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Review article

The role of glutamatergic neurotransmission in the motor and non-motor symptoms in Parkinson's disease: Clinical cases and a review of the literature

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ABSTRACT

Glutamate is the major excitatory neurotransmitter in the central nervous system and, as such, many brain regions, including the basal ganglia, are rich in glutamatergic neurons. The importance of the basal ganglia in the control of voluntary movement has long been recognised, with the effect of dysfunction of the region exemplified by the motor symptoms seen in Parkinson's disease (PD). However, the basal ganglia and the associated glutamatergic system also play a role in the modulation of emotion, nociception and cognition, dysregulation of which result in some of the non-motor symptoms of PD (depression/anxiety, pain and cognitive deficits). Thus, while the treatment of PD has traditionally been approached from the perspective of dopaminergic replacement, using agents such as levodopa and dopamine receptor agonists, the glutamatergic system offers a novel treatment target for the disease. Safinamide has been approved in over 20 countries globally for fluctuating PD as add-on therapy to levodopa regimens for the management of 'off' episodes. The drug has both dopaminergic and non-dopaminergic pharmacological effects, the latter including inhibition of abnormal glutamate release. The effect of safinamide on the glutamatergic system might present some advantages over dopamine-based therapies for PD by providing efficacy for motor (levodopa-induced dyskinesia) as well as non-motor (anxiety, mood disorders, pain) symptoms. In this article, we discuss the potential role of glutamatergic inhibition on these symptoms, using illustrative real-world examples of patients we have treated with safinamide.

1. Introduction

Glutamate is the principal excitatory neurotransmitter in the mammalian central nervous system (CNS). While glutamate is an important component of a healthy CNS, excessive glutamate concentrations or hyperactivity of glutamatergic nerve terminals can lead to neuronal damage and may be involved in the neurodegeneration associated with Parkinson's disease (PD) [1,2].

Glutamate is synthesised from its precursor glutamine, which is released from glial cells and taken into presynaptic terminals of glutamatergic neurons by excitatory amino acid transporters (EAATs). Here, glutaminase converts glutamine to glutamate. Upon neuronal stimulation, glutamate is released into the synaptic cleft and binds to pre- and post-synaptic receptors (Fig. 1) [3]. The effects of glutamate are mediated via activation of two classes of receptor – ionotropic glutamate receptors (ion channel-linked) and metabotropic glutamate (mGlu) receptors (G-protein-linked). Following its binding to receptors, glutamate is removed from the synaptic cleft by EAATs and glia transporters. The glutamate taken up into glial cells is converted back to glutamine by glutamine synthetase [4].

The glutamatergic system is involved in various functions of the healthy brain, including the control of movement via the basal ganglia circuitry in direct and indirect pathways (Fig. 2) [4]. In PD, the degeneration of nigrostriatal dopaminergic neurons causes chain reactions that ultimately result in glutamatergic overstimulation of the basal ganglia output nuclei and substantia nigra pars compacta, leading to motor symptoms/motor complications that characterise the disease [5].

Thus, glutamatergic neurotransmission is a potential focus for pharmacotherapy in PD. This paper describes cases of patients

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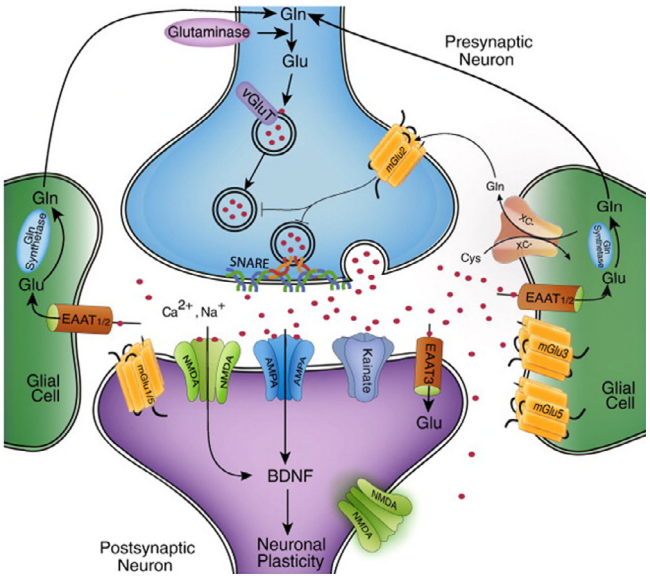

