Review on Potential combination therapy in treatment of Parkinson disease and related Dementia Disorders: Emphasises on Safinamide

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Abstract : With a focus on safinamide, the authors address management difficulties in PD and related Dementia disorders and present an overview of the current pharmacological strategic actions. Levodopa, Dopamine agonists, MAO-B inhibitors, NMDA Receptor agonists, and other inhibitors of enzymes are among some of the main therapeutic strategies used today to control Parkinson disease. With the rise in number of diverse neurodegenerative diseases that lead to dementia syndromes and have their own unique neurochemical pathologies. Since what works for one person may not work for another or, in the worst-case scenario, may make things worse, this has significant therapy implications. Safinamide, an α-aminoamide with multiple dopaminergic and non-dopaminergic ways of action, such as inhibition of sodium (Na+) channel, Inhibition of monoamine oxidase-B (MAO-B) and regulation of stimulated glutamate release can be helpful in the control of Parkinson Disease and related dementia disorders. According to cross-sectional research, up to 40% of PD patients experience dementia, which has a cumulative prevalence of 78% over 8 years and involves executive function and attention deficiencies, whereas memory dysfunction is caused by defective storage and retrieval mechanisms. Unified Parkinson's Disease Rating Scale's Scores are improved by safinamide when used alone or in conjunction with dopamine agonists and potential combination therapy can be used for treatment of related dementia disorders. With the similarities in the arise of various dementia disorders and multiple mode of actions of Safinamide, it can be coined that the potential of Safinamide in conjugate with the other drugs can potentially give a new hope in PD and related dementia disorders.

Keywords: Safinamide, Dementia disorders, monoamine oxidase-B, Parkinson's disease (PD).

I.   INTRODUCTION:

Dopamine insufficiency in the nigrostriatal pathway is a hallmark of Parkinson's disease (PD), a progressive neurodegenerative illness. The four main motor symptoms of Parkinson's disease (PD) are bradykinesia, rigidity, tremor, and postural instability. Dopaminergic neurons are lost as the disease worsens, which affects motor function. Later-life dementia manifests as a clinically complex illness with alterations in cognitive, behavioural, psychological, motor, and autonomic functions. These symptoms, which collectively have an impact on daily function, are intricately linked and have molecular underpinnings with cerebrovascular and neurodegenerative diseases [1,2,6]. Memory loss and a single other cognitive area are considered to be symptoms of dementia. These deficiencies show a deterioration from a prior functional level and are severe enough to impair daily living activities. However, cognitive dysfunction alone is insufficient to account for functional disability or a reduced quality of life in dementia patients [2,3]. To better comprehend the effects of PD, Parkinson's disease with dementia, and dementia with Lewy bodies on cognition and behaviour

Talking with the patient about the diagnosis and the illness's characteristics is the first step in management [4,15]. The disorder's motor and non-motor symptoms are then treated using a mix of medication, physical, occupational, and speech therapy. [5,13].

Levodopa, dopamine agonists (DAs), and monoamine oxidase (MAO)-B inhibitors are first-line choices for the symptomatic treatment of motor symptoms. Levodopa is particularly efficient in treating the motor symptoms of Parkinson's disease (PD) [29], Moreover, the onset of motor issues, such as reaction oscillations between effective ('on') and bad ('off') symptom management and medication-induced dyskinesias, typically limits its long-term use. As a result, adding additional medications to levodopa for the treatment of mid- to late-stage Parkinson's disease (PD) frequently entails adding DAs, MAO-B inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and amantadine [20]. In the past 10 years, Safinamide, α-aminoamide with multiple dopaminergic and non-dopaminergic mechanisms of action, including inhibition of Na+ channel inhibitor of monoamine oxidase-B (MAO-B), control of accelerated glutamate release is authorised for the management of PD and related dementia disorders. The medication is licenced for use in the EU as an adjunct therapy to levodopa alone or in combination with other PD drugs for the treatment of mid- to late-stage fluctuating PD [6,23]. This review emphasises on Safinamide in the potential combination therapy for PD and related dementia disorders.

