

Research Report

Long-Term Effects of Safinamide on Mood Fluctuations in Parkinson's Disease

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Abstract.

Background: Mood disorders are very frequent in Parkinson's Disease (PD), and their effective treatment is still a major unresolved issue: growing evidence suggests that glutamatergic system dysfunction is directly involved. Safinamide is a drug with an innovative mechanism of action, dopaminergic and non-dopaminergic, that includes the reversible inhibition of the monoamine oxidase-B (MAO-B) enzyme and the modulation of excessive glutamate release through the use- and state-dependent blockade of the sodium channels.

Objective: To investigate the effects of safinamide on mood over two-year treatment in PD patients with motor fluctuations.

Methods: This was a *post-hoc* analysis of the data from studies 016 and 018. The analysis focused on outcomes related to mood, namely: scores of the "Emotional well-being" domain of the Parkinson's Disease Questionnaire (PDQ-39), scores of the GRID Hamilton Rating Scale for Depression (GRID-HAMD) and the proportion of patients reporting depression as an adverse event over the entire treatment period.

Results: Safinamide, compared to placebo, significantly improved the PDQ-39 "Emotional well-being" domain after 6-months ($p=0.0067$) and 2 years ($p=0.0006$), as well as the GRID-HAMD ($p=0.0408$ after 6 months and $p=0.0027$ after 2 years). Significantly fewer patients in the safinamide group, compared to placebo, experienced depression as adverse event ($p=0.0444$ after 6 months and $p=0.0057$ after 2 years).

Conclusion: The favorable effect of safinamide on mood may be explained by the improvement in wearing off and by its modulation of glutamatergic hyperactivity and reversible MAO-B inhibition. Prospective studies are warranted to investigate this potential benefit.

Keywords: Glutamate, mood, Parkinson's disease, safinamide

INTRODUCTION

Parkinson's Disease (PD) is primarily considered as a motor disorder, but there is an increasing

recognition of a wide range on non-motor symptoms (NMS) such as low mood, pain, fatigue and sleep disorders, which often occur before motor symptoms [1].

Complex, interconnected neuronal pathways, regulated by a number of different neurotransmitters in addition to dopamine, are involved in the etiology of motor and non-motor symptoms. The development of agents interacting with several neurotransmission

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systems in the CNS might be very useful for the treatment of this disease [2].

Between NMS, mood disorders have been reported in up to 35% of PD patients, with a substantial negative impact on the quality of life of patients and their caregivers. These symptoms are often underdiagnosed and therefore undertreated; however, to optimize patients outcomes, they need to be managed effectively [3].

Glutamate is the most abundant excitatory neurotransmitter in the mammalian brain, and modulates many physiological brain functions, with a crucial role in synaptic transmission and plasticity. Several clinical studies have supported a key role for the glutamatergic system in the pathophysiology of mood disorders [4].

Drugs that inhibits voltage-activated channel activity (e.g. riluzole or lamotrigine), decreasing abnormal presynaptic glutamate release, are considered mood stabilizers [5].

Safinamide has a dual mechanism of action, dopaminergic and non-dopaminergic, that offers a unique approach to the management of motor symptoms and motor complications. The non-dopaminergic mechanism of action might be useful for the treatment of non-motor symptoms: safinamide, in fact, suppresses repetitive firing by use- and state-dependent sodium channel blockade, thus reducing excessive release of glutamate [6], and has shown to improve PD-related chronic pain [7]. This *post-hoc* analysis of the data from trials 016 and 018 was performed to evaluate the effects of safinamide 100 mg/day on mood disorders in PD patients with motor fluctuations.

MATERIALS AND METHODS

Patients

Study 016 (NCT01187966) was a Phase III, 24-week, double blind, placebo-controlled, parallel-group, randomized, multicentre and multinational trial comparing safinamide versus placebo as add-on therapy to stable doses of levodopa (alone or with other antiparkinson drugs) in patients with mid- to late-stage PD and motor fluctuations. The primary efficacy endpoint was the change from baseline to week 24 in daily ON time with no/non-troublesome dyskinesia as recorded by patients' diaries and the main secondary efficacy endpoint was the reduction in OFF time [8].

