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

Findling RL, McNamara NK, Youngstrom EA, *et al*. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2005;**44**:409–17.

Q Is divalproex more effective than lithium as a monotherapy for young people with bipolar disorder who are stabilised on lithium plus divalproex?

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 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 Scales 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 *v* 112 days with DVPX; p = 0.55) or time to study discontinuation for any reason (median: 91 days with lithium *v* 56 days with DVPX; 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% *v* 10%; p = 0.05), enuresis (30% *v* 6.7%; p = 0.05), and thirst (16.7% *v* 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.

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Commentary

The effectiveness of lithium and divalproex (DVP) alone in the acute treatment of mania in adults is well known.[1] However, in children and adolescents there are as yet no published placebo controlled treatment studies for acute mania.

The study by Findling *et al* used a discontinuation approach to examine whether lithium or DVP is better at maintaining stabilisation in young people with bipolar disorder. The initial sample included 5–17 year olds who could tolerate and did not have a history of non-response to lithium or DVP. Children were treated from the outset on combined medication. Unlike other bipolar samples,[2 3] 30% had no psychiatric comorbidity, or had mainly attention deficit hyperactivity disorder (ADHD), not oppositional defiant or anxiety disorders. About one third of the sample responded to the combined drug given openly. Responders' mean mania scores dropped to virtually zero, function scores improved very significantly, and response was maintained for four weeks to be eligible for discontinuation to only one medication. The study addressed maintenance on a single "mood stabiliser" and, somewhat by extension, effectiveness of either medication alone in treatment of acute mania in young people.

Without a placebo control, and/or a treatment arm that continued combined medication, we do not know whether single drug maintenance was better than nothing, or if combined treatment would have continued to work. We do know only 10% "survived" on single drug, it did not matter which; half the sample relapsed mostly into mania or dropped out by three months. The same study in adults also found participants relapsed mostly into depression on a single drug (although more adults had bipolar II than bipolar I disorder).[4]

The aforementioned limitations preclude a definitive stance on the utility of single lithium or divalproex for acutely or longitudinally manic children. However, if the rush to diagnose children with bipolar disorder is meant to justify single mood stabiliser treatment, there is little encouragement to do so from these data.

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1 American Psychiatric Association. Practice Guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;**159**(Suppl 4):1–50.
2 Tillman R, Geller B, Bolhofner K, *et al*. Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:1486–93.
3 Biederman J, Faraone SV, Wozniak J, *et al*. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. *J Affect Disord* 2004;**82**:S45–58.
4 Calabrese JR, Shelton MD, Rapport DJ, *et al*. A 20-month, double-blind, maintenance trial of lithium vs. divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry* (in press).