Safinamide for the treatment of Parkinson's disease

Keywords: Parkinson disease, safinamide, dyskinesia, levodopa, treatment

1. Introduction

The major unmet needs in the medical treatment of Parkinson disease (PD) are reduction of motor side effects from dopaminergic drugs, management of non-motor symptoms, relief of non-levodopa-responsive features, and disease modification. Motor fluctuations and OFF periods are a significant determinant of quality of life in PD and reducing their duration and severity can significantly improve motor function. This aim may be partly facilitated by the development of effective adjunctive drugs for dopamine replacement. Safinamide (Xadago), which is a first generation anticonvulsant, has pharmacological properties which are of interest in the context of neurodegenerative diseases, leading to research into its potential as an adjunct to levodopa in PD.

2. Current treatment strategies for PD

The diagnosis of PD remains essentially clinical, guided by recommendations such as the UK PD Society Brain Bank criteria for diagnosis of PD [1] or the recently updated clinical and research Movement Disorders Society criteria [2,3]. Once diagnosis is made, the next important issue is when to begin treatment [4].Once the decision has been made to initiate drug therapy, typical first line treatments are dopamine agonists, monoamine oxidase B (MAOB) inhibitors and levodopa, the choice of which is dependent on presenting symptoms, progression and individual patient factors. Some clinicians delay levodopa for as long as possible and others introduce it early at the lowest effective dose so as to limit the risk for motor complications. Over time, these first line drugs are often used in combination and adjunctive agents such as amantadine and apomorphine are added later [5]. Current pharmacotherapy for PD is primarily aimed at controlling the cardinal motor features of the disease and is not primarily directed at non-motor symptoms although it may alleviate certain features [6]. Non-motor systemic features such as, affective disturbance, constipation, gastro-intestinal symptoms, hyposmia, cardiac parasympathetic changes, sleep dysregulation, painand fatigue are being increasingly recognised as early (often prodromal), features

of PD [7,8]. Research is underway to develop biomarkers based on these prodromal features in order to facilitate early application of disease modifying and neuroprotective treatments [7,8]. Management of non-motor symptoms from the disease and from treatment side effects is currently managed predominantly symptomatically, which can be challenging since these symptoms are diverse and affect almost all body systems. Surgical treatment for PD, in the form of deep brain stimulation (DBS) of the subthalamic nucleus, globus pallidus interna or pedunclopontine nucleus, or lesioning has become an increasingly feasible option [9,10] and cost effective [11]. DBS has been proven in clinical trials to be superior to best medical therapy [12-14] and to be more effective in improving quality of life if used earlier in the course of the disease [15]. The effects of surgical therapy on non-motor features are under investigation and some may improve due to the DBS itself and others from a reduced drug burden [16]. There is a pressing need to develop formulations of levodopa that minimise OFF time, dyskinesias, motor fluctuations and improve quality of life and non-motor symptoms. Safinamide has been investigated as a levodopa adjunct to improve motor function in advanced PD.

3. Pharmacology of safinamide

Safinamide is a highly selective MAOB inhibitor, is orally absorbed (maximal concentration reached at 2-4 hours in a fasted state), has a half-life of about 24 hours, is plasma protein bound with little accumulation, has high bioavailability (>90%) and reaches steady state plasma levels within a week. It has been approved in Europe, North America and some parts of Scandinavia as an add-on therapy to levodopa and dopamine agonists for symptomatic control of motor symptoms [17] in mid to late stage PD with motor fluctuations. The doses that have been trialled in humans are 50 mg/day , 100 mg/day and 200 mg/day. Licensed doses in Europe are 50 or 100 mg daily (starting at the lower dose). Borgohain et al demonstrated that the 100mg/day dose produced more marked benefits (without an increase in adverse events) compared with the 50mg/day dose [18,19]. By 50mg/day, maximal MAOB inhibition activity has already been achieved [20], suggesting that the benefit from