II.   CURRENT PHARMACOLOGICAL MANAGEMENT IMPLICATED IN PARKINSON'S DISEASE:

Levodopa was first used to treat PD, nonetheless since then, other medications have been discovered with longer half-lives (>2 hours) and less long-term adverse effects. This effort has been further encouraged over the past ten years by advancements in our knowledge of the pathogenic processes underlying PD. Although there is evidence that some medications may achieve both goals, the majority of PD treatment choices focus more on improving motor symptoms than on neuroprotection [2,34]. Dopamine precursors (levodopa), enzyme inhibitors of monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT), N-

methyl-D-aspartate antagonist, dopamine agonists (DAs), are currently the main medications used to treat the symptoms of Parkinson's disease [22].

The standard for treating Parkinson's disease (PD) has been levodopa since it was first made available in the 1960s.It functions by replenishing striatal dopamine and is an amino acid precursor to dopamine. To prevent peripheral breakdown and improve central distribution, levodopa is coupled with an extracerebral dopa decarboxylase inhibitor (DDI), such as benserazide or carbidopa [22,37]. It is frequently the first choice for elderly patients and those with concomitant conditions because it has less neuropsychiatric adverse effects than other antiparkinsonian medications [2,34].

Failure to respond to levodopa can have a variety of causes, such as the use of an incorrect response indicator, such as tremor, inadequate doses, an inadequate length of treatment, and drug interactions (such as concurrent treatment with metoclopramide or risperidone).Before determining that a patient does not respond to levodopa, a trial of the drug should be administered for three months with a steady titration upward to at least 1000 mg per day or until the manifestation of dose-limiting adverse effects [21,34]. Less than 10% of individuals with pathologically proven Parkinson's disease fail to respond to an adequate trial of levodopa; this raises the potential of another ailment and shows that no pharmacological or surgical therapy is likely to be helpful. Dopamine agonists are different first-line treatments for Parkinson's disease even though they are somewhat less effective than levodopa [21,46]. The effectiveness of different dopamine agonists is comparable.

In comparison to levodopa, these medications have the potential benefit of reducing the risk of dyskinesia and motor fluctuations by a factor of two or three over the first four to five years of treatment, especially in individuals on dopamine-agonist monotherapy [37,59]. It is unknown how long the risk of motor problems is reduced when levodopa is combined with dopamine agonist; nonetheless, within a few years of a diagnosis, levodopa is frequently required in addition to dopamine-agonist medication to control progressive symptoms [7].

Anticholinergic medications are often avoided in the treatment of Parkinson's disease due to their negative side effects. Although there is insufficient evidence to suggest their particular efficacy in treating tremor, they may be added if tremor is extremely troublesome and unresponsive to other medications. Anticholinergic medications should not be used to treat patients over the age of 70 or for those who have dementia [8]. Amantadine and MAO-B inhibitors have fewer side effects and require less titration to reach therapeutic levels, but because the effects are often moderate, these medications typically offer insufficient symptomatic relief when used alone.

To minimise side effects, all antiparkinsonian medications are started at modest doses and gradually increased. To prevent a significant deterioration of parkinsonism or perhaps the neuroleptic malignant syndrome, it is advised to gradually stop taking these medications after receiving them for a long time [2,8,34]. However, pharmacological alternatives may be restricted and drug therapy may need to be personalised due to motor and non-motor problems. When motor difficulties become more problematic, parenteral routes of drug delivery are used because they offer a more physiologic, non-pulsatile delivery of dopamine.

Table 1: Initial treatment of Parkinson's disease and related dementia disorders [2,8,59].

Class	Drugs	Initial dose	Usual dose	Side effect
First line derivatives				
Dopaminergic agents	carbidopa, levodopa	25 mg + 100 mg TDS	1 to 2 tablets TDS	Nausea, vomiting, dizziness
	carbidopa, levodopa, entacapone	12.5 mg +50 mg + 200 mg TDS	-	Motor fluctuations, diarrhoea, rest as above
Dopamine agonists				
Non-ergot	Pramipexole	0.125 mg TDS	0.5-1.5 mg TDS	Nausea, vomiting, hypotension
Ergot	Pergolide	0.05 mg TDS	1 mg TDS	Retroperitoneal, pulmonary, cardiac fibrosis
Second line derivatives				
Anticholinergic agents	Benzotopine	0.5 mg BD	1 mg BD	Impaired memory, confusion, constipation
Selective MAO-B inhibitors	Selegline	5 mg OD	5 mg BD	Insomnia, SSRIs interaction, hallucinations
Multiple MOA agent	Safinamide	50-100 mg OD	100-200 mg OD	Nausea, vomiting, hallucinations

NMDA antagonists	Amantadine	100 mg OD	100 mg BD	Nausea, vomiting, hallucinations, confusion, constipation

