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Hypersexuality associated with safinamide☆

Hipersexualidad en relación con safinamida

Dear Editor:

Hypersexuality is one of the most frequent impulse control disorders (ICD) in Parkinson's disease. A recent systematic review[1] estimates prevalence at 2.5%, reaching 3.5% in other series.[2] This entity is probably underdiagnosed and is of great interest due to its possible social, economic, and legal consequences.

We present the case of a male patient with no relevant history who, at the age of 70, started follow-up at our centre due to idiopathic PD (Hoehn and Yahr stage of 2). He had no history of alcohol consumption, depression, addiction, or ICDs. Six years later, he is receiving treatment with levodopa/carbidopa at 600/300 mg/day; entacapone at 75 mg/day, rasagiline at 1 mg/day, and rotigotine at 8 mg/day. As symptoms were inadequately controlled and the patient presented difficulties adhering to rotigotine, this drug was replaced with extended-release pramipexole at 2.62 mg/day; the patient presented complex visual hallucinations with associated anxiety. Pramipexole was gradually suspended, with visual hallucinations resolving after withdrawal. Thirteen weeks later, we observed worsening of the motor symptoms and onset of cognitive impairment. We decided to substitute rasagiline with safinamide at 50 mg/day, observing a wash-out period of 14 days (and 15 weeks without pramipexole). Four days later, the patient was attended because he insistently and impulsively demanded sex every morning from his wife, who was dependent due to Alzheimer disease. Safinamide was immediately suspended due to this behaviour. Since then, the patient has not shown further hypersexuality or any other ICD episode during the follow-up period of 19 months.

Our patient developed hypersexuality symptoms coinciding in time with the onset of safinamide treatment and resolving after its suspension. His family refused reintroduction of the drug. Application of the Naranjo algorithm for assessing the likelihood of an adverse drug reaction returned a total score of 5 (probable reaction). This means that the adverse effect (which was unexpected, as it is not mentioned in the summary of product characteristics) presents a reasonable temporal relationship with the administration and suspension of the drug and is unlikely to be explained by other causes (concurrent disease or other drugs). The patient had experienced hallucinations in association with pramipexole and was showing the first symptoms of cognitive impairment; these symptoms may be associated with increased vulnerability to adverse drug reactions. The wash-out period of 14 days for rasagiline and 15 weeks for pramipexole makes it unlikely that these drugs favoured the appearance of hypersexuality. Some authors have suggested a dose-dependent association between levodopa in monotherapy and ICDs, but this hypothesis has been questioned due to the small sample sizes used in the studies.[3,4]

To determine the role of MAO-B inhibitors in this adverse effect, we conducted a literature search of articles published on PubMed between 1966 and 25 February 2018, combining the search terms ''hypersexuality'' and ''hypersexual disorders'' with ''selegiline,'' ''rasagiline,'' and ''safinamide'' with the Boolean operator ''AND''. We identified 3 cases associated with selegiline,[5,6] 2 with rasagiline in monotherapy,[7,8] and only one case of hypersexuality associated with safinamide in a patient treated with levodopa/carbidopa and ropinirole, which resolved one week after suspension of safinamide; this adverse drug reaction did not reappear in the 8-month follow-up period reported.[9] MAO-B inhibitors reduce dopamine catabolism and therefore increase dopamine levels in the brain. Although some authors initially suggested mood and libido stimulation due to selegiline metabolism in amphetamine and methamphetamine products as the cause, subsequent studies on rasagiline suggest that the effect is caused by an increase in dopamine. Safinamide, which presents highly selective MAO-B inhibition, would also cause an increase in extracellular dopamine levels in the striatum. It remains unclear whether other mechanisms, such as the role of glutamate in impulsive behaviour[10] or the inhibition of sodium and calcium channels, may play a role in the appearance of hypersexuality.

One study found a statistically significant association between rasagiline and ICDs in patients receiving simultaneous treatment with dopaminergic agonists,[11] as in the case reported with safinamide. To our knowledge, ours is the first case of hypersexuality associated with safinamide in a patient not receiving concomitant treatment with dopaminergic agonists. Based on our experience, we recommend caution in the management of patients with history of hallucinations caused by dopaminergic treatment or

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with cognitive impairment; patients and families should be informed about this rare event to favour early detection.

Conflicts of interest

Alfredo Puy-Núñez has received lecture honoraria from UCB, Teva, and Zambón.

Iria Cabo-López has received lecture honoraria from Bial and Zambón.

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Usefulness of exome sequencing in the study of spastic paraparesis and cerebellar atrophy: de novo mutation of the *KIF1A* gene, a new hope in prognosis☆

Utilidad del exoma en el estudio de la paraparesia espástica y la atrofia cerebelosa: mutación *de novo* en el gen *KIF1A*, una nueva esperanza pronóstica

Dear Editor:

Hereditary spastic paraparesis is a genetically and phenotypically heterogeneous group of neurodegenerative diseases characterised by spasticity and progressive weakness of the lower limbs. Inheritance may be autosomal dominant, autosomal recessive, or X-linked. To date, 72 different types have been described, and clearly defined causal mutations have not been identified for all of them.

We present the case of a 7-year-old boy with intellectual disability, autosomal dominant 9 associated with a heterozygous pathogenic variant of the *kinesin family member 1A (KIF1A)* gene (missense mutation, Chr2:241724479 C>T, exon 7, p.Arg216His).

The patient was first attended at the age of 3 due to a degree of psychomotor retardation: head control at 2.5 months, sitting unaided at 10 months, first two-syllable words at 13-16 months, and walking at 21 months. The patient was already attending school, but displayed slower learning than his peers, with poorer speech (although comprehension was preserved). His clinical history included birth by Caesarean section at 38 weeks of gestation, with an Apgar score of 10/10. Pregnancy and the neonatal period were uneventful (normal results in the endocrine and metabolic tests and normal growth). The parents were non-consanguineous.

Physical examination revealed hyperreflexia in the lower limbs (especially in the right side of the body), with bilateral extensor plantar reflexes and spastic gait. We observed no alterations in motor strength (minimally increased muscle

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