Adding mixed amphetamine salts to divalproex sodium improves ADHD symptoms in children with bipolar disorder and comorbid ADHD

Scheffer RE, Kowatch RA, Carmody T, *et al*. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in paediatric bipolar disorder after mood stabilization with divalproex sodium. *Am J Psychiatry* 2005;**162**:**58**–64.

Q Are mixed amphetamine salts plus divalproex sodium safe and effective in children with bipolar disorder and comorbid ADHD after stabilisation of manic symptoms with divalproex sodium?

METHODS

Design: Randomised controlled crossover trial.

Allocation: Not stated.

Blinding: Double blind.

Follow up period: Two weeks randomised treatment; 12 weeks open label follow up.

Setting: One hospital in Dallas, Texas, USA.

Patients: Thirty one children (mean age 9.8 years) with DSM-IV diagonosed bipolar I or II disorder and attention deficit hyperactivity disorder (ADHD). Eligible children had a Conner's Teachers and Parents Rating Scales hyperactivity score ⩾2 standard deviations above normal and Young Mania Rating Scale (YMRS) score ⩾14, whose manic symptoms stabilised after eight weeks' treatment with divalproex sodium. Main exclusions: other major psychiatric comorbidity; current psychotherapy; high suicide risk; IQ ⩽70; recent psychotropic use; history of substance abuse or of unresponsiveness to divalproex sodium.

Intervention: Divalproex sodium (median dose of 750 mg/day) plus mixed amphetamine salts (5 mg twice daily), or placebo for two weeks, followed by alternate treatment for two more weeks. A 12 week open label treatment phase followed.

Outcomes: Manic symptom severity (YMRS, higher score indicates greater severity); ADHD symptom severity (Clinical Global Impression (CGI) improvement scale, score range 1 (very much improved) to 7 (very much worsened)).

Patient follow up: 23/31 (74%) completed the study.

MAIN RESULTS

Adding mixed amphetamine salts to divalproex sodium improved ADHD symptoms but not manic symptoms at two weeks compared with adding placebo (mean CGI improvement score: 1.8 with mixed amphetamine salts *v* 3.7 with placebo, $p<0.0001$; mean YMRS score: 5.9 with mixed amphetamine salts *v* 7.1 with placebo, $p = 0.17$). Side effects were transient and of low to moderate severity and frequency. During open label follow up one of 23 participants had a worsening of manic symptoms, which resolved on discontinuation of mixed amphetamine salts.

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CONCLUSIONS

Mixed amphetamine salts plus divalproex sodium are safe and effective for the short term treatment of bipolar disorder and comorbid ADHD.

NOTES

Although there was no washout period between treatments, the authors found no statistical evidence for carry over effects. Children previously unresponsive to divalproex sodium were excluded so results may not apply to an unselected population. It is not clear whether the participants' characteristics were balanced at baseline.

Commentary

In 1999 our research group performed a chart review of clinic patients with bipolar disorder and ADHD, demonstrating that ADHD could be treated in children and adolescents with bipolar disorder, but only when ADHD treatments were sequenced after stabilisation of manic symptoms.[1] Around that time, a colleague requested my consultation on a young adult with bipolar disorder and ADHD who improved only when a stimulant medication was added to his mood stabiliser. The psychiatrist had been threatened with malpractice for initiating what was considered to be a contraindicated treatment. It is thus extremely gratifying to see in print the first double blind placebo controlled trial of a stimulant for the treatment of ADHD in the context of paediatric bipolar disorder.

Any debate as to whether children with symptoms of ADHD and mania have only one disorder (bad ADHD mimicking mania or mania mimicking ADHD) is vitiated by this report.[2] Scheffer *et al* found treatment with divalproex sodium brought improvement in manic symptoms in 80% of participants, but improvement in ADHD in only 7.5% of participants. Without a treatment specific for ADHD, its symptoms continued to be present. With the addition of mixed amphetamine salts 5 mg BID improvement in ADHD was nearly 2 points greater than with placebo, as measured by the CGI. Only one patient experienced a manic exacerbation, which resolved within four weeks.

Clinicians faced with the thorny issue of residual symptoms of distractibility, hyperactivity, and talkativeness in a child with bipolar disorder treated with a mood stabiliser must determine whether these symptoms represent residual symptoms of mania or untreated ADHD. This report highlights the importance of treating ADHD with a stimulant medication in such patients with stabilised mood symptoms. Although some may experience an exacerbation of mania (in this study one subject), many will improve without exacerbation of mania. Given the highly morbid nature of ADHD, this combined pharmacotherapy approach could benefit countless children and adolescents whose functioning is compromised by not one, but two serious psychiatric conditions.

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1 Biederman J, Mick E, Prince J, *et al*. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder *J Child Adolesc Psychopharmacol* 1999;**9**:247–56.
2 Faraone SV, Biederman J, Wozniak J, *et al*. Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry* 1997;**36**:1046–55.