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Is Safinamide Effective as an Add-on Medication in Treating Parkinson's Disease Motor Symptoms?

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ABSTRACT

Objective: The objective of this systematic review is to determine whether or not “Is safinamide effective as an add-on medication in treating Parkinson's disease motor symptoms?”

Study design: Review of three randomized, controlled studies published in peer reviewed journals in English between 2012-2014.

Data sources: The three randomized, double-blind clinical trials were found via PubMed and EBSCOhost Web. Articles were selected based on relevance, the date of publication, and whether or not they included patient outcomes.

Outcomes measured: Among other measures, each trial measured improvement in motor symptoms using the Unified Parkinson’s Disease Rating Scale (UPDRS) Part III (motor) scores, a clinician-scored motor evaluation.

Results: UPDRS III scores significantly improved in 100 mg/day safinamide experimental group compared to the placebo control group.

Conclusions: All three of the randomized clinical trials included in this review indicated that safinamide 100 mg/day is an effective add-on medication to dopaminergic drugs in improving motor function and reducing motor fluctuations.

Keywords: Safinamide, Parkinson’s disease, randomized or RCT

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease resulting in diverse clinical features that include nonmotor symptoms, motor symptoms, and classic signs like tremor, akinesia, and rigidity.[1] A single causative agent of PD is unknown. There is no direct evidence to support genetic or environmental factors as single causative agents but it is theorized that both are involved.[2] There is evidence of six genes that have been implicated as causes of familial PD.[2]

The worldwide incidence of PD is about 315 per 100,000 for people 40 years and older, specifically 1,903 per 100,000 for the 80+ age group.[3] With this data, the prevalence of PD is projected to be 7.5 million persons worldwide with a diagnosis.[3] The prevalence in men is higher than women for all age groups.[3]

The population with PD acquired medical expenses of approximately $14 billion in 2010, 57% of which is associated with nursing home services.[4] Estimated medical costs alone attributed to PD were about $8 million in 2010, and another $6 million was estimated as indirect costs to the PD population like reduced household income and lost employment.[4] The population with PD acquired approximately 1.9 million hospital inpatient days in 2010.[4] Excess health-care use attributed to PD in 2010 includes 1.26 million physician office visits, 57,000 outpatient visits, 31,000 emergency visits, 24,000 home health days, and 26,000 hospice days.[4]

Pathologically PD is characterized by progressive death of dopaminergic neurons within the substantia nigra pars compacta.[1] Levodopa remains one of the most effective drugs in treating PD because it's converted into dopamine after crossing the blood brain barrier, however, one of the long term effects of the drug is dyskinesia. The motor complications, such as motor

fluctuations and dyskinesia, from levodopa are treated with other medications like monoamine oxidase type B inhibitors, amantadine, anticholinergics, β-blockers, or dopamine agonists.[5]

Monoamine oxidase-B (MAO-B) inhibitors are used to treat dyskinesia due to dopaminergic drug therapy. Safinamide is a reversible inhibitor of MAO-B and also exhibits inhibition of stimulated release of glutamate.[6] The proposed connection between glutamate release and the development of dyskinesia supports the theory that safinamide, and its action against glutamate, will be successful in improving motor symptoms.[6] This paper evaluates three randomized, double-blind, controlled trials comparing the efficacy of safinamide 100 mg/day at improving motor symptoms versus a placebo group.

Objective

The objective of this systematic review is to determine whether or not safinamide is effective as an add-on medication in treating Parkinson's disease motor symptoms.

Methods

Three double-blinded, randomized controlled trials were used in this review. The population includes PD patients with mid to late PD or a PD diagnosis of less than 5 years in duration. The intervention used was safinamide 100 mg/day as add-on therapy to levodopa or other dopaminergic drugs compared to a placebo group. The outcome being measured was the change in motor symptoms with the addition of safinamide 100 mg/day. This was measured by clinician scoring with the UPDRS Part III score, which focuses on motor symptoms.

The key words used while searching for relevant clinical trials were safinamide, Parkinson’s disease, randomized or RCT. All the articles were obtained through PubMed and EBSCOhost Web, and were selected based on the date of publication and whether or not they

included patient outcomes. All three articles were published in English in peer-reviewed journals, two in 2014 and one in 2012. The inclusion criteria for the studies included patients with a clinical diagnosis of PD, and randomized, controlled, double blind clinical trials. Exclusion criteria included patients who had previous safinamide treatment, evidence of dementia or psychiatric illness, and patients who had disabling dyskinesia or wide fluctuations. More detail is displayed below in Table 1 for each individual study exclusion and inclusion criteria. The statistics used and reported were numbers needed to harm (NNH), relative risk increase (RRI), absolute risk increase (ARI), and p-values. The demographics and characteristics of the included studies are shown below in Table 1.

