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# Varenicline-induced grand mal seizure

Varenicline is a new drug approved by the FDA in 2006 for smoking cessation. It was developed from cytosine, a natural alkaloid compound. It acts as a partial agonist/antagonist for the alpha 4 beta 2 nicotinic acetylcholine receptor subtype. This receptor mediates the primary effects of nicotine in the brain activating the dopaminergic reward pathway in the mesolimbic system. The agonistic activity of varenicline at the nicotine-receptor determines a low to moderate dopamine level of stimulation hence reducing cravings and withdrawal symptoms (Coe *et al*., 2005). In addition, this drug acts as an antagonist at nicotine receptors, inhibiting the dopamine increase, thus decreasing the effects of smoking satisfaction often associated with nicotine use (Rollema *et al*., 2007). In a pooled analysis of two phase III trials, the most commonly reported adverse events with varenicline were nausea (28.8%), insomnia (14.2%), and headache (14.2%) (Garrison and Dugan, 2009). Several cases have been published reporting serious psychiatric side effects such as hallucinations, bradyphrenia, euphoric mood, psychotic disorders and suicidal ideation (Freedman, 2007). We report one patient with a generalised tonic-clonic seizure which occurred 12 weeks after the intake of this drug.

This 51-year-old man had a first generalised tonic-clonic seizure during wakefulness on March 2009 upon treatment with varenicline during the withdrawal phase at 1 mg/d. The drug was started at 1 mg/d for one week, followed by an increase to 2 mg/d for 10 weeks and reduced to 1 mg/d. The clinical examination was normal. EEG monitoring on awakening and brain MRI performed just after the seizure were normal. There was no medical history of epilepsy or febrile seizures. The patient had been HIV positive since 1994 but with no immunodeficiency syndrome. He was treated for four years with ritonavir (100 mg twice daily), fosamprenavir (700 mg twice daily) and the combination of tenofovir/emtricitab (200/245 mg once daily). In the family history, he reported a nephew with one seizure. Varenicline was suspected as the possible triggering factor for the seizure occurrence together with partial sleep deprivation the night before (he awoke at 3 a.m.). Varenicline was stopped immediately with no recurrence of seizure at 18 months follow-up. Another brain MRI scan and video-EEG recording during sleep were performed which were normal.

Serious neuropsychiatric events have been reported in patients taking varenicline and all patients should be observed for these symptoms including changes in behaviour, depressed mood, and suicidal ideation. The Australian Bulletin of adverse drug reactions (2008) has reported 15 cases of varenicline-induced seizures (Australian Bulletin, 2008). In this reported case study, the association between varenicline use and seizure occurrence was unlikely to be incidental due to the lack of personal medical history of epilepsy, the normal examinations (EEG and MRI) and the favourable long-term outcome. The seizure-inducing effect of the drug may have been promoted by the partial sleep deprivation the night before, but sleep deprivation alone cannot be considered responsible. Bennett *et al*. (1969) reported no EEG abnormalities in 118 healthy flying personnel following 24-72 hours of sleep deprivation. Among the antiretroviral drugs, convulsions have been very rarely reported in patients taking ritonavir in phase II/III studies but the relationship is uncertain (Rxlist.com). Ritonavir is not implicated in our case because this drug was taken for four years prior to the seizure and at a very low dosage (200 mg/day), almost 1/6 of the recommended dosage (1,200 mg/day). Moreover, once varenicline was stopped, no more seizures occurred while the patient was still taking ritonavir.

We believe that seizures should be considered as a potential side effect of varenicline and the drug should be prescribed with caution, in particular to those patients with a medical history of epilepsy or presenting risk factors for epilepsy.

## Disclosure

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