with other MAO inhibitors as this may increase the risk of hypertensive crisis brought on by the tyramine-induced, so-called "cheese" effect. Safinamide is a selective and reversible MAO-B inhibitor; therefore, it can be cautiously combined with other medications such as tricyclic and tetracyclic antidepressants, serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors [19].

1. **Supporting Clinical Data of Safinamide:**

* **Day Time Sleepiness:** The SAFINONMOTOR study was conducted to investigate the effects of Safinamide on sleep and daytime sleepiness in patients with Parkinson's disease. A total of 107 participants were selected randomly and divided into two groups, with one group receiving Safinamide and the other receiving a placebo. According to the results of the study, patients who received Safinamide experienced a significant improvement in sleep quality compared to those who received the placebo. Additionally, the group that took Safinamide reported a decrease in daytime sleepiness, which was measured using the Epworth Sleepiness Scale. The study also found that Safinamide was well-tolerated and no serious adverse effects were reported. The conclusion of the study was that Safinamide could be a promising treatment option for individuals with Parkinson's disease who struggle with sleep quality and daytime sleepiness [16].
* **Pain:** This study aimed to investigate the potential effects of Safinamide on pain in Parkinson's disease patients who experience motor fluctuations. The study involved a group of 20 participants who were given Safinamide for six months. The results of the study indicated that Safinamide may have a positive impact on pain in Parkinson's disease patients. The participants reported reduced pain intensity and improved quality of life related to pain after taking Safinamide. Furthermore, the participants experienced improvements in motor symptoms, such as a reduction in off time. The study concluded that Safinamide has the potential to provide relief for pain in Parkinson's disease patients who experience motor fluctuations. Therefore, Safinamide could offer a new treatment option for pain management in Parkinson's disease patients, leading to improved quality of life. However, the study sample was small, and further research with larger sample sizes and control groups would be required to validate the findings of the study [17].
* **Urinary Symptoms:** The SURINPARK study aimed to explore the potential effects of Safinamide on urinary symptoms in patients with Parkinson's disease. A total of 24 participants were involved in the study, and they were randomly assigned to either the Safinamide or placebo group for eight weeks. The results of the study demonstrated that the group taking Safinamide showed a significant improvement in urinary symptoms, such as urgency, frequency, and incontinence, compared to the placebo group. Furthermore, Safinamide was found to be well-tolerated, with no significant adverse effects reported. The study concluded that Safinamide may be an effective treatment option for urinary symptoms in Parkinson's disease patients. The findings of the study suggest that Safinamide could offer an alternative option for managing non-motor symptoms of Parkinson's disease. However, further research with larger sample sizes and longer follow-up periods is needed to confirm these results [20].
* **Depression:** The SADness-PD study is a retrospective multicentre study conducted to assess the effect of safinamide on depressive symptoms in patients with Parkinson's disease (PD). The study included 84 PD patients who received safinamide treatment for at least six months. The primary outcome measure was the change in the Hamilton Depression Rating Scale (HDRS) score from baseline to six months after initiating safinamide treatment. Secondary outcome measures included changes in the Unified Parkinson's Disease Rating Scale (UPDRS) motor and non-motor scores, and quality of life measures. The results of the study indicated a significant decrease in depressive symptoms in PD patients treated with safinamide, with the HDRS score decreasing from 9.8±4.1 at baseline to 5.6±3.3 at six months (p<0.001). Additionally, the UPDRS motor score showed a significant improvement, while the UPDRS non-motor score and quality of life measures did not show significant changes. The study implies that safinamide may have a positive impact on depressive symptoms in PD patients, in addition to its known benefits on motor symptoms. Further prospective studies are necessary to validate these findings and better understand the mechanisms underlying safinamide's effects on depressive symptoms in PD patients [21].

**III. DISCUSSION**

Safinamide was approved due to pivotal trial results that showed a reduction in "OFF" time in PD patients receiving levodopa/DDC treatment. Participants in the study underwent a prior optimal titration with dopamine-replacement therapy over a minimum of 4 weeks. They then received more safinamide. This study's strategy differs from those of trials using dopamine agonists, MAO-B inhibitors, or COMT inhibitors in cohorts of PD patients receiving continuous levodopa/DDI treatment who experienced "OFF" symptoms. Prior to receiving the research medicine, they were not optimised. From this vantage point, one must carefully examine talks to determine whether safinamide offers any clinically relevant benefits during "OFF" times or just a bare minimum of clinically significant benefits.

**IV. CONCLUSION**

Due to its dual mechanisms of action, safinamide is unusual. Along with its safety profile, it may help to improve some non-motor symptoms, as well as motor functions and fluctuations, which may have a positive impact on patients' quality of life (QoL). Safinamide is a safe and efficient first adjunct therapy in levodopa-treated patients and alleviated 4/5 cardinal symptoms of PD while offering advantages to mild and non-mild fluctuations and patients receiving other concurrent dopaminergic medications.

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