Table 1: Demographics and characteristics of included studies

Study	Type	Pts	Age	Inclusion criteria	Exclusion criteria	W/D	Intervention
Borgohain, 2014	RCT	669	30-80 y/o	• motor fluctuations (> 1.5 hours' off time/day) while receiving Levodopa and other dopaminergic treatments • clinical diagnosis of idiopathic PD >3 years in duration • Hoehn and Yahr stage I to IV during off • able to accurately maintain a diary	• late-stage PD experiencing severe, disabling peak-dose or biphasic dyskinesia, or unpredictable or widely swinging symptom fluctuations • evidence of dementia, major psychiatric illnesses, and/or mental illnesses	29	safinamide 100 mg/day or placebo as add-on therapy to Levodopa
Borgohain, 2014	RCT	669	mean age 60 y/o	• mid-late stage PD with motor fluctuations • completed Study 016 prior to Study 018 • treatment compliant, continue after Study 016 • discontinued from Study 016 but had completed scheduled efficacy evaluations at weeks 12 and 24	• experienced clinically significant adverse effects during Study 016 • showed clinically significant deterioration in motor symptoms	30	safinamide 100 mg/day or placebo as add-on therapy to a single dopamine agonist
Stocchi, 2012	RCT	270	30-80 y/o	• clinical diagnosis of idiopathic PD < 5 years in duration • Hoehn and Yahr stage I to III • stable dose of dopamine agonist for at least 4 weeks before screening	• diagnosis of substance abuse • end-of-dose wearing off, on/off phenomena, disabling dyskinesia, or wide fluctuations • previous safinamide treatment • diagnosis of psychosis or depression • hypersensitivity to anticonvulsants or antiparkinsonian agents • severe postural hypotension • PD medications (except for a single DA) during the 4 wks before screening • concomitant use of MAO inhibitors	9	safinamide 100 mg/day or placebo as add-on therapy to a single dopamine agonist

Outcomes measured

All three studies measured motor symptom outcomes with the UPDRS Part III scores, which is a measure of motor function done by a clinician.[6,7,8] Motor fluctuations or dyskinesia experienced by patients in the experimental treatment groups were compared to placebo groups to determine whether or not they experienced statistically significant improvement in their UPDRS part III total score.[6,7,8]

Results

This review of three RCTs compared patients with a PD diagnosis who were experiencing stable motor fluctuations while receiving levodopa treatment with changes after taking 100 mg/day of safinamide or a placebo. All three trials used safinamide 100 mg/day as an experimental group compared to another dose of safinamide and a placebo group. This systematic review focuses on the safinamide 100 mg/day experimental group in comparison to the placebo control group without mention of the other experimental treatment dose of safinamide. Dichotomous data was presented in all three RCTs to assess the safety and efficacy of the therapy.[6,7,8]

In the Borgohain study there were a total of 669 patients who enrolled, 224 patients randomized into the experimental safinamide 100 mg/day group and 222 patients randomized into the placebo group.[7] Patient return visits throughout the study were held at 52 different sites in India, Romania, and Italy.[7] Of the 224 patients in the safinamide 100 mg/day group, 195 completed the study with 4 lost to follow up and 2 reports of noncompliance.[7] Treatment

emergent adverse events (TEAEs) were experienced by 66% of patients in the safinamide 100 mg/day group, but more than 90% of reported TEAEs were considered mild or moderate.[7] Some of the common TEAEs reported by the safinamide 100 mg/day group were dyskinesia, cataract, back pain, headache, and hypertension.[7] Five deaths were reported in the safinamide 100 mg/day group, 2 considered unrelated to the drug, 2 causes of death were unknown, and 1 death was a result of a posttraumatic subdural hematoma 49 days after discontinuation of the study.[7] This cause of death was reported as a serious adverse event, but not considered a cause of death due to safinamide.[7] In the experimental safinamide 100 mg/day group, 18.3% experienced dyskinesia.[7] The ARI was calculated to be 0.06.[7] This means that patients taking safinamide 100 mg/day had a 6% absolute increase in experiencing dyskinesia. The NNH was calculated to be 17.[7] This means that for every 17 patients being treated with safinamide 100 mg/day, one additional would experience dyskinesia compared to control.

