LETTER TO THE EDITOR

To the Editor

Recurrent Impulse Control Disorder Associated with Rasagiline Treatment of Parkinson's Disease

Keywords: Parkinson disease, Impulse control disorders, Rasagiline, Pathological gambling, Ropinirole

A 42-year-old male was diagnosed with Parkinson's disease on the basis of a right-sided resting tremor, rigidity, and bradykinesia. The patient was a lifetime nonsmoker and had no history of gambling or alcoholism. As part of the Rasagiline Mesylate [TVP-1012] in Early Monotherapy for Parkinson's Disease Outpatients study, he was started on rasagiline 1 mg 1 year after his diagnosis. At the age of 44, because of increasing tremor and bradykinesia, ropinirole was introduced in a dose of 2 mg two times per day and increased over the next 7 years to 5 mg three times per day. Levodopa/carbidopa 100/25 mg three times per day was introduced at the age of 48 years (6 years into the disease course) and progressively increased to six tablets per day. At 52 years of age, the patient experienced pathological gambling, leading to a discontinuation of ropinirole. Although the gambling ceased, motor deterioration led to an increase of levodopa/carbidopa 100/25 mg to 10 tablets per day and remained stable thereafter. At the age of 56, the patient experienced a relapse of pathological gambling behaviour. At any opportunity, he would use online applications and websites, requiring that his wife hide all electronic devices. She described his behaviour as "focused and driven" towards the gambling, losing more than $10,000 in one sitting. His personality also changed, becoming more "aggressive, terse and irritable." Over the ensuing 11 months, the patient lost $180,000 and required refinancing of his home. Nonpharmacological measures were unsuccessful in reducing the gambling. Subsequently, rasagiline was discontinued 11 months after the start of the behaviours. Within 1 week of the discontinuation of the medication, the gambling and associated behaviours ceased and the patient's behaviour returned to his baseline with no adverse effect on motor function.

Impulse control disorders (ICDs) are a common complication of dopaminergic therapy. Studies show that about 14% of patients will develop them throughout their course of treatment. Dopamine agonists are the most common causative class of medication, with about 25% of patients treated with a minimal dose experiencing them.[1] Monoamine oxidase type B inhibitors such as selegiline and rasagiline are irreversible inhibitors of an enzyme involved in degradation of dopamine, thereby enhancing its synaptic availability. This class of medication is used as an adjunctive or initial treatment in Parkinson's disease and its heterogeneous response on clinical symptoms has been linked to polymorphisms in the dopamine D2 receptor gene.[2] Monoamine oxidase type B inhibitors have not been reliably linked to ICDs in large studies. One study showed a significant 2.12 odds ratio of ICDs in patients exposed to rasagiline versus unexposed in a multivariate analysis.[3] The significance was lost once selegiline treated patients were included in the analysis. Another study showed an odds ratio of 3.74 of having at least one ICD in a subgroup analysis, but the number of treated patients was low.[4]

We were able to find three cases in the literature describing ICDs in rasagiline-treated patients, two with hypersexuality and one with pathological gambling.[5,6] In all of these cases, the addition of rasagiline caused an onset of ICDs within 3 to 6 weeks. In one case, the patient was concomitantly on pramipexole; the outcome of that case was not reported.[5] Our case highlights the recurrence of ICDs in a patient in whom symptoms had previously remitted on withdrawal of a dopamine agonist 4 years earlier, despite rasagiline treatment and higher doses of levodopa. Subsequently, ICDs recurred without changes in ongoing antiparkinson medication; these completely resolved following the withdrawal of rasagiline. In addition to highlighting the potential role of rasagiline in contributing to ICDs, our case also highlights both that no medication change is necessary to trigger ICDs in an appropriately predisposed patient and that any medications affecting dopamine homeostasis, whether agonists or inhibitors of dopamine degradation, can trigger ICDs. An explanation for the delayed recurrence of the ICD may relate to disease progression and altered homeostasis in the limbic striatum. With constant synaptic dopamine levels, postsynaptic receptors may become more sensitive and trigger the cascade of altered reward, behaviour inhibition loss, and increased impulsivity. Indeed, post-synaptic dopamine receptor abnormalities exist in Parkinson's disease and there is evidence that the disease itself may predispose patients to impulsive and risk taking behaviour.[7] Where genetic polymorphisms may modulate positive motor response to rasagiline, it is conceivable that heterogeneity in adverse effects may be influenced by such polymorphisms. Furthermore, it is possible that the remote previous exposure to a dopamine agonist, combined with environmental, social, and psychological factors, may have somehow primed the patient to develop the pathological gambling and thereby lowered the threshold for its subsequent recurrence in the absence of further dopamine agonist exposure.

ICD management can be very challenging. First and foremost, it requires the discontinuation of offending agent. When the latter is a dopamine agonist, there is a qualitative risk that motor control and behavior (e.g. apathy, dopamine agonist withdrawal syndrome) may be adversely affected.[8] Few adjunctive pharmacologic options exist for adequate control of ICDs. Therefore, recognition of rare precipitants of ICDs, including ongoing rasagiline treatment, is necessary to prevent the social, financial, and personal toll that these behaviours can cause. Finally, our case supports a view that ICDs are a chronic condition that may manifest relapses on stable dopaminergic medication doses and despite discontinuation of the most common offending agents and therefore require ongoing monitoring by the physician, patient, and family.

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