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Original Contributions

Safety and Efficacy of Switching Psychiatric Patients from a Delayed-Release to an Extended-Release Formulation of Divalproex Sodium

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Abstract

This study evaluated the safety and efficacy of divalproex sodium extended-release (ER) when patients were switched from therapy with divalproex sodium delayed-release (DR) to divalproex sodium ER. This open-label, 7-day study included 55 patients with bipolar disorder, major depression, schizophrenia, schizoaffective disorder, Alzheimer's disease, dementia, or intermittent explosive disorder. Baseline plasma valproate concentrations were determined, and patients received their usual morning dose of divalproex sodium DR. At 9:00 p.m. the same day, they received divalproex sodium ER at a dose equal to their total daily dose of divalproex sodium DR. Valproate concentrations were monitored, and efficacy was measured with the Positive and Negative Syndrome Scale (PANSS). Side effects were assessed using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale. Valproate concentrations for 52 patients remained within the therapeutic range. Inpatient PANSS scores significantly improved from baseline to final evaluation on all subscales. For the combined inpatient and outpatient populations, a small but statistically significant improvement from baseline to final evaluation was seen for positive, general, and total PANSS subscale scores. At study's end, patients reported a significant decrease in the number and severity of adverse events; 54 of 55 patients elected to continue therapy with once-daily divalproex sodium ER. This study suggests that divalproex sodium ER is at least as effective as the DR formulation for treating patients with psychiatric illness and may be better tolerated. The ER formulation offers the advantage of once-daily dosing, which may help improve compliance.

Medication noncompliance among patients with medical illnesses has been reported to range from 15% to 85%. 1 Psychiatric patients, in particular, are frequently noncompliant with medications. In a study of patients with bipolar disorder, Keck and associates reported a noncompliance rate of up to 64%. 2 In addition, noncompliance is the most frequent cause of relapse for this patient population. 3 Although many factors are associated with medication noncompliance, it is thought that physicians can help promote compliance by prescribing medications that require a minimal number of doses per day. In a study of headache patients by Mulleners and associates, compliance increased as the number of medication doses decreased. Compliance among these patients was 80% when patients had the convenience of once-daily dosing, as compared with 60% for twice-daily and 54% for three-times-daily dosing. 4

Divalproex sodium delayed-release (DR) has been used for many years and has been shown to be effective in the treatment of acute mania associated with bipolar disorder. 5,6 The time to peak plasma concentration (T_{max}) occurs within 3 to 4 hours after the DR tablet is taken, and the functional half-life ($t_{1/2}$) is relatively short at 8 to 17 hours. 7 These pharmacokinetic parameters require that divalproex sodium DR be administered in a twice-daily dosing regimen. The United States Food and Drug Administration (FDA) recently approved an extended-release (ER) formulation of divalproex sodium, with a current indication of migraine prevention. This once-daily dosing formulation offers 10% to 20% less fluctuation in valproate plasma concentrations than divalproex sodium DR delivered twice daily, with maximum plasma concentrations (C_{max}) occurring 7 to 14 hours after ER dosing. 8 In addition to the advantage of once-daily dosing, the steadier valproate plasma concentrations may offer more effective mood stabilization and a reduction in the occurrence of adverse events.

If efficacy of once-daily dosing with divalproex sodium ER is equal to or better than that provided by the multiple-dose formulation, compliance may be improved. Moreover, compliance may be further enhanced if a lower incidence of adverse events is associated with divalproex sodium ER. The present study was designed to evaluate the safety and efficacy of divalproex sodium ER when patients were switched from treatment with the divalproex sodium DR formulation to that with the ER formulation.