Fig. 1. Schematic representation of a glutamatergic neuronal synapse, showing the synthesis and release of glutamate (Glu), its receptors and modes of deactivation. Glutamine (Gln) is converted to Glu by glutaminase [though glutamate may also be derived from the TCA cycle (not shown)]. Glu is packaged into presynaptic vesicles by vesicular Glu transporter (VGluT) proteins and synaptically released in a voltage-dependent manner through vesicular interactions with SNARE proteins. Synaptically-released Glu is recycled from the extracellular space by excitatory amino acid transporters (EAATs) expressed predominantly on astroglia. In astrocytes, Glu is converted to Gln by Gln synthetase and exported extracellularly to be taken up again by neurons. Additionally, system x-C is a cystine/glutamate antiporter expressed on glia that also contributes to Glu recycling. Glu receptors are present on presynaptic and postsynaptic neurons as well as on glial cells. These include both ionotropic receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], N-methyl-D-aspartate [NMDA] and kainite) and metabotropic receptors (mGluRs). The effect of Glu is determined by the receptor subtype, localisation (synaptic, perisynaptic and extrasynaptic) [3]. BDNF, brain derived neurotrophic factor.

who benefited from the use of safinamide [(S)-(+)-2-[4-(3-fluoro benzyloxy-benzylamino) propionamide], an agent targeting the glutamatergic system. Safinamide is a dual-mechanism drug that acts on both dopaminergic and non-dopaminergic targets, particularly dopaminergic and glutamatergic neurotransmission. It selectively and reversibly inhibits monoamine oxidase-B (MAO-B), thus restoring striatal dopaminergic tone and reduces subthalamic/nigral glutamatergic hyperactivity through use-dependent sodium channel blockade, which prevents calcium channel opening and results in the inhibition of abnormal glutamate release [6,7]. Safinamide is approved in over 20 countries globally, including 14 in the European Union, the United States, and Canada, for the treatment of PD as add-on therapy to levodopa regimens for the management of 'off' episodes (i.e. when levodopa efficacy wanes) [8,9]. In clinical studies, safinamide significantly reduced 'off' time and increased 'on' time without troublesome dyskinesia in patients receiving levodopa who were experiencing wearing-off phenomenon [10–13].

2. Motor symptoms and glutamate

PD is characterised by motor symptoms, including resting tremor, bradykinesia and rigidity in the neck and/or extremities [4]. These symptoms arise primarily as a result of decreased dopaminergic tone due to degeneration of dopamine neurons in the substantia nigra. This is accompanied by glutamate overactivity in projections from the subthalamic nucleus, leading to increased activity in the basal ganglia output nuclei that inhibits the thalamus and, ultimately, reduces facilitatory input to motor areas in the frontal cortex. Consequently, PD patients have difficulty initiating movement, and once initiated, movement is slow and may be difficult to stop [4].

Levodopa is a dopamine precursor used to increase dopaminergic neurotransmission in patients with PD. Yet despite treatment, PD symptoms frequently re-emerge and patients experience fluctuation between mobility and immobility ('on' and 'off' states, respectively) [4]. Such motor fluctuations are a significant problem, since they occur in the majority of patients after a few years of taking levodopa and significantly impact patients' mobility and ability to perform activities of daily living, and they can be difficult to manage [14]. An additional complication of long-term levodopa use is troublesome involuntary movements, referred to as levodopa-induced dyskinesia (LID) [15].