Study 018 (NCT01286935) was the long-term extension (up to 24 months) of study 016. The primary endpoint was the mean change from baseline (study 016 start) to study end (two years) in the total Dyskinesia Rating Scale (DRS) score evaluated during ON time. The main secondary efficacy endpoints were changes in ON time (without troublesome dyskinesia) and OFF time [9].

Both protocols and patient materials were approved by Independent Ethics Committees and Health Authorities in all the participating countries. All patients signed an informed consent form and the studies were conducted according to the Declaration of Helsinki.

Patients with depressive symptoms and those already treated with antidepressant were excluded. Treatments with tri-tetracyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs) were not permitted in both studies. Selective serotonin reuptake inhibitors (SSRIs) were allowed at study entry at the lowest therapeutic dose and had to remain stable throughout the trials. The doses of levodopa and other PD treatments were optimized before study start and should remain stable, whenever possible, during the treatment period. However, in both studies the doses could be changed in case of deterioration in motor symptoms or occurrence of adverse events.

Safinamide significantly improved the daily ON time (with no/non-troublesome dyskinesia) and reduced the OFF time maintaining the efficacy up to two years. In the trial 018, the primary endpoint (reduction in dyskinesia) was not met, despite a substantial decrease in DRS score in the safinamide group compared to placebo. Nonetheless, in the subgroup of patients with moderate-severe dyskinesia at baseline, safinamide 100 mg/day significantly improved the Dyskinesia Rating Scale score. The incidence of treatment-emergent adverse events and serious adverse events was similar in safinamide and placebo groups.

Outcome measures

This is a *post-hoc* analysis of the data from studies 016 and 018, evaluating the effects of safinamide 100 mg/day oral tablets versus placebo on the scores of the PDQ-39 "Emotional well-being" domain, the scores of the GRID-HAMD scale and on the proportion of patients reporting the adverse event "depression".

Statistical methods

Comparisons of the mean change from baseline (PDQ-39, GRID-HAMD) for the active-treatment group to placebo were performed using ANCOVA models with treatment group and centre as fixed dummy effects and baseline value as continuous covariate. Results are reported as least square means with associated two-tailed 95% confidence intervals (CIs) and two-tailed *P*-values.

For dichotomous outcome variables (depression adverse events), the absolute number and proportion in percent were tabulated together with two-sided *P*-values for the active-treatment group to placebo which were computed using the Fisher's Exact test.

The intention-to-treat (ITT) patient populations were used for all *post hoc* analyses while the last observation carried forward (LOCF) approach was applied to account for missing data at study termination. SAS software version 9.4 was used for all statistical analyses.

RESULTS

Results of the analyses of the changes from baseline to 6 and 24 months in the PDQ-39 "Emotional well-being" domain in studies 016 and 018 are shown in Fig. 1.

In study 016 the LS mean change from baseline was -5.14 (95% CI: $-7.98, -3.54$) for the safinamide

group and -1.37 (95% CI: $-3.65, +0.31$) for the placebo group.

In study 018 the LS mean change from baseline was -4.56 (95% CI: $-7.40, -3.46$) for the safinamide group and $+0.10$ (95% CI: $-0.07, +0.97$) for the placebo group.

Safinamide 100 mg/day was associated with significantly greater improvements from baseline to 6 months of the score of the PDQ-39 domain "Emotional well-being" compared with placebo: mean difference vs placebo for the changes from baseline -3.77 (95% CI: $-6.49, -1.05$; $p=0.0067$). The improvements observed were maintained in the long-term: mean difference of safinamide vs placebo -4.66 (95% CI $-7.30, -2.02$; $p=0.0006$). Results of the analyses of the changes from baseline to 6 and 24 months in the GRID-HAMD scores in studies 016 and 018 are shown in Fig. 2.

In study 016 the LS mean change from baseline was -1.06 (95% CI: $-1.57, -0.67$) for the safinamide group and -0.49 (95% CI: $-0.97, -0.07$) for the placebo group. In study 018 the LS mean change from baseline was -0.76 (95% CI: $-1.40, -0.59$) for the safinamide group and $+0.11$ (95% CI: $-0.14, +0.95$) for the placebo group.

