

MUCH ADO ABOUT SOMETHING OR NOTHING: BEHAVIORAL PROBLEMS WITH LEVETIRACETAM USE IN EPILEPSY PATIENTS

Discontinuation of Levetiracetam because of Behavioral Side Effects: A Case-Control Study

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BACKGROUND: Levetiracetam (LEV) is a recently approved anticonvulsant (AED) with proven efficacy and safety in the treatment of partial seizures. LEV may cause behavioral abnormalities that can be severe and require discontinuation of this drug. Risk factors for discontinuing LEV have not been established.

OBJECTIVE: To determine incidence of behavioral abnormalities severe enough to require discontinuation of LEV and to identify risk factors for such behavioral abnormalities.

METHODS: All patients treated with LEV at MINCEP between January 2000 and February 2002 constituted the study population ($n = 553$). Patients who had discontinued LEV for behavioral reasons were selected as index cases. Case controls were patients starting LEV immediately after the index case. Potential risk factors for LEV discontinuation included age, gender, cognitive function, history of psychiatric diagnosis, epilepsy syndrome, number of AEDs, titration rate, maximal dose of LEV, and LEV level at maximal dose.

RESULTS: Thirty-eight (6.9%) patients discontinued LEV because of behavioral abnormalities. Variables associated with LEV discontinuation included faster titration rate to maximal dose, history of a psychiatric disorder, and diagnosis of symptomatic generalized epilepsy. Patients who discontinued LEV owing to behavioral reasons had significantly lower maximal LEV doses than did controls.

CONCLUSIONS: This study identified variables associated with discontinuation of LEV due to behavioral abnormalities. Slower titration of LEV should be considered in those patients at higher risk of discontinuing LEV for behavioral reasons.

COMMENTARY

White et al. report on a retrospective study of patients at a single, large center who discontinued levetiracetam (LEV) use because of behavioral side effects. Control cases were chosen sequentially from the series. Results suggest that three factors contributed significantly to the behavioral abnormalities that lead to treatment withdrawal: (a) fast titration rate; (b) previous psychiatric history; and (c) generalized symptomatic epilepsy. Although retrospective analysis of the group limits interpretation of the data, it more accurately reflects experience in clinical practice and indicates a higher incidence (6.9%) of behavioral abnormalities than previously reported (see following discussion). Some questions still remain unanswered: Would the risk be decreased, resolved, or eliminated by an adjustment in titration rate or by a change in co-medication dose? Was there a history of behavioral or psychiatric adverse events with prior AED introduction? Did behaviors worsen as seizures were controlled?

Five prospective trials (1–5) reported behavioral and psychiatric experiences in adults administered LEV, with variable outcomes. Harden (6) combined the collective experience of the controlled, preapproval trial data and reports an overall rate of depression in 4.0% of patients, compared with a placebo incidence of 2.3% and nervousness in 3.9% of patients, compared with 1.8% placebo. Severe depression occurred in 0.7%, and personality disorder issues were reported in 0.5%. Data from the report of Cerighino et al. indicate that behavioral abnormalities occurred at a rate of <10% with doses of 1,000 mg/d and 3,000 mg/d (1). The pivotal trial of Shorvon et al. (2) reports an incidence rate of depression of 1.9% (1,000 mg/d) to 5.7% (2,000 mg/d), compared with a placebo rate of 2.7%. Ben-Menachem and Falter (3) noted no adverse behavioral events other than somnolence and asthenia in the add-on phase of a monotherapy conversion trial. Betts et al. (4) found that somnolence was the most common adverse experience, leading to withdrawal in 11% of 80 patients enrolled in the active arm of the trial and occurring in 26% to 45% overall. They reported one patient with hallucination, among the 86 patients in the open phase of the protocol. Bergey et al. (5) described an adverse-events incidence rate of 13% to 29%, which were “mostly neuropsychiatric or somnolence” at titration rates of 250 mg twice daily versus 500 mg twice daily regimens, respectively.

Retrospective reviews of clinical experience of adults since the approval of LEV (6–8) reported generally higher incidences of adverse effects. Asconape et al. (7) reported results from an experience of 101 patients, with 31% demonstrating behavioral abnormalities, 29% irritability, 10% aggression, and 5% hallucinations. Only 6.9% of the group was rated as having symptoms severe enough to require LEV discontinuation. One psychosis was found in this group. Mild or moderate behavioral disturbances, not requiring discontinuation of LEV, were present in 13% of the patients. A history of behavioral disturbance occurred in 61%, and mental retardation, in 29% of individuals who experienced LEV adverse behavioral events, compared with prior behavioral disturbance in 44% and mental retardation in 15.7% of those patients who had no LEV-associated behavioral change. Korby et al. (8) reported on 50 patients who converted to monotherapy. They had a 13% incidence of adverse behavioral events, which did not correlate with LEV dosage, serum LEV level, IQ, or history of behavioral events or psychiatric diagnoses. A subgroup with depression and mood swings actually improved.

Pediatric behavioral and psychiatric adverse events, including psychosis, have been reported in the literature and are described as having onset within 3 months of therapy initiation and being reversible in four patients with prior cognitive deficits (9). Wheless and Ng (10) reported that 26% of 39 participants evaluated in their pediatric trial actually improved in cognition or behavior.

All of these reports suggest that behavioral and psychiatric adverse events may occur in patients with epilepsy who receive LEV. LEV was approved by the Food and Drug Administration for adjunctive use in refractory partial epilepsy patients. Whether the experience will be the same in monotherapy for *new onset* epilepsy patients or in patients who may be receiving LEV for other off-label conditions remains to be observed. Other than a “fast” titration rate, defined as initiation at 500 mg twice daily, no consensus exists regarding predictive risk factors. Uniformly, the most frequent complaints are irritability and de-

pression, with psychosis being rare. All of these symptoms have been reversible. No apparent reason exists to fear administering LEV for the treatment of epilepsy patients—even if the IQ is low or with or without a history of psychiatric or behavioral problems. Close observation and adhering to the all-familiar mantra of “Go Slow and Go Low” to guide treatment initiation, once again, seems prudent.

by Patricia E. Penovich, M.D.

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