Bipolar disorder in young people: divalproex sodium no more effective than lithium for maintenance


**METHODS**

**Design:** Randomised controlled trial.

**Allocation:** Unclear.

**Blinding:** Double blind.

**Follow up period:** 76 weeks.

**Setting:** Single site outpatient setting, USA; recruitment between July 1998 and May 2002.

**Patients:** 139 young people aged 5–17 years with bipolar I or bipolar II disorder (DSM-IV diagnosis) and who had at least one manic or hypomanic episode in the previous three months. Main exclusion criteria: history of manic episodes with either lithium serum concentration >1.0 mmol/l or divalproex sodium (DVP) concentration >80 µg/ml; pregnancy; recent substance misuse disorder; pervasive developmental disorder or mental retardation; or significant medical comorbidity.

**Intervention:** All participants received lithium plus divalproex sodium for up to 20 weeks (target serum concentration: 0.6 to 1.2 mmol/l and lithium and 50 to 100 µg/ml DVP). The 60 participants who achieved four consecutive weeks in bimodal remission (Children’s Depression Rating Scale-Revised (CDRS-R) score <40, Young Mania Rating Scale (YMRS) <12.5, and Children’s Global Assessment Scale (CGAS) >51) were randomised to either lithium or divalproex sodium monotherapy for 76 weeks.

**Outcomes:** Time to mood relapse or study discontinuation; bipolar symptoms (hypomania and mania: YMRS; depression: CDRS-R) and global functioning (Clinical Global Impression of Severity and Improvement and CGAS).

**Patient follow up:** All participants (100%) were included in analyses. However, only 6/60 (10%) of participants completed 72 weeks’ treatment, with 63% of withdrawals mood related and 20% withdrawing for other reasons.

**MAIN RESULTS**

Lithium and divalproex groups did not differ in time to mood relapse (median: 114 days with lithium vs 112 days with DVP; p = 0.55) or time to study discontinuation for any reason (median: 91 days with lithium vs 56 days with DVP; p = 0.72). Bipolar symptoms and global functioning worsened in both treatment groups; there were no significant differences between treatments (p > 0.37 for all comparisons). Compared with divalproex, lithium increased emesis (30% vs 10%; p = 0.05), enuresis (30% vs 6.7%; p = 0.05), and thirst (16.7% vs 0%; p = 0.02). More people taking divalproex reported headache or stomach pain than with lithium, but the difference was not significant (p > 0.1 for both).

**CONCLUSIONS**

Divalproex sodium is not superior to lithium as a maintenance treatment for young people with bipolar disorder who have been stabilised on a combination of lithium plus divalproex sodium.