higher doses is due to alternative, non MAOB mechanisms, some of which are not fully elucidated. However, doses over 100 mg/day have not conferred significant benefit for early or late PD study primary end points [21]. It is a once per day oral dose with no need for dose readjustments once it is established. Tyramine potentiation with hypertensive crisis does not occur [22] as safinamide is selective (1000 fold) for MAOB and not for monoamine oxidase A (MAOA) [20, 23], so safinamide is not subject to any dietary restrictions. Table 1 summarises important drug interactions and contraindications for patients using safinamide [17]. Safinamide has linear pharmacokinetics and metabolism is via aminidase enzymes and the cytochrome p450 system is not induced. Dose reduction is not required in renal impairment. A lower dose is recommended in the presence of significant hepatic impairment. Overall, safinamide has a good safety profile with no specific safety concerns or major adverse events identified [24].

4. Safinamide mechanisms of action

MAOB, a mitochondrial bound enzyme, metabolises about 80% of dopamine in humans via deamination. Safinamide ((+)-(S)-2-[[p-(mfluorobenzyl)oxy]benzyl]amino] propionamide monomethanesulfonate) is a small molecule, water soluble alpha aminoamide drug with two main defined mechanisms of action: MAOB inhibition (thereby inhibiting dopamine breakdown), sodium and calcium channel modulation and glutamate inhibition. The main evidence for glutamate inhibition comes from pre-clinical research into safinamide as an anticonvulsant. Excess glutamate release, stimulated in rate by veratrine and potassium chloride, was attenuated by safinamide [25]. The mechanism for this may be NMDA receptor antagonism [26]. Safinamide acts as a reversible MAOB inhibitor to reduce dopamine re-uptake at synaptic junctions. This increases dopamine levels at synaptic junctions and also increases the time it is available as a neurotransmitter. Safinamide also has a non-dopaminergic mechanism of action by blocking site 2 of voltage gated N type sodium channels and blocking calcium channels during their inactivated state, which acts to inhibit glutamate release. Glutamate, dopamine and GABA receptors themselves are not affected by

safinamide. L type calcium channels are unaffected, so safinamide does not have any cardiovascular effects.

Animal studies (mouse, rat and primate) have shown that safinamide concentrations are 9-16 times higher in the brain than in the plasma and that safinamide, in dopamine deficient mice, potentiates levodopa induced dopamine release [27]. Safinamide has no Catechol-O-methyltransferase (COMT) activity [21] and as mentioned its MAOB activity is saturated at doses below those that produce clinical motor improvements. Although safinamide has known effects on glutamate, ion channels and free radicals, none of these actions sufficiently explain sustained peripheral dopamine levels with safinamide.

The action of safinamide on voltage gated sodium channels and on reducing glutamate release has led to exploration of potential neuroprotective properties. Safinamide in a neuroprotective context has been studied in a number of disease models, not only PD. In a neuroinflammatory pathology using a rat model of multiple sclerosis (autoimmune encephalomyelitis), safinamide has been shown to reduce axonal degeneration, demyelination and attenuate loss of function, even after a deficit has already been induced [28]. This may occur via a sodium channel mediated reduction of glutamate driven calcium influx and neuronal excitotoxicity [28]. Additionally, in the same model, safinamide was noted to reduce local microglial and macrophage activity, increase glutathione and reduce superoxide production [28].The theme of safinamide minimising oxidative damage runs through to its putative effect on microglia. Morsali et al in their rat model showed that safinamide acted directly on cultured microglial cells to reduce superoxide formation by NADPH oxidase inhibition and to increase glutathione levels [28]. In 1-methyl 4-phenyl 1,2,3,6 tetrahydropyridine (MPTP) treated mice, safinamide administered 4 hours after the toxin attenuates nigral cell body degeneration [27], which is in agreement with with Morsali's findings. A rat study using toxins such as veratridine to induce neuronal death demonstrated that safinamide reduced glutamate and gamma-aminobutyric acid (GABA) release, thereby attenuating excitotoxic neuronal death [27]. Neuroprotection, or

neuronal preservation, has been demonstrated in kainic acid induced lesions and in ischaemic neuronal destruction in rodent models [27]. There have been no clinical studies to test the hypothetical protective properties of safinamide.

