Brivaracetam-Induced Behavioral Changes

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Brivaracetam is structurally related to levetiracetam and has a similar mechanism of action by binding to SV_2A but with approximately 20-fold higher affinity and greater selectivity. It has good oral bioavailability, low protein binding, and short half-life. It is available in oral and intravenous (IV) formulations. Its clearance is increased by enzyme inducers. The commonly reported adverse experiences occurring more often than placebo were somnolence, dizziness, fatigue, and irritability. It has been approved by the Food and Drug Administration (FDA) for treatment of partial onset seizures.[1] Overall, 13% of brivaracetam-treated patients across the 50 to 200 mg/d doses experienced a psychiatric adverse reaction compared with 8% of placebo-treated patients, and 1.7% of brivaracetam-treated patients discontinued the study medication due to a psychiatric adverse reaction compared with 1.3% of placebo-treated patients.[2,3] Retrospective review studies of brivaracetam treatment have been published in Germany. Psychiatric treatment-emergent adverse effects included irritability, aggression, depression, and psychosis.[4]

Although brivaracetam is recently being adopted by most physicians for treating epilepsy, not many cases of behavioral side effects have been reported. In our letter, we are reporting six cases where patients developed behavioral changes after the administration of brivaracetam.

The cases have been reported to the best of our knowledge. *Brivaracetam* (UCB 34714) is chemically related to *levetiracetam*. It possesses a greater than 10-fold *binding affinity* for the *synaptic vesicle* protein 2A (SV2A) than that of levetiracetam and also shows an ability to inhibit Na^+ channels. Single oral doses of brivaracetam, up to 1,000 mg and repeated oral doses up to 800 mg/d twice a day, were well tolerated in healthy volunteers and in patients. Treatment-emergent adverse events were mostly central nervous system (CNS) related and transient, and their intensity was usually mild or moderate. Repeated intake of the drug reduced their incidence.[5] In their literature review, Li et al suggested that behavior disturbances are less common following brivaracetam treatment compared with levetiracetam.[6] Subramonian and Farrah, in their study on the overall psychiatric or behavioral adverse effects of levetiracetam, suggested an improvement in symptoms with brivaracetam treatment.[7] The FDA has warned about the possible adverse effects of brivaracetam, namely, irritability, depression, aggressive behavior, and anxiety. Behavioral side effects of the drug have been reported. These include irritability, aggression, and psychosis. We have observed changes in a wide range of patients and they did not have anything in common with respect to their history, diagnosis, preexisting morbidity, or organicity. All the blood investigations yielded results within the normal range, and there were no focal deficits during examination. EEG, video EEG, and ambulatory EEG were conducted to exclude the possibility of seizure-related behavioral variants. The cases are mentioned in ►**Table 1**.

The drug was initially well tolerated, but over time, these symptoms emerged and progressively worsened. They were diagnosed after ruling out common medical causes. Fortunately, all these symptoms were reversible. Upon discontinuing brivaracetam, the symptoms vanished within a week, and a swift return to the normal behavioral state was observed.

Brivaracetam has been claimed to cause very little behavioral changes. Because of this, it is being preferred over levetiracetam and other antiepileptics. Behavior changes from brivaracetam are less commonly reported, but we observed marked changes in behavior and with greater intensity as compared to other drugs. These result in distress to both the patient and the family. In some cases, inpatient treatment was required. In conclusion, it is essential to carry

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Table 1. List of cases

Case Age/ gender	Diagnosis	Electroencephalogram (EEG)	Neuroimaging	Drug history	Neuropsychiatric manifestations
Case I 15 y/F	Temporal lobe epilepsy	Left temporal spike with slow wave discharge	Left mesial temporal lobe sclerosis on magnetic resonance imaging (MRI)	Brivaracetam and oxcarbazepine	After 45 d, extreme aggression was reported
Case II 22 y/M	Temporal lobe epilepsy	Right temporal spike with sharp wave discharge	Right lateral temporal lobe sclerosis on MRI	Brivaracetam and oxcarbazepine	After 30 d, extreme fearfulness and aggression were reported
Case III 65 y/M	Idiopathic generalized epilepsy	Generalized intermittent slow wave epileptiform discharge	Normal study on MRI	Sodium valproate, oxcarbazepine, phenytoin, and brivaracetam	After 3 mo, irritability and aggression were reported
Case IV 25 y/M	Posttraumatic epilepsy	Intermittent generalized slow wave discharge	Noncontrast computed tomography (NCCT) of the head showed ill-defined hypodensities in the left frontotemporal lobe suggestive of resolving contusions	Brivaracetam	After 30 d, irritability and aggression were reported
Case V 19 y/M	Idiopathic generalized epilepsy	Polyspikes and polyspike A wave	Normal study on MRI	Brivaracetam	After 60 d, verbal aggression was reported
Case VI 22 y/M	Temporal lobe epilepsy	Left-sided temporal spike	Left temporal lobe sclerosis on MRI	Brivaracetam	After 60 d, bouts of impulsive acts and aggression were reported

out further studies on a larger scale to assess the adverse effect of brivaracetam.

Conflict of Interest
None declared.

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