

SAFINAMIDE: AN ADDITIONAL APPROACH FOR PATIENTS WITH PARKINSON'S DISEASE

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 treatment for Parkinson's disease-related motor alterations in patients who are already taking levodopa. Safinamide has been studied for its potential neuroprotective effects and its impact on various non-motor symptoms (NMS) in related to Ph.D Research has indicated that safinamide can improve depressive symptoms in Parkinson's patients, reduce daytime sleepiness, and enhance overall sleep quality. Additionally, it has been discovered to have advantageous impacts on cognitive function in patient's with PD-related mild cognitive impairment. Additionally, safinamide has been investigated for its role in managing pain in PD patients with erratic motor function, 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 alternative for these NMS. Overall, safinamide appears to be a potential approach for treating several non-motor symptoms of PD, and its neuroprotective properties make it valuable in managing the illness's advancing nature. But further study is required to properly comprehend its mechanisms of action and validate its effectiveness in larger, longer-term clinical trials.

Keywords: Safinamide, Non-Motor symptoms, Parkinson's disease, Neuroprotective.

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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 typical movement disorder [1]. A wide range of non-motor symptoms are linked to Parkinson's disease (PD). 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. Hyposmia and pain-related sensory dysfunction are essentially ubiquitous, as are issues with the control of the sleep-wake cycle. 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: Parkinson's disease (PD)-related disability and mortality rates are increasing at an alarming rate, surpassing the increase seen in any other neurological disorder worldwide. PD has doubled in prevalence over the previous 25 years. During the same year, PD accounted for 5.8 million disability-adjusted life years, represented by 81% rise since 2000. In addition, the illness resulted in 329,000 fatalities, a rise of nearly 100% from 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 development of Lewy bodies (LBs), indicative of PD and are associated with loss of neurons in certain areas of the brain and peripheral nervous system (PNS) that control autonomic function.

The production of several protein species, including monomers, oligomers, protofibrils, and fibrils, with varied conformations and characteristics, is a complex process that contributes to the accumulation of α -synuclein in Parkinson's disease (PD). 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 CNS, 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 CNS and PNS [4, 5].

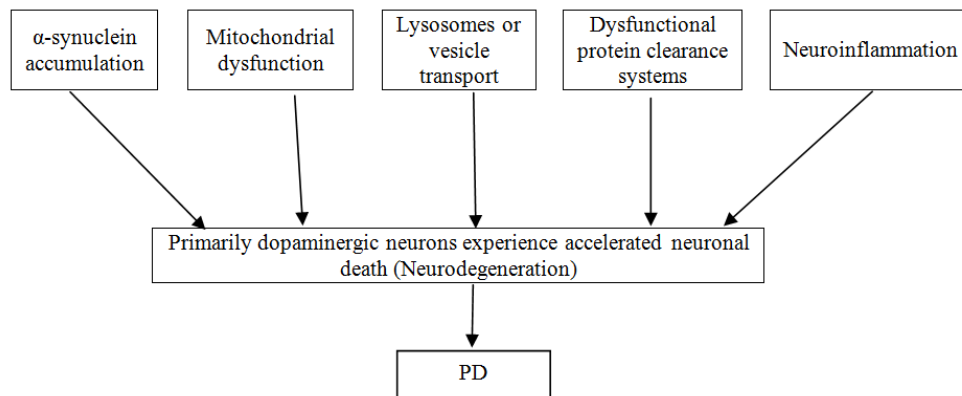


Figure 1: Pathophysiology Progression in Parkinson's Disease [4, 5]

- Parkinson's disease (PD) is significantly impacted by mitochondrial dysfunction. Studies have revealed that the substantia nigra pars compacta (SNpc) in PD brains lacks the mitochondrial complex-I, a crucial element of the electron transport chain. Comparing PD patients to healthy ones, skeletal muscle and platelets of PD patients showed deficiencies in complex-I. 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. Numerous genes linked to familial Parkinson's disease also affect mitochondrial homeostasis, including PINK1 and parkin. Furthermore, α -synuclein can interfere with mitochondrial function by accumulating within the organelles, resulting in damage to complex-I activity as well as elevated 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 pathophysiology of PD [7].
- Research on Parkinson's disease brains has revealed elevated levels of the autophagosome marker LC3-II, indicating that the nigral neurons have an accumulation of autophagic vacuoles. However, it was discovered that the levels of molecular chaperones from the family of heat-shock proteins, such as hsc70 and hsp35, as well as critical lysosomal membrane proteins LAMP1 and LAMP2A, were dropped. 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 significant genetic risk factor for PD suggests that the lysosome-autophagy system malfunction plays a significant role in the onset of Parkinson's disease [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. Despite original speculation that this inflammatory response was secondary, evidence now points to its potential role in disease causation. 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. Additionally; α -synuclein can directly activate

microglia and start inflammatory processes, suggesting that the immune system's engagement can exacerbate neuronal dysfunction [9].

3. 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 regarded as the most successful therapy 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 to postpone the onset of levodopa-related motor problems in the early stages of Parkinson's disease. The commonly used dopamine agonists include Pramipexole, Ropinirole, and Rotigotine. Pramipexole's beginning dosage is 0.125 mg three times per day, 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):** Dopamine and other neurotransmitters are broken down by the enzyme monoamine oxidase, which is inhibited by MAOIs. 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 MAOI 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. Levodopa concentrations are consequently raised in the brain, thereby prolonging its duration of action. The COMT enzyme is inhibited by entacapone and tolcapone 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:** Acetylcholine, a neurotransmitter that is too active in PD patients' brains, is blocked by anticholinergics. These drugs are used to treat the tremors and rigidity associated with PD. Trihexyphenidyl and benztropine are two commonly used anticholinergics. Benztropine is typically begun at 0.5 mg once daily, but the initial dose of trihexyphenidyl is 1 mg twice 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 monomethane sulfonate and it is achiral 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 PD. The conclusion of the study was that Safinamide could be a promising treatment for individuals with PD who struggle with sleep quality and daytime sleepiness [16].