5. Clinical studies of Safinamide in early and later stage PD

Following successful phase 2 and pilot studies [21,29], phase 3 clinical trials were commenced to assess the efficacy of safinamide as adjunct to dopamine therapy. These studies, and those that followed them are summarised in Table 2. Study 015 (NCT00642889) was a 2012 phase 3 trial of safinamide, comparing 100 mg/day (n=90), 200 mg/day (n=89) and placebo (n=90) over 24 weeks [30]. It demonstrated a significant improvement in the primary outcome measure, Unified Parkinson's Disease Rating Scale (UPDRS) part 3 for the 100 mg/day dose with no added benefit at 200 mg/day. A 12 month extension of study 015 (n=227) was undertaken (study 017 (NCT00642889)) as an international multicentre, randomised, double-blind, placebo-controlled, parallel-group trial of safinamide (same regimes as study 015) as an add-on to levodopa in early PD [31]. The primary outcome measure for study 017 was time from baseline (enrolment in 015) to the requirement for a change in therapy. A significant difference between the safinamide and placebo groups was not seen in this study, although post hoc landmark analysis demonstrated lower rates of change in treatment plan for the 100mg/day safinamide group [31]. The promising results from studies 015 and 017 set the stage for larger scale trials of safinamide. The 016 study (NCT01187966) was a double blind, placebo-controlled, randomised international multicentre trial (n=669) comparing safinamide as an add-on to levodopa at doses of 50 mg/day (n=223), 100 mg/day (n=224) and placebo (n=222) over 24 weeks [18]. The primary outcome measure of Study 016 was change from baseline values in mean daily total ON time with no or non-troublesome dyskinesia. Patients who completed study 016 without significant safinamide related side effects or clinical deteriorating progressed into study 018 (NCT01286935) , which assessed the long term efficacy and safety of safinamide as an add on to levodopa [19]. The primary outcome measure of study 018 (n=619) was

change from baseline in dyskinesia over the 18 months that the study ran, making a total of 2 years assessment for those who completed studies 016 and 018. ON time with no/non-troublesome dyskinesia was significantly improved in both studies, OFF time was reduced and UPDRS part 3 improved (a secondary outcome measure in both studies). Reduction in dyskinesia, the primary outcome of study 018 was not significant. However, interpretation of this data was difficult due to the fact that not all patients enrolled had dyskinesia. The subgroup which had dyskinesia showed significant reduction in this with the addition of safinamide to their levodopa regime. Studies 016 and 018 did not have any major safinamide related adverse events. A recent addition to the body of evidence supporting the use of safinamide is SETTLE (Safinamide in Idiopathic Parkinson's Disease With Motor Fluctuations, as add-on to Levodopa, NCT00627640), a double blind, parallel group trial (n=549) comparing 100 mg/day (n=274) and placebo (n=275) over 24 weeks in patients on levodopa and other PD medications with motor complications [32]. The safinamide dose was increased to 100mg/day from a starting dose of 50 mg/day after two weeks if no adverse effects had occurred. As with study 016, the primary outcome measure for this study was change in mean daily ON time from baseline to 24 weeks with no troublesome dyskinesias. Safinamide achieved significance in the primary outcome measure, and in keeping with earlier studies, UPDRS part 3 was significantly improved (a secondary outcome measure) [32]. Dyskinesia was noted as a severe side effect in 5 (1.8%) of the safinamide group versus 1 patient (0.4%) of the placebo group, but other than this, safinamide was overall well tolerated. All current trials of safinamide have used motor features as their primary outcome measures and include non-motor assessment tools in their secondary outcome measures. Olanow and Stocchi review the reported post hoc and pooled analyses of non-motor effects of safinamide from secondary outcome measures in study 016, 018 and SETTLE [33]. The key findings of interest were that safinamide was associated with improved clinical global impression rating, UPDRS part 2, PDQ-39, pain, mood and wellbeing [18,19,32-35]. However, there are no published studies specifically powered to investigate the non-motor effects of safinamide as the study end point, so further research in this area is required.