III. SAFINAMIDE:

The first-time safinamide mesylate was synthesized in 1989 at Farmitalia Carlo Erba's medicinal chemistry department (Milan, Italy). Safinamide was initially researched as a potential antiepileptic medication after it was discovered that milacemide, from which safinamide is produced, has anticonvulsant efficacy. Safinamide is an alpha-aminoamide having multiple mechanisms of action. But as of pour solubility of original molecule to improve the characteristics its is converted into salt form which is having the chemical formula $C_{17}H_{19}FN_2O_2 \cdot CH_4O_3S$ [2,3]. The central nervous system and the tissues of the periphery of the body are both affected by the *in vivo* inactivation of bio-genic and diet-derived amines, which is largely mediated by MAO. Serotonin and noradrenaline are mostly deaminated in the gut by the MAO isoenzyme A (MAO-A). In the striatum, MAO-B isoenzyme predominates [5,13]. The substrate for MAO-A and MAO-B is dopamine. Selective inhibitors of MAO-B action of safinamide reduce the catabolism of dopamine and so raise its levels in the basal ganglia, without influencing the metabolism of other amines that are catabolized by MAO-A. [22,23].

IV. MECHANISM OF ACTION:

Safinamide was initially tested as an antiepileptic medicine because it blocks sodium and calcium channels, but its selective and reversible MAO-B inhibitor activity has raised questions about its possible applications in Parkinson's disease (PD) [5,22]. In addition to its voltage-sensitive channel blocking and MAO-B inhibitory activities, safinamide has also been studied for its potential neuroprotective and neurorescuing effects. It can be administered in conjunction with LD or a DAA and can lessen some non-motor symptoms as well as the motor symptoms of PD [38,40].

Safinamide also inhibits dopamine absorption and glutamate release; this last effect is shared with amantadine, a drug that has some promise for treating Parkinson's disease (PD) dyskinesia. The sigma-1 receptor is primarily inhibited by safinamide as its mode of action. Safinamide's potency is lower and is in the micromolar range for sodium channel blockage at other sites. and the high micromolar range for glutamate release and calcium channel blockage [13,62]. Its ability to inhibit MAO-B is sub micromolar in strength.

Unique chaperone proteins called sigma-1 receptors are found in the endoplasmic reticulum of cells. Thou, the role of sigma-1 receptor inhibition in PD is unclear; this mode of action may not be relevant to safinamide's antiparkinsonian effect [2,5]. Free radicals are produced during dopamine processing, and it is thought that these free radicals help cause oxidative stress in nigral cells. Safinamide may lower the formation of free radicals by preventing the dopamine metabolism by inactivating MAO-B, however this is anticipated to be a class effect [50].

Safinamide is a good candidate for investigation as a neuroprotective drug in PD related dementia disorders against excitotoxicity and oxidative damage that result in neuronal cell death in Parkinson's disease (PD) due to its various pharmacodynamic activities [62,63].

Table 2: According to Mode of action Safinamide's position within the PD treatment spectrum [1,5,16,64].

Dopaminergic therapy	Non-dopaminergic therapy
Levodopa **Carbidopa**	**Anticholinergics** Benztropine Trihexyphenidyl
Dopamine agonists Ropinirole Pramipexole Apomorphine	**Anti-glutamatergic agents** Amantadine Memantine Safinamide
MAO-B inhibitors Safinamide Rasagiline Selegline	**Surgical approaches** Ablative surgery Gene therapy
Drug agents for dementia and neuroprotective action	
A2A receptor antagonists	Istradefylline
Glutamate antagonist	Memantine, Kynurenines, Amantadine
Drug with multiple mechanism	Safinamide, Levetiracetam, Zonisamide

V. PHARMACOKINETIC PROPERTIES:

Safinamide, when taken orally, has good pharmacokinetic characteristics that are proportionately and linearly related to the dose taken. In plasma peak concentrations were obtained 2.5 -4 hours after a single dose and 5.5-6 hours after a repeat dose, indicating good systemic absorption [3,10]. The absorption is thorough and consistent, and food has little to no impact on it. Safinamide did not appear to accumulate much in patients with normal excretory function because concentration at steady state was 1.5–1.7 times higher than the peak concentration following a single dose [9,10]. The extravascular tissue binding (94%) is allegedly higher than

the plasma protein binding (92%). High levels of safinamide are found in the CNS. About 1.6 and 7% of the medicine is eliminated in the faeces and urine, respectively, in unchanged form, indicating almost full absorption and very little biliary excretion. Safinamide undergoes a significant amount of biotransformation [19]. The principal step is mediated by amidases and produces safinamide acid. It is metabolized to O-debenzylated safinamide. The N-dealkylated amine, also a metabolite of safinamide is then oxidized to a carboxylic acid and glucuronidated. Metabolism is also mediated by cytochrome P450s [19,32].