Long-term levodopa treatment is thought to lead to overactivity of the direct pathway and underactivity of the indirect pathway, resulting in cortical excitation and dyskinesia [15]. While the pathophysiology of LID is complex, overactivity of glutamatergic corticostriatal projections is a critical factor in the dysfunction of the direct pathway and therefore the development of LID [15]. These findings suggest that a drug that reduces glutamatergic activity may even have an anti-dyskinetic effect. Indeed, both safinamide and amantadine (an *N*-methyl-D-aspartate [NDMA] receptor antagonist) dose-dependently reduced dyskinesia in a primate model of LID [16]. Further, abnormal cortical facilitation was found in PD patients experiencing LID (n = 20), indicating overactive glutamatergic neurotransmission in the primary motor cortex [17]. The degree of abnormality correlated with the severity of dyskinesia. Two weeks' safinamide treatment normalised cortical facilitation markers. Importantly, a phase III trial findings suggested safinamide may have a positive impact in patients with moderate-to-severe dyskinesia at baseline [11]. The case reported below provides real-world evidence of successful management of motor fluctuations and a reduction in LID after safinamide initiation.

2.1. Case report 1

A 65-year-old male diagnosed with PD 6 years previously (confirmed by Betacid-SPECT, with normal findings on magnetic resonance imaging) had initial symptoms of resting tremor of the legs and right arm, and hyposmia. Levodopa/carbidopa/entacapone 100/25/200 mg/day was initially prescribed. Two years later, transdermal rotigotine patch (4 mg/24 h) was prescribed, but this was associated with the onset of psychosis. Clozapine 12.5 mg/day was then added, resulting in a reduction in hallucinations and good control of tremor (clozapine is used in our hospital as treatment of last resort for therapy-resistant tremor with good effect [18]). One year later, the patient had developed wearing off and end-of-dose dyskinesias while receiving levodopa 400 mg/day. Safinamide was initiated at 50 mg/day and 2 weeks later increased to 100 mg/day. This was associated with good effects on motor fluctuations and dyskinesia, as shown by a decrease in the patient's total Unified Parkinson's Disease Rating Scale (UPDRS) score in the on state from 65 before safinamide to 59 during safinamide. The most marked improvement was seen in UPDRS Part IV, which changed from 9 to 5; other UPDRS subscores showed small decreases (Part II from 19 to 18 and Part III from 36 to 35) or remained unchanged (Part I was 1 before and during safinamide). However, the patient stopped taking safinamide 6 months later because of leg oedema (the patient suspected a relationship and could not be convinced otherwise; he would not consider rotigotine as a possible cause because he did not want to discontinue it). The leg oedema did not resolve after discontinuing safinamide. Rasagiline 1 mg/day was prescribed in place of safinamide, with no reduction of his leg oedema, and the dyskinesia and motor fluctuations re-emerged. At consul-

