Levetiracetam—Through a Psychiatric Prism

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Levetiracetam use by neurologists is currently rife for its broad therapeutic potential in epilepsy and obvious "somatic" tolerability. Nonetheless, its use is fraught with a host of psychiatric and behavioral sequelae that especially perplex child psychiatrists. This report sheds some light on the psychiatric sequelae associated with levetiracetam while highlighting clinical correlates and management issues.

Case Report

A 10-year-old Kuwaiti boy previously diagnosed with low-functioning autism spectrum disorder and comorbid epilepsy recently experienced an increase in seizure activity. He was taking valproate 1,000 mg/d and risperidone 1 mL/d for associated challenging behaviors with good therapeutic response. He had recently been seen by a neurologist who suggested add-on levetiracetam 500 mg/d. Although tighter antiepileptic control was achieved, he soon experienced behavioral decompensation with pronounced psychomotor agitation, self-injurious behavior, and heteroaggression toward his key caregiver. No medical or environmental cause of this behavioral dyscontrol could be detected apart from the new prescription.

An increase of risperidone to 1.5 mL/d (in 2 divided doses) did not help and instead induced bilateral acral tremors and transaminitis (alanine aminotransferase: 130 U). Aripiprazole 10 mg (cross-titrated against risperidone) for 4 weeks failed to control his behavior, although his liver function test results normalized and tremors markedly diminished. Consultation with the neurologist to switch levetiracetam to topiramate 200 mg/d over another 4 weeks resulted in adequate seizure control. He was maintained on aripiprazole with remarkable behavioral control.

The patient's delayed behavioral response to aripiprazole over 6 weeks until levetiracetam was discontinued indicates that levetiracetam was the culprit agent. Six months have elapsed at writing of this report, and the child is maintained well on aripiprazole, valproate, and topiramate with excellent tolerability.

Discussion

Levetiracetam is a broad-spectrum antiepileptic drug with demonstrable efficacy and safety. It decreases high-voltage N-type Ca^{2+} channel current and reduces effects of zinc and β-carbolines at γ-aminobutyric acid–A and glycine receptors.[1]

Apart from legitimate neurologic indications, levetiracetam has been trialed to address a multitude of psychiatric disorders given its unique mode of action. Use in such indications is largely driven by open-label trials wherein levetiracetam was shown to have a positive efficacy signal in social anxiety disorder, panic disorder, refractory posttraumatic stress disorder, and treatment-resistant bipolar disorder. It has also been successfully trialed for Tourette syndrome in 1 randomized controlled trial (RCT) and tardive dyskinesia in another.[1] In relation to autism, mixed results were obtained. An earlier RCT[2] was negative wherein levetiracetam did not improve behavioral disturbances of autism. A more recent single (physician)–blinded prospective RCT[3] demonstrated a decrease in subclinical epileptiform discharges with resultant cognitive function and behavioral gains.

Despite this therapeutic potential and benign somatic side effect profile, levetiracetam use is associated with psychiatric sequelae at rates almost twice that of placebo, which has challenged psychiatrists since the clinical use of levetiracetam by neurologists is currently a first-line option.[4] In 1 study,[5] the trend of prescribing levetiracetam in the child and adolescent population with epilepsy increased from 5% to 32%.

The most commonly reported side effects of levetiracetam are agitation and aggression (1%–10%). Emotional lability, psychosis, and suicidality have also been reported. It has been noted that some patients subsequently stopped taking the medication because of these side effects.[4] Delirium in association with levetiracetam has also been reported in the literature [6]

Psychiatric sequelae related to levetiracetam have not been shown to be dose-dependent in the majority of cases.[7] Rapidity of titration schedule has been recognized as a risk factor for side effects, which are commonly noted in the first 4 weeks of treatment. Psychiatric sequelae have been linked to genetic variation in dopamine signaling in epileptic patients.[7]

Clinical correlates have been recognized and include the pediatric population (37% vs 13% in adults), history of status epilepticus, history of febrile seizures, intellectual disability, organicity, and, albeit less importantly, a positive past psychiatric history.[8] If behavioral decompensation occurs, levetiracetam should be discontinued. If the neurologist deems that discontinuation is not feasible, add-on lamotrigine might be helpful.[9] It behooves clinicians who prescribe levetiracetam to be vigilant and mindful of these behavioral side effects that might contribute to drug discontinuation.

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