Safinamide has a slow rate of systemic clearance and a 26-hour terminal half-life. The terminal half-life of radioactively labelled safinamide in this instance was 22 hours [10,46]. This makes once-daily administration possible. On day 5 to 6 of the once-daily dosage treatment plan, a steady-state concentration is reached. The safety and tolerability of safinamide have been established. The biochemical analyses of the blood and urine as well as the vital signs did not differ from the other group members in any way. Healthy subjects receiving safinamide intravenously experienced no different pressor response than those receiving a placebo [25,32].

VI. PHARMACODYNAMIC PROPERTIES:

Uncertainty surrounds the specific mechanism by which safinamide reduces PD symptoms. In addition to the reversible and selective inhibition of MAO-B, Sodium channel antagonism, and suppression of glutamic action on *in vitro*, safinamide also has a combination of dopaminergic and non-dopaminergic mechanisms of action, as was previously described [2,31,38]. The dopaminergic mode of action involves powerful, highly reversible, selective MAO-B inhibition, which raises the dopamine concentrations in the brain [5,40].

In animal models, safinamide has been shown to exhibit neuroprotective properties and to be able to prevent excitotoxin-induced hippocampal cell death. When given before 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to subjects, a toxin known to cause parkinsonism, safinamide has been shown to completely prevent dopamine depletion and cell death in the substantia nigra. Selegiline and rasagiline, two other MAO-B inhibitors [38,50], also have this preventative effect. The selectivity of safinamide for MAO-B has been shown to be 100 times higher as compared with other class drugs. The selectivity of MAO-B over MAO-A also greater than the other class specific drugs [19,62,63].

Increasing the safinamide's dose provided above the dose that can achieve the complete inhibition of Monoamine oxidase-B results in an additional clinical improvement, indicating that safinamide may have additional mechanisms of action in addition to this action [13,46,62]. Inhibiting glutamic release by inhibiting the activity of Sodium channels is how the non-dopaminergic mode of action works. The Sodium channel is state and concentration dependently inhibited. When compared to the resting potential, safinamide has more potent at membrane that have depolarized potentials, where the most of the channels are inactivated. This suggests that safinamide interacts preferentially with the inactivated sodium channel and are kept dormant and are not allowed to become active by safinamide [10,59].

VII. DRUG AND FOOD INTERACTIONS:

Safinamide does have any specific food interactions but high lipid containing food can prolong the bioavailability [16]. Safinamide has no inhibitory action on any of the cytochrome P450 isoenzymes involved in the metabolism of pharmaceuticals, including $CYP_1A_{1/2}$, CYP_2C_9, CYP_2C_{19}, CYP_2D_6, CYP_2E_1, and CYP_3A_4, according to *in vitro* investigations, with the exception of CYP_2E_1. However, this activity is insignificant at therapeutic levels. No presently marketed medications are known to induce or inhibit the high capacity amidases involved in the metabolism of safinamide in a way that results in clinically significant drug interactions [34,47].

Safinamide's plasma concentration is reduced by around 30% by enzyme-inducing antiepileptic medications like phenobarbital and carbamazepine, and its half-life is also shortened by these medications, but Safinamide has no effect on the plasma concentrations of these medications or on those of lamotrigine, valproic acid, or carbamazepine [12].

VIII. CLINICAL TRAILS:

Safinamide's effectiveness, tolerability, and safety in PD patients have all been examined in several research.

Safinamide dosages of 50-200 mg given with a Dopamine agonist improved motor function during a 6-week period with a substantial improvement in the motor score on the Unified Parkinson's Disease Rating Scale (UPDRS) [25]. The same doses of safinamide were administered to eleven individuals in conjunction with levodopa, and this resulted in a notable reduction in motor fluctuations. There are currently only abstracts available for this Phase III study on safinamide. According to their findings, combining 50-100 mg of safinamide with a single dopamine agonist is both safe. Out of 679 individuals who were randomly assigned, 167 finished the full 24 weeks of treatment [4,25].