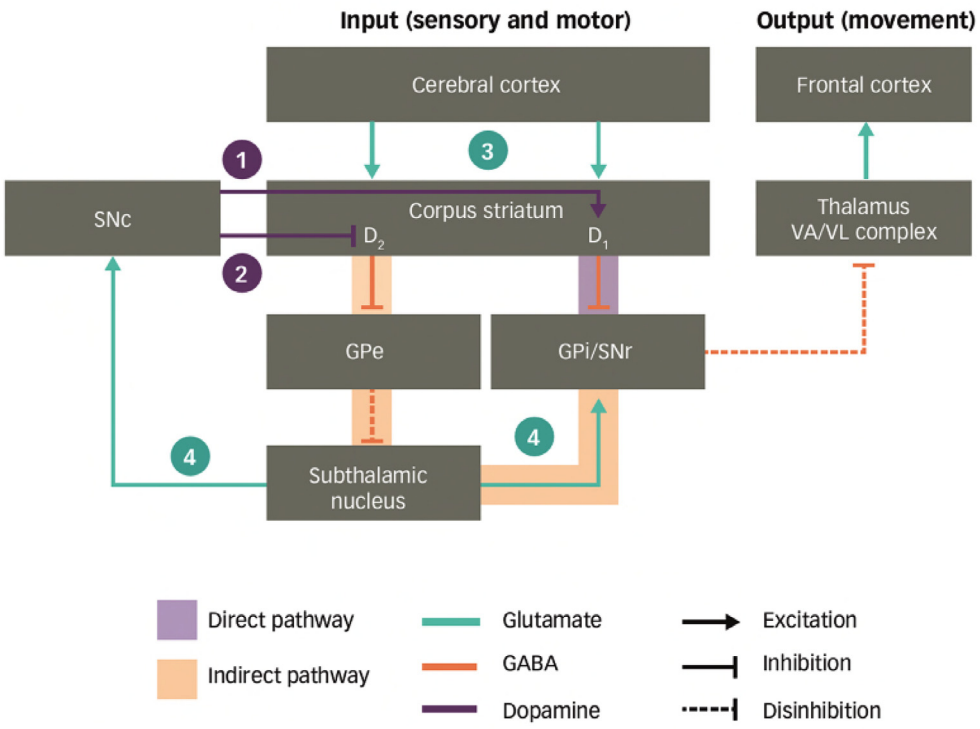

Fig. 2. The role of neurotransmitters in the basal ganglia functional motor circuitry. D1/D2 = dopamine type 1 or 2 receptors expressed in striatal neurons; GABA = gamma-aminobutyric acid; GPe = external globus pallidus; GPi = internal globus pallidus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; VA/VL = ventral anterior/ventral lateral [4].

tation, the patient's UPDRS score was 65. It was not possible to add amantadine because of the previous hallucinations and a QTc of 452 ms. Rasagiline was stopped and safinamide was restarted (50 mg/day for 2 weeks, then 100 mg/day). The higher dosage was also associated with good reductions in dyskinesia and motor fluctuations; his UPDRS score was then 59. The leg oedema remained unchanged.

The above case illustrates the importance of effective motor control for patients with PD. In this patient, safinamide significantly improved motor symptoms, including LID. Although the patient believed safinamide had caused his leg oedema, leading him to discontinue its use, the most likely causative agent was the dopamine agonist rotigotine. Further, the superior effect of safinamide in controlling motor fluctuations compared with rasagiline meant it was reintroduced and became the therapy of choice for this patient.

3. Non-motor symptoms and glutamate

The occurrence of non-motor symptoms, including pain, depression and anxiety, is a significant component of PD. Indeed, patients often refer to non-motor disturbances as being even more distressing and disabling than the classical motor symptoms of PD. Non-motor symptoms can be problematic at all stages of disease development, including early PD, where symptoms such as constipation and loss of smell can have a detrimental impact on daily life [19]. In advanced PD, non-motor complications, such as hallucinations, cognitive impairment, depression and autonomic disturbances, have been described as the predominant problems, occurring in ≥70% of patients [20,21]. Maintenance of QOL is a significant unmet need in PD management, and effective treatment of non-motor symptoms should lead to improved QOL.

3.1. Pain in Parkinson's disease

Pain is prevalent in patients with PD, estimated to affect 68–95% of patients, depending on the type of pain assessed [22]. Pain in PD is classified into five different types: musculoskeletal (felt as an ache around the joints, arms or legs), dystonia-related, radicular or neuropathic, primary/central and akathisia-related [22]. There is a high incidence of depression and reduced QOL in patients with PD who report pain symptoms [23]. Pain in patients with PD is poorly managed and characterised by underuse of analgesics [23].

There is clinical evidence that pain may be a premotor sign in early disease [24]. PD patients may also be predisposed to the development of pain, as evidenced by a low heat pain threshold and abnormal pain-evoked responses in PD patients both with and without pain (whether in an 'on' or 'off' state) [25,26]. This suggests that the increased risk of pain may be linked to PD pathophysiology. The nigrostriatal damage associated with PD may disrupt the usual control by the basal ganglia of cerebral areas that process nociceptive input [27]. Abnormal central nociceptive processing may result from nigral and extra-nigral pathology, involving the cortical areas, brainstem nuclei and spinal cord [28].

While the neurobiology of pain in PD is complex, involving multiple neurotransmitter systems [29] the glutamatergic system is of particular interest because of its role in pathophysiological nociception [2]. The primary afferent neurons that transmit peripheral sensory information and pain signals to the spinal cord are mostly glutamatergic; stimulation results in the excessive release of glutamate from central terminals in the spinal cord and the activation of ionotropic receptors on secondary neurons [2]. Abnormal central nociceptive processing can be targeted using antagonists of ionotropic glutamate receptors, including NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptor antagonists, which decrease nociceptive transmission [30]. However,

these agents have a narrow therapeutic window due to their adverse effects. The development of selective mGluR ligands has allowed researchers to further investigate the role of glutamate in the modulation and control of pain [31] and whether they can potentiate the effect of other drugs (such as antidepressants or opioids) used in neuropathic pain therapy.