In another Borgohain study that was a continuation of the preliminary Borgohain study, 544 of the original 669 patients enrolled in a second continuation study that ended 78 weeks from the start of the first.[6] The randomized assignment of patients to treatment groups was computer generated into an experimental safinamide 100 mg/day group and a placebo group.[6] Return visits at the 52 sites where the study was being conducted were held every 12 weeks.[6] Participants in the safinamide 100 mg/day experimental group were compliant to the study, with 0 reports of noncompliance.[6] Of the 180 patients in the safinamide 100 mg/day group at the start of the second study, 150 patients completed the study with 7 lost to follow up.[6] TEAEs were similar across the treatment groups and the placebo control group.[6] The highest incidence of newly emergent TEAEs, most common reported including worsening PD, dyskinesia, cataract,

constipation, back pain, etc., was seen in the placebo group with 85.1% of patients affected.[6] No treatment related deaths occurred during the study.[6] In the experimental safinamide 100 mg/day group, 27.8% experienced dyskinesia.[6] The ARI was calculated to be 0.06 and NNH was calculated to be 17, the same as in the preliminary Borgohain study.[6] This means that for every 17 patients being treated with safinamide 100 mg/day, one additional would experience dyskinesia compared to control.

In the Stocchi study, 270 patients were randomized into study groups.[8] The study was conducted at 26 centers in Italy, Spain, the United Kingdom, India, Argentina, Chile, and Colombia with return visits at weeks 2, 4, 8, 12, 18, and 24.[8] Of the 90 patients in the experimental safinamide 100 mg/day group, 81 patients completed the study with 0 reports of noncompliance and 0 lost to follow up.[8] TEAEs experienced across all study groups were mostly mild or moderate, and <10% experienced TEAEs in each group.[8] Some of the most common included, nausea, abdominal pain, peripheral edema, dizziness, and tremor.[8] Patients who reported severe TEAEs, retinal vein occlusion and iron-deficiency anemia, in the safinamide 100 mg/day group totaled to 2.2% of the group, none of which caused death.[8] In the experimental safinamide 100 mg/day group, 2.2% experienced dyskinesia.[8] The ARI was calculated to be -0.045.[8] This means that patients taking safinamide 100 mg/day had a -4.5% absolute increase in experiencing dyskinesia. The NNH was calculated to be -22.[8] This means that for every 22 patients being treated with safinamide 100 mg/day, one fewer would experience dyskinesia compared to control.

Table 2: Treatment effects

Study	p-value	CER	EER	RRI	ARI	NNH
Borgohain, 2014	0.0006	0.126	0.183	0.45	0.06	17
Borgohain, 2014	0.0002	0.217	0.278	0.28	0.06	17
Stocchi, 2012	0.0419	0.067	0.022	-0.67	-0.045	-22

Discussion

Safinamide, brand name Xadago, has been approved for treatment as an add-on to levodopa or in combination with other medications for mid to late stage PD patients experiencing motor fluctuations in the European Union, Iceland, Norway, and Lichtenstein.[9] With a new drug application under review, the launch of safinamide is anticipated in the United States in the beginning months of 2016.[9] A once daily preparation, safinamide 100 mg/day needs no laboratory monitoring, can be taken with or without food without affecting absorption, and doesn't cause hallucinations or impulse control disorders like other PD medications.[9,10]

Safinamide is contraindicated for use in a patient with severe hepatic impairment as well as contraindicated for use in combination with other MAO inhibitors due to the risk of developing hypertensive crisis.[9] It is not recommended to use safinamide with dextromethorphan and to be used with caution with sympathomimetic medicines.[9] Use of tricyclic antidepressants, selective serotonin re-uptake inhibitors, and serotonin norepinephrine can cause severe adverse events when used with safinamide.[9] If used with caution, antidepressant medications can be administered at the lowest effective doses with safinamide because of the selective and reversible nature of safinamide as a MAO-B inhibitor.[9] This does not apply to fluvoxamine or fluoxetine,

which should be avoided when the patient is already taking safinamide.[9] Currently, there doesn't seem to be any ongoing trials with safinamide.[9]

The RCTs on the effectiveness of safinamide in reducing motor fluctuation were limited by the age of the patient population. The Borgohain studies included a wide range of patients from 30-80 years old, but this didn't include the subset of early onset PD which can affect someone as early as 21 years old.[6,7,11] Early onset PD is characterized as 21-40 years old at the time of diagnosis, which comprises about 10% of the PD population.[11] It would have been valuable to evaluate the effectiveness of the novel drug on a patient who is more likely to have familial PD with a diagnosis at a young age versus idiopathic PD.

Conclusions

Is safinamide effective as an add-on medication in treating Parkinson's disease motor symptoms? The answer is yes. All three double-blinded RCTs provided statistically significant data that displayed improvement in UPDRS part III total scores after treatment with safinamide 100 mg/day compared to placebo.[6,7,8] The benefit of safinamide 100 mg/day as an add on medication to dopaminergic therapy in treating dyskinesia in patients with PD outweighs the mostly mild TEAEs recorded during the trials. For future study, more frequent return visits to study sites, similar to the Stocchi study schedule, can be recommended to improve patient compliance and dedication to the clinical trial.

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