The first drug studied in clinical trials as a DAA supplement was safinamide. Patients who received safinamide as an adjuvant to DAA involved in the aforementioned study who were taking a steady dose of a DAA showed a significantly greater response. The findings of a small open-label research were consistent. The efficacy and safety of a 50-100mg and a 150-200mg dose range of safinamide in combination therapy to a stable dose of DAA were evaluated and found safe [9,11,14].

Clinical studies on PD patients with LID investigated the potential antidyskinetic characteristics of safinamide. Phase II, placebo-controlled, parallel-group experiment included a total of 26 patients. The maximum reduction in Unified Dyskinesia Rating Score served as the major outcome indicator [28]. The patient diaries' total on and off times and the UPDRS scale's alterations served as secondary end goals. However, the analysis of the 100 mg/day safinamide subgroup revealed a significant improvement in the DRS scores. The DRS ratings for the 50 mg/day and 100 mg/day safinamide groups did not change significantly even after 2 years. Analysis of the patient's journal revealed that, even after two years of therapy, the improvement noted at six months persisted [35]. Non-demented PD patients were included in a Phase II clinical trial to examine the potential impact of safinamide on cognitive impairment linked to PD [42,44]. The Grid-Hamilton Depression Rating scale, the PD Cognitive Rating Scale, the change in cognitive dysfunction, and the Grid-Hamilton Depression Rating scale were the key outcome measures [45]. Safinamide showed positive results in every rating scale indicating multiple actions and the favourability towards the treatment of PD and Dementia disorders.

IX. POTENTIAL COMBINATION THERAPY WITH A FOCUS ON SAFINAMIDE:

In the treatment, Safinamide has a special pharmacological profile that makes it an excellent therapy option for PD and related dementia disorders, which is primarily characterised by dopaminergic and glutamatergic neurotransmission, suggesting it may be further used in different combinations with other class drugs to achieve a significant action [3,10,46].

Parkinson's disease (PD), safinamide combines two effective pharmacologic principles: suppression of MAO-B and reduction of aberrant glutamate release. Safinamide may be thought to be similar to selegiline or rasagiline [5,38,39]. But, unlike rasagiline or selegiline, it does not have an irreversible impact on the MAO-B's activity. Consequently, it is distinct from other MAO-B inhibitors. The action of NMDA receptors is not blocked by safinamide. Amantadine works by antagonistically interacting with NMDA receptors. In addition to its ability to mimic dopamine, this substance also possesses some anticholinergic characteristics [36]. Safinamide, on the other hand, modifies potassium and sodium channels in a way that ultimately leads to a decreased aberrant glutamate release. Safinamide differs from NMDA antagonists in this way. This compliments the fact that safinamide can be combined with NMDA antagonists to achieve a greater overall effect against Parkinson's Disease [35,39].

Additionally, a tendency that has not been seen with other MAO agents but the increased usage of levodopa + safinamide and the combination of levodopa + DA + safinamide [22,44]. Given that safinamide has been shown to reduce both motor and non-motor fluctuations, has a low rate of side effects that have been reported in studies, and most importantly, has been shown to improve non-motor symptoms like pain and depression as well as quality of life impairment, this tendency may be explained [8,46].

The addition of safinamide to levodopa and other dopaminergic medicines was generally well tolerated, with the majority of side effects being of mild to moderate severity. Other than use of Levodopa as combination therapy Carbidopa, Entracapone, and Benserazide can potentially be used with Safinamide to further enhance the effectiveness against PD and related Dementia disorders [61]. Although entacapone has already been compared, more research is needed to determine whether Safinamide is a more effective treatment for all types of motor problems when used in conjunction with a COMT inhibitor [16,41]. Safinamide has been demonstrated to enhance ON time and decrease OFF time, but it also inhibits glutamate release similarly to amantadine, which is at least suspected of enhancing or even preventing motor problems, such as dyskinesia [51,53,60]. Future safinamide experiments should look into this idea, specifically in conjunction with Levodopa/Carbidopa/Entacapone.

X. SAFETY AND TOLERABILITY:

In studies on people, safinamide was well tolerated. Neither the Ames test nor the DNA repair test revealed safinamide to be genotoxic [41]. Both the *in vivo* micronucleus test and investigations on the mutagenicity of mouse lymphoma cells *in vitro* have shown negative results. There was only an 11% dropout rate during the clinical trials [42]. There were no noticeable changes in the patient's vital signs, lab findings, ECG, or outcomes from other tests. There have been reports of negative side effects including nausea, urinary tract infections, faintness, headaches, pain, and brief moderate dyskinesia [6,44].