Post-hoc analyses of 24-week and 2-year studies of safinamide examined the effect of the drug on concomitant pain treatments and scores on pain-related items of the Parkinson's Disease Questionnaire – 39 (PDQ39) [32,33]. The analyses found significant improvements in 'painful cramps or spasms' and 'unpleasantly hot or cold' scores, and a significant reduction in the number of concomitant pain treatments, with significantly more patients receiving safinamide than placebo not using pain treatments at the end of the treatment periods.

The PAINinPD study [34] directly assessed the effect of safinamide on pain in 13 patients with mild-to-moderate PD, motor fluctuations while receiving levodopa and a history of pain for the preceding 12 weeks who received safinamide 100 mg/day for 12 weeks. Pain was assessed using the King's Parkinson's Disease Pain Scale (KPPS), the Intensity and Interference subscales of the Brief Pain Inventory (BPI), and the Numerical Rating Scale (NRS) [primary outcomes]. Secondary outcomes included effects on the PDQ39, Clinical Global Impression of Change (CGI-C) and UPDRS parts III and IV. Significant effects were seen on all primary outcomes, and on the UPDRS parts III and IV, PDQ39 total and bodily discomfort scores, CGI-C and proportion of pain responders (defined as those patients having a >50% improvement from baseline on the NRS). No correlation was found between the mean change in UPDRS part III-IV and any pain outcome, except for a correlation between change in the UPDRS part IV and the NRS score. These results, along with others from previous post-hoc analyses and meta-analyses [32,33,35], indicate that safinamide mainly directly affects pain in PD and only partially improves pain through an indirect pathway secondary to the improvement in motor complications, probably through its dual mechanism of action. The next case report discusses the use of safinamide in a patient from the PAINinPD study.

3.2. Case report 2

A 68-year-old male first presented 10 years previously with tremor and bradykinesia/rigidity of the right (dominant) hand. Initial treatment was pramipexole prolonged-release (PR) 1.05 mg/day and selegiline 5 mg/day, which provided significant improvement of both tremor and bradykinesia. Over the next 5 years, the clinical picture remained stable with resting tremor localised to the upper right limb and bradykinesia/rigidity to both right upper and lower limbs. At 5 years after treatment initiation, the dosage of pramipexole PR was 1.57 mg/day and of selegiline was 10 mg/day. His bradykinesia/rigidity of the right limbs had worsened and spread to both the left upper and lower limbs. For this reason, levodopa/carbidopa 100/25 mg three times/day was added, which resulted in significant improvements in parkinsonian motor symptoms.

Over the following years, the patient developed motor complications characterised by wearing-off phenomena and nocturnal bradykinesia associated with musculoskeletal, radicular neuropathic and dystonic pain localised to the lumbar back and lower limbs, which was only partially improved by increasing levodopa/-carbidopa 100/25 mg to five times/day.

This patient was then enrolled in the PAINinPD study. The patient was examined in the 'on' phase before and 12 weeks after add-on therapy with safinamide 100 mg/day. A significant improvement between baseline and the final assessment was observed for the following scores: total KPPS (48 vs 24), BPI Intensity (20 vs 14), BPI Interference (53 vs 15), NRS (9 vs 2), PDQ39 bodily discomfort (8 vs 4), UPDRS part III (21 vs 8), UPDRS part IV (9 vs 4), and total PDQ39 (48.72 vs 30.77). No treatment-emergent adverse effects were reported in this patient.

The improvement of motor fluctuations seen in the above patient after safinamide initiation (i.e. reduction of UPDRS part III and IV scores) was as expected. However, independent of the motor improvement, this case confirms the effect of safinamide on pain symptoms. The fact that pain was present and persisted despite the use of dopaminergic agents (pramipexole and levodopa) suggests that the unique anti-glutamatergic properties of safinamide may have been responsible for its effects on this non-motor symptom. Indeed, a recent systematic review and meta-analysis found that safinamide was the most efficacious among all studied therapies for reducing pain in PD [35].

