Unless we develop some form of evidence-based approach, we will remain at risk of myth building and recycle a 21st century version of Freud's maligned "primal horde."

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VALPROATE-INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

To the Editor:

We report the case of a child with intermittent explosive disorder, treated with sequential polypharmacy including valproate (VPA), who experienced hyperammonemia with an abnormal EEG suggestive of VPA-related hyperammonemic encephalopathy (VHE). This is the first reported instance of VHE in a pediatric psychiatric setting.

VPA is a commonly prescribed antiepileptic. In this setting, hyperammonemia and VHE have been documented in both adults (Verrotti et al., 2002) and children (Verrotti et al., 1999). Several mechanisms have been proposed, but the etiology appears multifactorial and is incompletely understood. There is evidence that polypharmacy, carnitine deficiency, or congenital urea cycle abnormalities may predispose to VHE (Verrotti et al., 2002).

Valproate-related encephalopathy has received less attention among psychiatrists than among neurologists. A recent study investigating the efficacy of VPA for childhood bipolar disorder suggests that the side effects of VPA in children with bipolar disorder are similar to those of adults with bipolar disorder (Kowatch et al., 2003). Notably, though, VHE in psychiatric patients has been reported only in adults (Barrueto and Hack, 2001; Elgudin et al., 2003).

In light of this dearth of information regarding VHE in juveniles with psychiatric disorders, we report the case of M., a 9-year-old adopted boy with intermittent explosive disorder, hospitalized for increasing aggressive behavior, including biting and throwing furniture both at home and school. A neurological evaluation before admission ruled out seizures as the cause of his outbursts. His prenatal history was unknown due to his adoptive status, although intrauterine substance exposure was suspected. His IQ was measured at 70 by the Wechsler series.

M.'s hospital course was marked by severe maladaptive behaviors, high levels of noncompliance, and physical aggression unresponsive to behavioral therapy. Daily medication management was begun to improve mood stability. At admission, his medications included 1,500 mg/day VPA (begun 7 months earlier). A serum VPA measured at admission showed slight elevation at 107 μg/mL, prompting a decrease in VPA to 1,000 mg. Repeat serum VPA measurement showed a drop to 99 μg/mL. Seroquel was added and titrated to 125 mg b.i.d. to target aggression.

One week after admission, M. was noted to be increasingly irritable and oppositional, demonstrating less participation in milieu activities, inability to follow through with commands, and an increase in the number of violent outbursts requiring seclusion. A typical outburst began with M. displaying very low frustration tolerance when unable to get his way. Redirection by staff would fail, and he would be given a "time out" in an open hallway. Within seconds, M. would escalate into a violent tantrum, hitting and kicking the adult escort. Recurrent episodes such as this resulted in seclusion and prompted the addition of 300 mg lithium b.i.d. for increased mood stability. However, no significant improvement was noted. In fact, M. was reportedly more irritable and confused. During seclusion, he would repeatedly bang his head or body against the door for several minutes. Medication toxicity was considered as a possible etiology of his near-delirious behavior, and VPA was further reduced from 1,000 to 500 mg/day. Appropriate laboratory tests were performed, including serum ammonia levels. Lithium levels were normal at 0.9 mmol//L, VPA slightly elevated at 113 μg/mL, and ammonia significantly elevated at 127 μg/dL. Liver function tests were normal with aspartate aminotransferase at 31 U/L and alanine aminotransferase at 14 U/L, suggesting hyperammonemia without hepatic injury. VPA was discontinued immediately.

Concurrently, M. developed a mild upper extremity tremor, suggesting an adverse effect secondary to lithium. However, in the setting of the recently diagnosed hyperammonemia, possible seizures or encephalopathy were considered as a primary etiology. An EEG obtained the day that VPA was discontinued showed symmetrical 5- to 6-Hz waves, with no evidence of focal slowing or epileptiform abnormalities, consistent with a diffuse encephalopathy. This was attributed to the hyperammonemia, which has

been implicated in encephalopathy via inhibition of glutamate uptake by astrocytes, triggering neuronal injury (Verrotti et al., 2002). Lithium was discontinued, and the tremor resolved. Serum ammonia normalized 4 days after discontinuation of VPA, at 55 μg/dL. Liver function levels remained baseline. Due to persistent severe intermittent aggressive behavior, chlorpromazine was titrated to 75 mg/day in three divided doses, with partial efficacy and two reported episodes of mild dystonia. Subsequently, 5 mg diazepam t.i.d. was added, resulting in a decrement of closed seclusion events by approximately 70% and improved dystonia. Two weeks before discharge, 150 mg carbamazepine b.i.d. was added for additional mood stabilization. His discharge diagnoses were intermittent explosive disorder, oppositional defiant disorder, and borderline mental retardation.

This case urges caution when assessing the etiology of worsening aggression in a child treated with VPA. Valproate-related encephalopathy is more common with polypharmacy and with associated liver malfunction (Verrotti et al., 1999). Manifestations of VHE in our patient included increased violence and diffusely symmetrical 5- to 6-Hz waves on EEG without evidence of liver dysfunction. In summary, we suggest that child psychiatrists consider VPA-related encephalopathy when challenged by a patient whose aggression appears refractory to VPA treatment and that serum ammonia levels and a baseline EEG be considered as part of a comprehensive workup in the course of acute medication management.

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ZALEPLON OVERDOSE ASSOCIATED WITH SLEEPWALKING AND COMPLEX BEHAVIOR

To the Editor:

Zaleplon is a nonbenzodiazepine hypnotic with a short half-life, established efficacy, and a reportedly benign side effect profile (Israel and Kramer, 2002). We report the case of an adolescent who developed an episode of sleepwalking with potentially dangerous complex behavior after an overdose of zaleplon.

P. was a 14-year-old boy treated in our clinic for major depressive disorder, moderate. He responded to 20 mg/day paroxetine with full remission of depressive symptoms except insomnia. Diphenhydramine and trazodone in doses up to 50 and 100 mg, respectively, did not improve sleep and caused excessive daytime drowsiness. He then responded well to 10 mg zaleplon. Three weeks after starting zaleplon, he took two extra tablets of zaleplon from his medication bottle stored in his parents' medicine cabinet to "get better sleep." Several hours later, his parents were awakened by noises and the smell of gasoline coming from their garage. They investigated and found their son spilling a significant amount of gasoline on the garage floor while trying to fill the family lawn mower in an apparent attempt to mow the lawn. His parents noted that he had moderately slurred speech, was slow in responding to questions, was moderately confused, and was uncoordinated and moving slowly. His parents found the empty bottle of zaleplon in their medicine cabinet. Judging by the prescription date, it should have contained 20 tablets. They then took their son to the emergency department.

On arrival in the emergency department, P. appeared confused and sleepy. Physical examination, electrolytes, complete blood count, liver function tests, and electrocardiogram revealed no abnormalities. He remained in the hospital 8 hours and awakened without recollection of his activities after ingesting the two extra zaleplon tablets. Mental status examinations 1 week and 1 month later were normal, and P. consistently denied intentional overdose on zaleplon.

New onset of somnambulism has been reported after prolonged sleep deprivation (Joncas et al., 2002), but P. did not have a history of sleep deprivation. One case study described zaleplon-induced sleepwalking in a person without previous somnambulism (Harazin and Berigan, 1999). This study referenced two case reports in which zaleplon-induced sleepwalking in persons with a history of somnambulism. P. had no history of sleepwalking. Somnambulistic individuals are reported to experience more disturbed sleep than controls during the first nonrapid eye movement/rapid eye movement sleep cycle (Guilleminault et al., 2001). We did not