6. Conclusions

Safinamide is a valuable add on therapy for levodopa to improve motor function in PD. Clinical trials so far have demonstrated it to be effective in increasing ON time without a significant increase in troublesome dyskinesias. Additionally it is showing promise in amelioration of non-motor features of PD and studies specifically powered to detect non-motor effects would be of interest.

7. Expert opinion

The management of 'OFF' periods in PD is a significant clinical challenge. Whilst drugs such as safinamide, the MAOB inhibitors and COMT inhibitors reduce OFF time, the effect is relatively short-lived, with a mean daily reduction of only 45 minutes to an hour. The practical approach to PD fluctuations can run from modifying levodopa dose, fractionation and frequency to the introduction of safinamide, a MAOB or a COMT inhibitor. All these strategies carry a risk of initiating or exacerbating dyskinesias, although these are unlikely to be troublesome in the early stages. Some physicians may wish to lower the dose of levodopa under these circumstances. Alternatively, if the dyskinesias become troublesome the introduction of amantadine can be considered.

Even with improvements in motor function and quality of life, particularly if achieved without the worsening of dyskinesia, there remains a significant unmet need in managing PD fluctuations and non levodopa responsive motor symptoms such as falls and balance dysfunction. This will ultimately need to be addressed by modifying levodopa formulations to reduce the incidence of motor complications. Current drugs to manage motor fluctuations will still likely need to be used as adjuncts to long-acting levodopa preparations to manage wearing off. However, ultimately the best strategy to treat both motor deficits and motor complications will be to slow or prevent the progress of neurodegeneration. Effective drugs for modifying the course of PD will need to slow neurodegeneration not only in dopaminergic but also non-dopaminergic neurons, otherwise the non-motor aspects of PD will remain unaffected. Recent developments in the repurposing of drugs

for neuroprotection in PD targeting the lysosomal or mitochondrial pathways appear to show promise in this area, at least in laboratory and early phase clinical studies. The development of immune based therapies to reduce alpha-synuclein levels is also an important focus of research.

Achieving the goal of effective disease modification in PD may be several years away. In the interim, drugs such as safinamide provide enhanced symptom control of motor function in advanced PD, and improve quality of life. The mechanisms of action of safinamide represent a novel departure from standard approaches in terms of its non-MAOB inhibitory effects.

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Table 1: Drug interactions, contraindications and cautions for safinamide [17,30]
- Other monoamine oxidase inhibitors (risk of hypertensive crisis) - Pethidine (adverse effects between monoamine oxidase inhibitors and pethidine) - Sympathomimetics (caution rather than contraindication) - Caution with antidepressants (use at lowest effective dose) - Increased risk of falls when combined with anxiolytics and anti-hypertensives - Increased risk of psychosis when combined with amantadine - Increased risk of neuropsychiatric disturbance when combined with dopamine agonists - Contraindicated in patients with retinal pathology - Contraindicated in hepatic impairment