XI. CONCLUSION:

A derivative of α-aminoamide called safinamide has both dopaminergic and non-dopaminergic effects. It works as a glutamate release inhibitor, a potent reversible and selective MAO-B inhibitor, and a Sodium channel antagonist. Safinamide has a favourable dose-dependent and linear pharmacokinetic profile. It undergoes a great deal of biotransformation mediated by CYPs. With varying degrees of effectiveness, safinamide has been tested as an addition to dopamine agonists treatment in the early stages of Parkinson's disease, as a supplement to levodopa in the middle stages of the illness, and as an antidyskinetic medication. Because of the number of mechanism of actions of Safinamide, it has potential for the combination therapy with other drugs of classes COMT inhibitors, NMDA inhibitors, and glutamate inhibitors not only limiting its combination with dopamine agonists.

XII. ACKNOWLEDGMENT:

XIII. REFERENCES:

1. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA. 2014;311(16):1670–83.
2. National Institute for Health and Care Excellence. Parkinson's disease in over 20s: diagnosis and management. 2009. Accessed 16 sept 2022.
3. Sprenger F, Poewe W. Management of motor and non-motor symptoms in Parkinson's disease. CNS Drugs. 2013;27(4):259–72.
4. Bach JP, Riedel O, Klotsche J, Spottke A, Dodel R, Wittchen HU. Impact of complications and comorbidities on treatment costs and health-related quality of life of patients with Parkinson's disease. J Neurol Sci. 2012;314(1–2):41–47.
5. Blair H. A., Dhillon S. Safinamide: A Review in Parkinson's Disease. Springer International Publishing Switzerland 2017.published on 21 Jan 2017. DOI: 10.1007/s40263-017-0408-1.
6. Cattaneo C, Barone P, Bonizzoni E, et al. Effects of safinamide on pain in fluctuating Parkinson's disease patients: a post-hoc analysis. J Parkinson's Dis. 2016; DOI:10.3233/JPD-160911.
7. Clarke CE, Davies P. Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease. J Neurol Neurosurgy Psychiatry 2000; 69:590-4.
8. Goetz CG, Koller WC, Poewe W, Rascol O, Sampaio C. Management of Parkinson's disease: an evidence-based review. Movment Disorder 2002;17: Supply 4: S1-S166.
9. Antonini A, Meng J, Lister J, et al. Long-term extrapolation of safinamide clinical efficacy in mid- to late-stage Parkinson's disease patients [abstract plus poster]. In: 10th international congress on non-motor dysfunctions in Parkinson's disease and related disorders. 2014.
10. Müller T, Foley P. Clinical pharmacokinetics and pharmacodynamics of safinamide. Clin Pharmacokinet. 2017;56(3):251–261.