By binding to monoamine transporters such as the dopamine transporter, serotonin reuptake transporter, and norepinephrine transporter (NET) at larger doses, safinamide is said to function through a multimodal mechanism of action by blocking the breakdown of both endogenous and exogenous DA in the brain. Another study is a randomized, double-blind, placebo-controlled study that 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. For 24 weeks, participants were randomly assigned to receive safinamide or a placebo in addition to their current treatment. The study found that safinamide significantly reduced depressive symptoms compared to placebo, with more people achieving a clinically meaningful drop in their depression scores. Following this, a study was conducted for inspection of cognitive effects of safinamide, which was one randomized, double-blind, placebo-controlled trial examining if safinamide was effective at enhancing cognitive performance in those with PD-related moderate cognitive impairment (MCI). In addition to its effects on NMS, safinamide also demonstrated to lessen PD patients' motor symptoms. 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 employed in *in vitro* preclinical pharmacokinetic research. Safinamide has been demonstrated in some *in vitro* studies to inhibit the dopamine transporter sites that has been showing no affinities for the various isoforms of D1, D2, D3, D4, and D5 dopamine receptor subtypes, at low doses, it inhibits the absorption of [3H] DA and [3H] 5-HT, and it is 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. In mice, rats, and monkeys, the proportions were 16, 16, and 9, respectively. Safinamide was additionally

demonstrated in vitro to have no effect on the peripheral or central effect of aromatic L-amino-acid decarboxylase (AADC) or COMT activity. [18].

2. 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].

3. 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].

4. Supporting Clinical Data of Safinamide

- **Day Time Sleepiness:** The SAFINONMOTOR trial was designed to look at the impact of Safinamide on insomnia and daytime drowsiness in Parkinson's disease patients. A total of 107 people were chosen at random and split into two groups, one of which received Safinamide and the other group received a placebo. According to the study's findings, patients who got Safinamide had significantly better sleep quality than those who received a placebo. Furthermore, the group who took Safinamide experienced less daytime sleepiness, as judged by the Epworth Sleepiness Scale. The study also discovered that the Safinamide medication was tolerated well, with no serious side effects identified. The study concluded that Safinamide could be an appealing treatment option for those with Parkinson's disease for those who struggle with sleep quality and daytime sleepiness [16].
- **Pain:** The purpose of this study was to look at the potential impact of Safinamide is on distress in people with Parkinson's disease who had motor fluctuations. The trial included 20 people who received Safinamide for a period of six months. The study's findings suggested that Safinamide might have an anti-pain effect in patients with Parkinson's disease. After taking Safinamide, the subjects reported lower pain intensity and better pain-related quality of life. Furthermore, the participants' motor symptoms improved, such as decreasing in off time. According to the findings of the study, Safinamide has the ability to provide pain alleviation in people with Parkinson's disease who have motor fluctuations. As a result, Safinamide may provide an innovative approach for alleviating pain in patients with Parkinson's disease, resulting in 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 trial sought to investigate the potential impact of Safinamide on urine symptoms in Parkinson's disease patients. The study included 24 volunteers who were assigned at random to participate in the Safinamide or a control group for a period of eight weeks. When juxtaposed to the placebo group, the group using Safinamide exhibited a significant reduction in urine symptoms such as urgency while frequency, and incontinence. Safinamide was also found to be tolerated well, with no notable side effects noted. The study found that Safinamide may be a useful therapy choice for Parkinson's disease patients with urine symptoms. The study's findings show that Safinamide may provide an alternate option for treating non-motor signs associated with Parkinson's disease. However, to corroborate these findings, more study with bigger samples and longer periods of follow-up is required. [20].
- **Depression:** The SADness-PD study is a multicenter, retrospective study that looked at the impact of safinamide on depressed symptoms in Parkinson's disease (PD) patients. The study comprised 84 Parkinson's disease patients who had been taking safinamide for a minimum of six months. The shift in the Hamilton Depression Rating Scale (HDRS) score from the baseline to six months after starting safinamide medication was the primary end measure. Modifications in the Unified Parkinson's Disease Rating Scale (UPDRS) motor and non-motor scores, as well as quality of life assessments, were included as secondary end measures. The study's findings revealed a substantial reduction in depressed symptoms in Parkinson's disease participants who received safinamide, with the HDRS score dropping from 9.84.1 at baseline to 5.63.3 after six months (p0.001). Furthermore, the UPDRS motor score revealed aThe UPDRS non-motor rating as well as quality of life indicators improved significantly, but not significantly. The study suggests that, in addition to its established benefits for motor symptoms, safinamide might have a good impact on depressed symptoms in Parkinson's disease patients. More prospective research is needed to corroborate these results and better comprehend the processes underlying safinamide's benefits on depressed symptoms in Parkinson's disease 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. Prior to participating in the trial, study participants got dopamine replacement treatment for at least 4 weeks at the recommended dosage. Next, and they 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 improving some non-motor symptoms, motor functions, and fluctuations, it also has a good safety

record, which may have a positive impact on patients' quality of life (QoL).Safinamide is a first-line adjunct therapy that is safe and effective for levodopa-treated patients. It has been shown to reduce all five of the cardinal symptoms of Parkinson's disease (PD) and has benefits for people with mild and severe fluctuations, as well as those on other concurrent dopaminergic drugs.

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