Table 2: Clinical studies evaluating the efficacy of safinamide as an L-dopa treatment adjunct in PD								
Author and year	Study design	Number of patients	Notable inclusion/exclusion criteria	PD stage	Intervention	Primary outcome measures	Results for primary outcome measure	Subgroup analyses of interest
Stocchi et al, 2004 [29]	Randomised, placebo controlled, double blind phase 2 study of safety, dose and efficacy in early PD	172	Caucasian patients only included. Patients with motor fluctuations excluded.	Early stage	0.5 mg/Kg, 1 mg/Kg safinamide or placebo as an add on to dopamine replacement or as a monotherapy	More than 30% improvement in UPDRS 3	Significant achieved at 1mg/Kg dose and better result as an adjunct to dopamine replacement rather than a monotherapy	
Stocchi et al, 2006 [21]	Open pilot single centre study	13	H&Y stage 3-4 idiopathic PD. Two groups: one with stable dose L-dopa and motor fluctuations, second group was patients on single dopamine agonist. Non-Caucasian patients excluded	Moderate stage	Dose testing with progressive 2 week increments of 100mg/day, 150 mg/day, 200 mg/day safinamide to max tolerated of the 3 doses in addition to dopamine replacement therapy	UPDRS3	Improvement in UPDRS 3 and reduction in motor fluctuations	
Stocchi and study 015 investigators, 2012 (NCT00642889) [30]	Randomised, double-blind, placebo controlled, parallel group study	270	H&Y stage 1-2 idiopathic PD, < 5 years duration and on a stable dopamine replacement	Early stage	Randomisation to 100 mg/day safinamide, 200 mg/day safinamide or placebo to be taken in addition to one dopamine replacement therapy	UPDRS3 at 24 weeks	Statistical significance for the 100mg/day dose group for primary end point. Both safinamide doses improved secondary outcome, clinical global index	No
Schapira and study 017 investigators, 2013 (NCT00-642889) [31]	12-month extension of study 015. Blinded placebo versus two doses of safinamide as an add on to dopaminergic therapy in early PD	227	Inclusion: idiopathic PD <5 years' duration, H&Y stage I-3, on a single dopamine replacement. Exclusion criteria were dementia and significant cognitive decline	Early stage	Patients received safinamide 100 mg/day or 200 mg/day or placebo added to a single dopamine agonist in early PD.	Time from baseline (randomization in Study 015) to An increase in PD treatment needs or stopping safinamide due to lack of effectiveness	Neither safinamide dose achieved statistical significance for the primary endpoint.	Post hoc analysis showed the 100mg/day dose was associated with lowered intervention rate with dopamine therapy and improved UPDRS scores (secondary outcomes)
Borgohain and 016 investigators, 2014 (NCT01187966) [18]	Phase III, multicentre, randomised, double blind, placebo controlled, parallel group study	669	Late stage PD, dementia, severe and unpredictable dyskinesia were exclusions	Mid-to-late-stage (H&Y mean 2.8, disease duration over 3 years) with motor fluctuations on dopaminergic therapy	Randomisation to safinamide 100 mg/ day, safinamide 50 mg/day, or placebo for 24 weeks as an add on therapy to L-Dopa	Change in mean daily total ONON time with no or non-troublesome dyskinesia	Significantly increased ONON time with no worsening in dyskinesia at 50mg and 100 mg doses compared with placebo	Both doses associated with improvement in UPDRS 3 (secondary outcome measure) with safinamide at both doses
Borgohain and 018	2 year extension of	544	Inclusion criteria were compliance	As for study 016	As for study 016 with	Mean change from study 016	No difference in	Also demonstrated

investigators, 2014 (NCT01286935) [19]	016 investigator group study as a multicentre randomised double blind placebo controlled parallel group study		and completion of study 016. Those discontinued from study 016 but who underwent scheduled efficacy evaluations at 12 and 24 week points could be included. Exclusion included clinically significant adverse events or motor deterioration in motor during study 016		groups kept the same as in study 016	baseline using the Dyskinesia Rating Scale during ON time	dyskinesias between patients and Placebo when whole cohort analysed. Subgroup analysis showed improvement in dyskinesia in those with significant baseline dyskinesia	increased ON time and UPDRS 3.
Schapira et al, 2016. SETTLE Study (NCT00627640) [32]	Phase 3 double bond, placebo controlled, randomised trial of safinamide as an add on to Levodopa in idiopathic PD with motor fluctuations	549	Key inclusion criteria was more than 1.5 hours per day of "OFF" time despite pharmacotherapy optimized to minimize motor fluctuations	Moderate	Safinamide 100 mg/day for 24 weeks (built up from an initial dose of 50 mg/day) versus placebo	Change from baseline ONON time without troublesome dyskinesia	Significance in the primary outcome measure achieved with increased mean daily ONON time 1.42 hours for safinamide group and 0.57 hour for placebo group	Improvement in UPDRS3
Abbreviations: H&Y - Hoehn and Yahr scale; UPDRS - unified Parkinson's disease rating scale; SETTLE - Safinamide in Idiopathic Parkinson's Disease With Motor Fluctuations, as add-on to Levodopa								