11. Leuratti C, Sardina M, Ventura P, et al. Disposition and metabolism of safinamide, a novel drug for Parkinson's disease, in healthy male volunteers. Pharmacology. 2013;92(3–4):207–16.
12. Marquet A, Kupas K, Johne A, et al. The effect of safinamide, a novel drug for Parkinson's disease, on pressor response to oral tyramine: a randomized, double-blind, clinical trial. Clin. Pharmacol. Ther. 2012;92(4):450–7.
13. European Medicines Agency. Safinamide: summary of product characteristics. 2014. http://www.ema.europa.eu. Accessed on 22 sept 2022.
14. De Rijk MC, Breteler MM, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995; 45:2143-6.
15. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51:745-52.
16. Seithel-Keuth A, Johne A, Freisleben A, Kupas K, Lissy M, Krosser S. Absolute bioavailability and effect of food on the disposition of safinamide immediate release tablets in healthy adult subjects. Clin Pharmacol Drug Dev. 2013;2(1):79–89.
17. Riley D, Lang AE, Blair RD, Birnbaum A, Reid B. Frozen shoulder and other shoulder disturbances in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989; 52:63-6.
18. Rajput AH, Birdi S. Epidemiology of Parkinson's disease. Parkinsonism. Relat. Disord. 3(4), 175–186 (1997)
19. Przuntek H, Mu˙ller T, Riederer P. Diagnostic staging of Parkinson's disease: conceptual aspects. J. Neural. Transm. 111(2), 201–216 (2004).
20. Mu˙ller T, Erdmann C, Muhlack S, Bremen D, Przuntek H, Woitalla D. Inhibition of catechol-O-methyltransferase contributes to more stable levodopa plasma levels. Mov. Disord. 21(3), 332–336 (2006).
21. Mu˙ller T, Russ H. Levodopa, motor fluctuations and dyskinesia in Parkinson's disease. Expert Opin. Pharmacother. 7(13), 1715–1730 (2006).
22. Onofrj M, Bonanni L, Thomas A. An expert opinion on safinamide in Parkinson's disease. Expert Opin. Investig. Drugs 17(7), 1115–1125 (2008).
23. Chazot PL. Safinamide (Newron Pharmaceuticals). Curr. Opin. Investig. Drugs 2(6), 809–813 (2001).
24. Fariello RG. Safinamide. Neurotherapeutics 4(1), 110–116 (2007).
25. Goetz CG, Leurgans S, Raman R. Placebo-associated improvements in motor function: comparison of subjective and objective sections of the UPDRS in early Parkinson's disease. Mov. Disord. 17(2), 283–288 (2002).
26. Caccia C, Maj R, Calabresi M et al. Safinamide: from molecular targets to a new anti-Parkinson drug. Neurology 67(7 Suppl. 2), S18–S23 (2006).
27. Morsali D, Bechtold D, Lee W et al. Safinamide and flecainide protect axons and reduce microglial activation in models of multiple sclerosis. Brain 136(Pt 4), 1067–1082 (2013).
28. Cattaneo C, Caccia C, Marzo A, Maj R, Fariello RG. Pressor response to intravenous tyramine in healthy subjects after safinamide, a novel neuroprotectant with selective, reversible monoamine oxidase B inhibition. Clin. Neuropharmacol. 26(4), 213–217 (2003).
29. Gregoire L, Jourdain VA, Townsend M, Roach A, Di PT. Safinamide reduces dyskinesias and prolongs l-DOPA antiparkinsonian effect in parkinsonian monkeys. Parkinsonism Relat. Disord. 19(5), 508–514 (2013).
30. Stocchi F, Arnold G, Onofrj M et al. Improvement of motor function in early Parkinson disease by safinamide. Neurology 63(4), 746–748 (2004).
31. Müller, T. Current status of safinamide for the drug portfolio of Parkinson's disease therapy. Expert Review of Neurotherapeutics, 13(9), 969–977 (2013).
32. Marzo A, Dal Bo L, Monti NC, et al. Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity. Pharmacol Res. 2004;50(1):77–85.
33. Santos García, D., et al Present and Future of Parkinson's Disease in Spain: PARKINSON-2030 Delphi Project. Brain Sciences, 11(8), 1027 (2021). DOI:10.3390/brainsci11081027.
34. National Collaborating Centre for Chronic Conditions. Parkinson's Disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care; Royal College of Physicians: London, UK, 2006; ISBN 1-86016-283-5.
35. Borgohain, R.; Szasz, J.; et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Mov. Disord. 2014, 29, 1273–1280
36. Ambrozi L, Danielczyk W. Treatment of impaired cerebral function in psychogeriatric patients with memantine–results of a phase II double-blind study. Pharmacol. psychiatry. 1988;21(3):144–146.
37. Marzo A, Dal Bo L, Ceppi Monti N, et al. Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity. Pharmacol. 2004; 50:77–85.
38. Bartl J, Müller T, Grunblatt E, Gerlach M, Riederer P. Chronic mono-amine oxidase-B inhibitor treatment blocks monoamine oxidase-A enzyme activity. J Neural Transm. 2014;121(4):379–383.
39. Ambermoon P, Carter A, Hall WD, Dissanayaka NN, O'Sullivan JD. Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. Addiction. 2011;106(2):283–293.
40. Müller T, Riederer P, Grunblatt E. Simultaneous determination of MAO-A and -B activity following first time intake of an irreversible MAO-B inhibitor in patients with Parkinson's disease. J Neural Transm (Vienna) 2017;124(6):745–748.
41. Fava M, Rosenbaum JF, Kolsky AR, et al. Open study of the catechol-O-methyltransferase inhibitor tolcapone in major depressive disorder. J Clin Psychopharmacol. 1999;19(4):329–335.
42. Podurgiel S, Collins-Praino LE, Yohn S, et al. Tremorolytic effects of safinamide in animal models of drug-induced Parkinsonian tremor. Pharmacol Biochem Behav. 2013; 105:105–111.