Safinamide 100 mg/day resulted also in greater improvements in GRID-HAMD scores from baseline, compared with placebo (mean difference vs placebo -0.57 ; 95% CI $-1.13, -0.02$; $p=0.0408$) that were maintained in the long-term (mean difference of

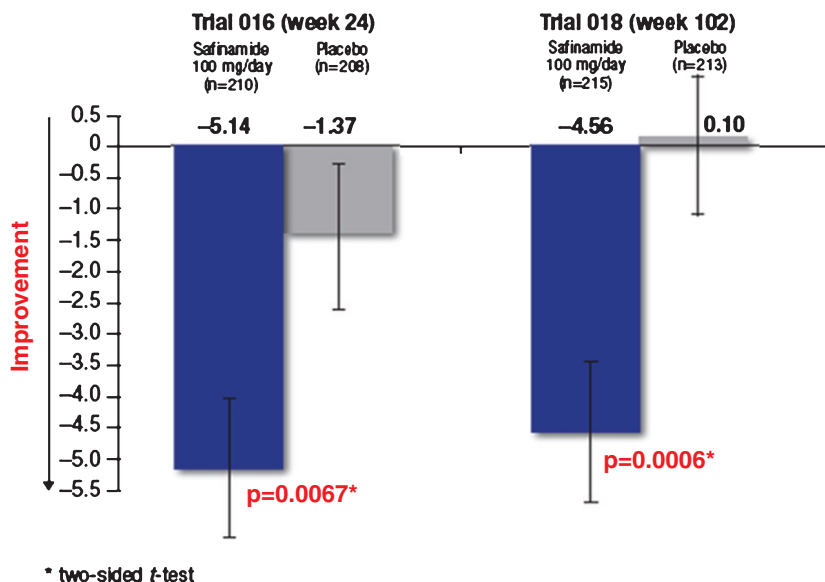


Fig. 1. Trials 016 and 018: changes (LS means \pm SD) in PDQ-39 "Emotional well-being" scores. LS = least squares; SD = standard deviation; PDQ-39 = Parkinson's Disease Questionnaire 39 items.

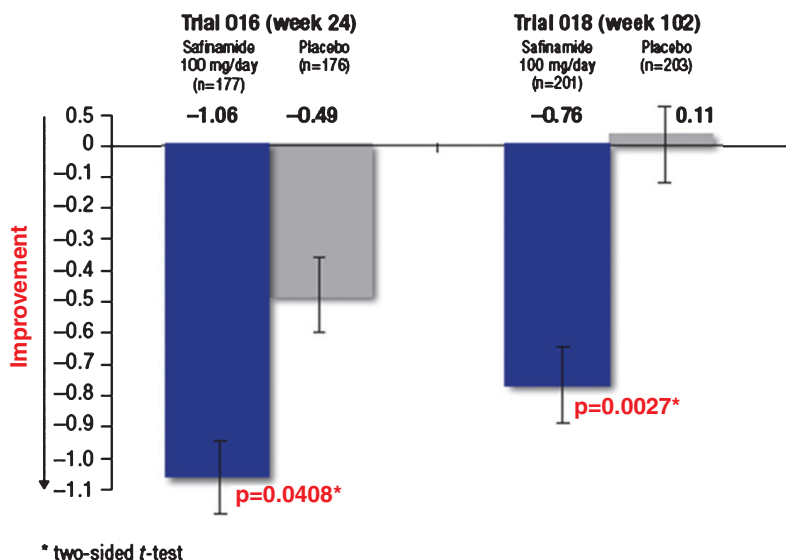


Fig. 2. Trials 016 and 018: changes (LS means \pm SD) in GRID-HAMD scores. LS=least squares; SD=standard deviation; GRID-HAMD=Grid version of the Hamilton Rating Scale for Depression.

Table 1
Trials 016 and 018: proportion of patients reporting depression as adverse event

Trial	Visit	Safinamide 100 mg/day		Placebo		P-value [†]
		N	n (%)	N	n (%)	
016	week 24	224	4 (1.8%)	222	12 (5.4%)	0.0444
018	week 102	180	3 (1.7%)	175	14 (8.0%)	0.0057

[†]Two-sided Fisher's Exact test. N=total number of patients; n (%)=number (percentage) of patients reporting depression as adverse event.

safinamide vs placebo -0.87 ; 95% CI $-1.44, -0.30$; $p=0.0027$).