References:

1. NICE – CG35 Parkinson's Disease: National clinical guideline for diagnosis and management in primary and secondary care. https://www.nice.org.uk/guidance/cg35/evidence/full-guideline-194930029 ***UK clinical guideline**
2. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601. doi: 10.1002/mds.26424. Review.
3. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015 Oct;30(12):1600-11. doi: 10.1002/mds.26431. Review.
4. Schapira AH, Obeso J. Timing of treatment initiation in Parkinson's disease: a need for reappraisal? Ann Neurol. 2006 Mar;59(3):559-62. Review.
5. Schapira AH. Treatment options in the modern management of Parkinson disease. Arch Neurol. 2007 Aug;64(8):1083-8. Review
6. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 2009 May;8(5):464-74. doi: 10.1016/S1474-4422(09)70068-7. Review
7. Mahlknecht P, Seppi K, Poewe W.The Concept of Prodromal Parkinson's Disease. J Parkinsons Dis. 2015;5(4):681-97. doi: 10.3233/JPD-150685. Review.
8. Goldman JG, Postuma R. Premotor and non-motor features of Parkinson's disease. Curr Opin Neurol. 2014 Aug;27(4):434-41.
9. Zrinzo, L. MRI guided and MRI verified deep brain stimulation : accuracy, safety and efficacy. http://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.565447
10. deSouza RM, Moro E, Lang AE, Schapira AH. Timing of deep brain stimulation in Parkinson disease: a need for reappraisal? Ann Neurol. 2013 May;73(5):565-75.
11. Fundament T, Eldridge PR, Green AL, Whone AL, Taylor RS, Williams AC, Schuepbach WM. Deep Brain Stimulation for Parkinson's Disease with Early Motor Complications: A UK Cost-Effectiveness Analysis. PLoS One. 2016 Jul 21;11(7):e0159340
12. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenzl S, Mehdorn HM, Moringlane JR, Oertel W, Pinsker MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J; German Parkinson Study Group, Neurostimulation Section. A randomized trial of deep-brain stimulation for Parkinson's disease.N Engl J Med. 2006 Aug 31;355(9):896-908. Erratum in: N Engl J Med. 2006 Sep 21;355(12):1289
13. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, Rothlind J, Sagher O, Reda D, Moy CS, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein J, Stoner G, Heemskerk J, Huang GD; CSP 468 Study Group. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009 Jan 7;301(1):63-73
14. Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, Scott R, Ives N, Rick C, Daniels J, Patel S, Wheatley K; PD SURG Collaborative Group. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol. 2010 Jun;9(6):581-91
15. Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltête D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G; EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med. 2013 Feb 14;368(7):610-22.

16. Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. Lancet Neurol. 2012 May;11(5):429-42. doi: 10.1016/S1474-4422(12)70049-2. Review
17. Deeks ED. Safinamide: first global approval. Drugs. 2015 Apr;75(6):705-11. doi: 10.1007/s40265-015-0389-7. Review.
18. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 016 Investigators. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations.Mov Disord. 2014 Feb;29(2):229-37 ***clinical trial**
19. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 018 Investigators. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Mov Disord. 2014 Sep;29(10):1273-80. ***clinical trial**
20. Marzo A, Dal Bo L, Monti NC, Crivelli F, Ismaili S, Caccia C, Cattaneo C, Fariello RG .Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity. Pharmacol Res. 2004 Jul;50(1):77-85.
21. Stocchi F, Vacca L, Grassini P, De Pandis MF, Battaglia G, Cattaneo C, Fariello RG. Symptom relief in Parkinson disease by safinamide: Biochemical and clinical evidence of efficacy beyond MAO-B inhibition. Neurology. 2006 Oct 10;67(7 Suppl 2):S24-9
22. Di Stefano AF, Rusca A. Pressor response to oral tyramine during co-administration with safinamide in healthy volunteers. Naunyn Schmiedebergs Arch Pharmacol. 2011 Dec;384(6):505-15
23. Fariello RG. Safinamide. Neurotherapeutics. 2007 Jan;4(1):110-6. Review.

24. Perez-Lloret S, Rascol O. The safety and efficacy of safinamide mesylate for the treatment of Parkinson's disease. Expert Rev Neurother. 2016;16(3):245-58. doi: 10.1586/14737175.2016.1150783. Review.
25. Salvati P, Maj R, Caccia C, Cervini MA, Fornaretto MG, Lamberti E, Pevarello P, Skeen GA, White HS, Wolf HH, Faravelli L, Mazzanti M, Mancinelli E, Varasi M, Fariello RG. Biochemical and electrophysiological studies on the mechanism of action of PNU-151774E, a novel antiepileptic compound. J Pharmacol Exp Ther. 1999 Mar;288(3):1151-9.
26. Müller T, Foley P. Clinical Pharmacokinetics and Pharmacodynamics of Safinamide. Clin Pharmacokinet. 2017 Mar;56(3):251-261. doi: 10.1007/s40262-016-0449-5. Review.
27. Caccia C, Maj R, Calabresi M, Maestroni S, Faravelli L, Curatolo L, Salvati P, Fariello RG. Safinamide: from molecular targets to a new anti-Parkinson drug. Neurology. 2006 Oct 10;67(7 Suppl 2):S18-23. Review.
28. Morsali D, Bechtold D, Lee W, Chauhdry S, Palchaudhuri U, Hassoon P, Snell DM, Malpass K, Piers T, Pocock J, Roach A, Smith KJ. Safinamide and flecainide protect axons and reduce microglial activation in models of multiple sclerosis. Brain. 2013 Apr;136(Pt 4):1067-82
29. Stocchi F, Arnold G, Onofrj M, Kwiecinski H, Szczudlik A, Thomas A, Bonuccelli U, Van Dijk A, Cattaneo C, Sala P, Fariello RG; Safinamide Parkinson's Study Group. Improvement of motor function in early Parkinson disease by safinamide. Neurology. 2004 Aug 24;63(4):746-8
30. Stocchi F, Borgohain R, Onofrj M, Schapira AH, Bhatt M, Lucini V, Giuliani R, Anand R; Study 015 Investigators. A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients. Mov Disord. 2012 Jan;27(1):106-12.
31. Schapira AH, Stocchi F, Borgohain R, Onofrj M, Bhatt M, Lorenzana P, Lucini V, Giuliani R, Anand R; Study 017 Investigators. Long-term efficacy and safety of safinamide as add-on therapy in early Parkinson's disease. Eur J Neurol. 2013 Feb;20(2):271-80 ***clinical trial**
32. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, Anand R. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol 74 (2), 216-224. 2017. ***clinical trial**
33. Olanow WC, Stocchi F. Safinamide – A New Therapeutic Option to Address Motor Symptoms and Motor Complications in Mid- to Late-stage Parkinson's Disease. European Neurological Review,2016;11(Suppl. 2): 2–15
34. Xadago Product Information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002396/WC500184965.pdf

35. Cattaneo C, Barone P, Bonizzoni E, Sardina M. Effects of Safinamide on Pain in Fluctuating Parkinson's Disease Patients: A Post-Hoc Analysis. J Parkinsons Dis. 2016 Oct 11.