3.3. Anxiety and mood disorders

Depression and anxiety are common in PD, occurring with a prevalence of approximately 17% and 31%, respectively [36,37], although frequencies vary between studies. Mood disorders have a significant negative impact on a patient's prognosis and QOL [38].

Depression and anxiety are thought to develop before dopamine cell loss in the substantia nigra pars compacta, and therefore before motor symptoms are evident. They may originate from brainstem monoamine pathology affecting the locus coeruleus and dorsal raphe nucleus at the early stages of the disease [39,40], whereas depression and anxiety manifesting later in the course of PD probably reflect alterations in multiple neurotransmitter pathways [40]. These changes primarily affect the monoamines (such as dopamine, noradrenaline, and serotonin) [39] but there is increasing evidence from preclinical and clinical studies for the involvement of glutamatergic and GABAergic transmission in depression and anxiety in PD [2].

Proof-of-concept regarding the involvement of the glutamatergic system in mood disorders was based on clinical data with ketamine, an NMDA receptor antagonist found to exert a rapid antidepressant effect in patients with depression [41]. Post-mortem studies provide evidence of glutamate abnormalities in mood disorders [42] and magnetic resonance spectroscopy studies found increased glutamate and/or glutamine levels in the basal ganglia of patients with depression [43,44]. In preclinical models of depression, striatal mGlu5 receptor expression was increased, leading to hyperactivity of mGlu5 receptor signalling [45] and thereby contributing to depression-like symptoms, which are prevented by mGluR5 antagonists [46–48].

Anxiety disorders are also associated with glutamate hyperactivity, especially in excitatory synapses of the amygdala, which like the basal ganglia, form part of the limbic system. Limbic and paralimbic brain structures have been extensively implicated in the mediation of fear and anxiety, and are richly innervated by glutamatergic pyramidal cells [49,50]. Drugs such as NMDA and AMPA receptor antagonists and allosteric mGluR modulators have anxiolytic effects according to studies in animal models and in humans [51].

Clinical studies have shown an effect of safinamide on mood symptoms in patients with PD. For example, Cattaneo et al. [52] performed a post-hoc analysis of two phase III trials of safinamide that focused on mood outcomes. They found significant improvements in mood as determined by the 'emotional well-being' domain of the 39-item Parkinson's disease questionnaire (PDQ39). In addition, real-world clinical practice data in patients with PD and depression showed an improvement in depression symptoms (based on the Hamilton Depression Rating Scale) 1 and 3 months after starting safinamide [53]. In a recent open-label prospective study specifically designed to assess the change in non-motor symptom burden in PD patients after initiating treat-

ment with safinamide, a significant and consistent improvement in mood status was found using the Non-Motor Symptoms Scale, Beck Depression Inventory-II and the emotional wellbeing domain of PDQ-39 [54].

The following real-world case specifically illustrates the effect of safinamide on anxiety.

3.4. Case report 3

A 58-year-old woman was diagnosed with PD after presenting with resting tremor and re-emergent postural tremor in her left hand, bilateral asymmetric rigid-akinetic syndrome predominant on her left side and persistent pain in her left shoulder. Her gait was slow with decreased left arm swing. In addition to motor symptoms, she reported increasing anxiety and mood instability during the previous 2 years, reporting worrying about her temper and medical condition, losing interest in her usual activities and troubles with concentrating. Passage hallucinations were reported when she was directly asked about different perceptual problems.

Rotigotine 4 mg/day was initiated, which improved the patient's anxiety, motivation and shoulder pain; there were clear improvements in her slowness, rigidity and tremor only after the dosage was increased to 8 mg/day.