After 6 months, significantly fewer patients receiving safinamide 100 mg/day reported depression as adverse event compared with those receiving placebo (respectively, 1.8% vs 5.4%, $p=0.0444$). The proportion of patients with depression as adverse event remained stable in the safinamide group over the extension period, while increased in the placebo group (at 24 months, respectively, 1.7% vs 8.0%, $p=0.0057$) (Table 1).

DISCUSSION

PD is a complex neurodegenerative illness with both motor and non-motor symptoms. During the course of the disease, many patients experience some mood disturbances including depression and anxiety, characterized by major disruption in their

mood and emotions [10]. This affective symptomatology is costly from economic, social and personal standpoints.

Even if mood deteriorations can arise as a result of specific parkinsonian symptoms, such as motor fluctuations [11], dysfunction in dopaminergic pathways contributes to mood disorders. Pramipexole, a dopamine-agonist, has been shown to improve depressive symptoms in PD patients [12], and inhibition of monoamine oxidase enzyme increases the levels of biogenic amines (in particular dopamine) in the synaptic cleft, enhancing mood and motivation [13].

Moreover, recent studies have provided strong evidence that glutamate and other neurotransmitters, in addition to monoamines, are involved in the pathophysiology and treatment of mood disorders [14]. Glutamate levels are tightly regulated by sodium-dependent glutamate transporters, which maintain low concentration of the neurotransmitter protecting neuronal cells against excitotoxicity [15].

Blockade of voltage-dependent sodium channels is functionally related to the inhibition of excessive glutamate. Mood stabilizing agents, like valproic acid, lamotrigine and riluzole, modulate glutamate neurotransmission by blocking sodium channels [16].

The add-on of safinamide 100 mg/day to a stable dose of levodopa (alone or in combination with other PD medications) was associated with an improve-

ment in mood in PD patients over two years. During the entire treatment period, significantly fewer patients receiving sildenafil experienced depression as adverse event compared with patients receiving placebo. These results could certainly be a consequence of the improvement in motor symptoms and fluctuations, but this may not be the only explanation. After 2-years treatment, there was an increase in ON time and a decrease in OFF time in both placebo and sildenafil groups, albeit to a greater extent in the sildenafil group [9]. However, the positive effect of treatment on mood scores was substantially greater in the sildenafil group than the placebo group suggesting that the benefit may not be solely due to improved motor symptom control. The mechanism of glutamatergic modulation cannot be ruled out as contributing to the positive effect seen on mood in the sildenafil group.

The notion that the beneficial effect of sildenafil may be explained by both its reversible MAO-B inhibition and by the modulation of glutamatergic hyperactivity, is supported by the finding that rasagiline, which is solely a MAO-B inhibitor, has been found to have no significant effects on depression in PD patients [17].

There are some limitations to be considered in this *post-hoc* analysis: the original trials were not designed to investigate mood as a primary endpoint, and patients with depressive symptoms and those already treated with antidepressant were excluded. These findings should therefore be considered as exploratory, and must be confirmed in larger clinical trials.

Conclusion

Mood disorders have been reported as a frequent comorbidity in PD and can occur in both early and late stages of the pathology. In some cases, they may precede the development of motor fluctuations affecting the quality of life and the daily function of patients [18].

While the treatment paradigms for motor symptoms are well established, there is a lack of clear guidelines pertaining to the cure of the emotional disturbances.

Despite some limitations, the results of these analyses showed that sildenafil 100 mg/day may have a favorable effect on mood that might be explained by the improvement in wearing off and by its modulation of glutamatergic hyperactivity and reversible MAO-B inhibition.

Further investigations are necessary to assess the potential benefits of sildenafil on mood and their clinical relevance.

CONFLICT OF INTEREST

Thomas Müller is member of the Scientific Advisory Board of Zambon SpA. Carlo Cattaneo, Gabriele Lazzeri, Charlotte Keywood, and Ioannis Kottakis are employees at Zambon SpA, the Pharmaceutical Company that is marketing sildenafil in Europe. Erminio Bonizzoni is a consultant statistician for Zambon SpA.

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