43. Keyser DL, Rodnitzky RL. Neuroleptic malignant syndrome in Parkinson's disease after withdrawal or alteration of dopaminergic therapy. Arch Intern Med 1991; 151:794-6.

44. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2002; 58:11-7.

45. Marshall V, Grosset D. Role of dopamine transporter imaging in routine clinical practice. Mov Disord 2003; 18:1415-23.

46. Nutt, J. G., & Wooten, G. F. (2005). Diagnosis and Initial Management of Parkinson's Disease. New England Journal of Medicine, 353(10), 1021–1027. DOI:10.1056/nejmcp043908.

47. Giossi R, Carrara F, Mazzari M, et al. Overall efficacy and safety of safinamide in Parkinson's disease: a systematic review and a meta-analysis. Clinical Drug Investig. 2021; 41:321–39. DOI: https://doi.org/10.1007/s40261-021-01011-y.

48. Youdim MBH. Monoamine oxidase inhibitors, and iron chelators in depressive illness and neurodegenerative diseases. J Neural Transm. 2018; 125:1719–33. https://doi.org/10.1007/s00702-018-1942-9.

49. Overall JE, Gorham DR. The Brief Pyschiatric Rating Scale. Psychol. Rep. 1962; 10: 799–12

50. Huang YH, Chen JH, Loh EW, Chan L, Hong CT. The effect of monoamine oxidase-B inhibitors on the alleviation of depressive symptoms in Parkinson's disease: meta-analysis of randomized controlled trials. Ther Adv Psychopharmacol. 2021; 11:1–9.

51. Rojo A, Aguilar M, Garolera MT, Cubo E, Navas I, Quintana S. Depression in Parkinson's disease: clinical correlates and outcome. Parkinsonism Relat Disord. 2003; 10:23–8.

52. Su W, Liu H, Jiang Y, et al. Correlation between depression and quality of life in patients with Parkinson's disease. Clin Neurol Neurosurg. 2021;202: 106523. DOI: 10.1016/j.clineuro.2021.106523.

53. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies: report of the consortium on DLB international workshop.1996; 47: 1113–24

54. McKeith, I., & Cummings, J. (2005). Behavioural changes and psychological symptoms in dementia disorders. The Lancet Neurology, 4(11), 735–742. doi:10.1016/s1474-4422(05)70219-2.

55. Ballard C, Holmes C, McKeith I, et al. Psychiatric morbidity in dementia with Lewy bodies: A prospective clinical and neuropathological comparative study with Alzheimer's disease.1999; 156: 1039–45.

56. Prinsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease a systematic review and meta-analysis. Mov. Disord. 2014;29 (13):1583–90. https://doi.org/10.1002/mds.25945.

57. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30 (12):1591–601. https://doi.org/10.1002/mds.26424.

58. Liguori C, Mercuri NB, Stefani A, Pierantozzi M. Effective treatment of restless legs syndrome by safinamide in Parkinson's disease patients. Sleep Med 2018; 41:113–4. 10.1016/j.sleep.2017.09.017.

59. Malek, N., & Grosset, D. (2012). Investigational agents in the treatment of Parkinson's disease: focus on safinamide. Journal of Experimental Pharmacology, 85. doi:10.2147/jep.s34343.

60. Smith Y, Wichmann T, Factor SA, et al. Parkinson's disease therapeutics: new developments and challenges since the introduction of levodopa. Neuropsychopharmacology Rev. 2012; 37:213-46.

61. Stocchi F. The hypothesis of the genesis of motor complications and continuous dopaminergic stimulation in the treatment of Parkinson's disease. Parkinsonism Relat. Disord. 2009;15: S9-S15.

62. Riederer P, Lachenmayer L, Laux G. Clinical applications of MAO-inhibitors. Curr Med Chem 2004; 11:2033-43.

63. Binda C, Wang J, Pisani L, et al. Structures of human monoamine oxidase B complexes with selective noncovalent inhibitors: safinamide and coumarin analogs. J Med Chem. 2007;50(23):5848–5852.

64. Caccia C, Maj R, Calabresi M, et al. Safinamide: from molecular targets to a new anti-Parkinson drug. Neurology 2006;67: S18-23.