Three years after starting treatment with rotigotine, and in order to better control her resting tremor, levodopa 150 mg three times daily (450 mg/day) was added, with good control of tremors and improvement of general mobility and hand dexterity. Two years later, the patient reported worsening anxiety, lack of energy and motivation. The pain in her shoulder had returned, and symptoms in her left foot had characteristics of early morning akinesia or an initial manifestation of wearing-off. She reported that her anxiety was the symptom that fluctuated most during the day, and that 15–20 min after taking levodopa, the symptoms improved or dissipated. Despite frequent fatigue and anergia, she had difficulty falling asleep because of inner tension and uncomfortable generalised body sensations. The Neuropsychiatric Fluctuations Scale for PD detected severe inability to relax during 'off' episodes, with associated mild sadness, lack of energy and confidence, and concentration difficulties. No specific neuropsychiatric symptoms were detected during 'on' periods. By using a visual analogue scale (VAS = 0–10) the patient's 'off' episodes were characterised predominantly by anxiety (9/10), fatigue (8/10), pain (6/10) and mild sadness (2/10). During the follow-up after starting safinamide therapy, changes in anxiety, fatigue, anergia, and pain were subsequently assessed by VAS for each symptom.

Safinamide 50 mg/day was initiated. During the first month of treatment, 'off' episode duration decreased from 45 to 60 min to 15 min before the 14:00 h levodopa dose, with no new episodes of fatigue and anergia in the evenings; episodes of early-morning anxiety were still present (VAS 4/10). At 1 month, safinamide was increased to 100 mg/day (taken in the morning), and 2 weeks later, her anxiety had completely resolved, both when she was walking at midday and when waking up (VAS 0/10), and no episodes of foot dystonia appeared. Six months after starting safinamide, the patient remained free of wearing-off phenomena, and the improvements in her anxiety, fatigue, anergia and shoulder pain had had a major impact on her daily life and family relationships.

The above case illustrates the complexity of symptoms seen in patients with PD and the differing impact of each PD symptom for patients. Over her disease course, this patient had presented with both classic motor symptoms and some non-motor symptoms (pain and anxiety). It appears that the latter symptoms, particularly anxiety, most significantly affected her QOL. While the effect of safinamide on anxiety may simply reflect a dopaminergic effect, prior dopamine-based therapy (rotigotine and levodopa) were not able to manage the full constellation of symptoms experienced by the patient. It was only when a non-dopaminergic agent (i.e. the anti-glutamatergic effect of safinamide) was added that all the patient's symptoms were well controlled.

4. Conclusions

Glutamatergic neurotransmission within the basal ganglia is involved in the development of numerous symptoms in patients with PD, from classic motor symptoms to non-motor symptoms, such as anxiety/mood disorders and pain. This neurotransmission is, therefore, an additional target for the pharmacotherapy of PD.

Safinamide is an approved treatment for PD with a unique mechanism of action that includes inhibition of excessive glutamate release when nerve terminals are overactive. While the direct effects of safinamide on glutamate release have only been demonstrated in animal models [6,7,55,56], there is indirect evidence of such an effect in humans [17]. Safinamide as add-on therapy to levodopa reduces 'off' time and increases 'on' time without troublesome dyskinesia [10–13], and may be effective in managing pain and mood disorders. Other PD drugs, including other MAO-B inhibitors, do not share safinamide's anti-glutamatergic effects, which may explain its effectiveness for both motor and non-motor symptoms. It must be noted, however, that the clinically relevant improvements in motor symptoms occurring during safinamide can contribute considerably to the improvement of non-motor symptoms.

Clinical trial data provides robust evidence on efficacy and tolerability in highly selected groups of patients, whereas data from real-world studies and case reports (such as those described here) can provide useful additional information, such as effects on symptoms that may not have been assessed directly in clinical trials. The cases described in this article illustrate clinical scenarios where safinamide is an appropriate choice as add-on treatment in patients with PD.

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Declaration of Competing Interest

Javier Pagonabarraga has received honoraria as Speaker and as member of Advisory Boards for UCB, Abbvie, Bial, Zambon, Allergan and Ipsen. Michele Tinazzi declares no conflict of interest. Carla Caccia is a preclinical consultant for Zambon SpA. Wolfgang Jost has or had speaker and advisor roles for Abbvie, Bial, Desitin, UCB and Zambon.

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Conflicts of interest/financial disclosures

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Informed consent

All patients gave informed written consent for publication.

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