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Glutamatergic overactivity in Parkinson's disease with fatigue: open label study on possible impact of safinamide

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Introduction: Fatigue is a disabling a common non-motor symptom of Parkinson's disease (PD) and its pathophysiology is not yet fully elucidated [1-2].

Objective: To test the hypothesis that fatigue in PD may be related to high levels of extracellular glutamate associated with neuroinflammation, a pathological hallmark of PD, by verifying the impact of safinamide, a drug that targets both dopaminergic and glutamatergic systems, in reducing fatigue in fluctuating PD patients.

Methods: The validated version of FSS and PFS-16 were administered to 39 fluctuating PD patients with fatigue before and after a 24-week treatment period with safinamide 100mg as add-on therapy. An assessment of secondary variables such as depression, quality of life, motor and non-motor symptoms was conducted.

Results: After 24 weeks of treatment with safinamide, both FSS ($p<0,001$) and PFS16 ($p=0.02$) scores were significantly lower than at baseline. Moreover, 46,2% and 41% patients scored below the cut off for the presence of fatigue according to FSS and PFS, respectively (responders). At follow up, a significant difference emerged between responders and non-responders in BDI, PSQI (PSDI, mobility, ADL), and NMSS (total score, sleep/fatigue, apathy/mood, urinary). No difference emerged between groups in demographic or clinical characteristics.

Conclusions: Fatigue improved in fluctuating PD and more than 40% of patients were "fatigue-free" after 6-months treatment with safinamide, pointing to a possible role of glutamatergic overactivity in promoting this symptom. Moreover, patients without fatigue at follow up, displayed significant better scores in QOL domains, such as mobility or activities of daily living, although disease severity remained stable, supporting the hypothesis that fatigue is a primary manifestation of PD that could considerably affect QOL. PD-related fatigue is a complex phenomenon, and its pathogenesis is multifactorial [3], possibly involving also non-dopaminergic systems. Drugs that interact with multiple neurotransmission systems, such as safinamide, could be useful in reducing this symptom.

References:

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