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BRIEF REPORT

Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder

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Abstract

Autism is a neurodevelopmental disorder characterized by impairment in three core symptom domains: socialization, communication, and repetitive/stereotyped behaviours. Other associated symptom domains are also affected including impulsivity/aggression, self-injury, anxiety, and mood lability. Divalproex has been shown to have efficacy in treating epilepsy, bipolar disorder, mood lability, and impulsive aggression. The present study evaluated the use of divalproex in the treatment of repetitive, compulsive-like symptoms of autism spectrum disorder (ASD). Thirteen individuals with ASD participated in an 8-wk, double-blind, placebo-controlled trial of divalproex sodium vs. placebo. There was a significant group difference on improvement in repetitive behaviours as measured by the Children's Yale–Brown Obsessive Compulsive Scale (C-YBOCS) ($p = 0.037$) and a large effect size ($d = 1.616$). This study provides preliminary support for the use of divalproex in treating repetitive behaviours in ASD. Further research is needed to evaluate the specificity and mechanism of action of these findings.

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Introduction

Autism spectrum disorders (ASDs), including autistic disorder, pervasive developmental disorder, and Asperger's syndrome are characterized by significant impairments in three core behavioural domains: social interaction, communication, and the presence of stereotyped patterns of behaviour and restricted repetitive interests. In ASD, the stereotyped behaviour/restricted interest domain includes ritualistic behaviours such as counting, tapping, finger twisting, or repeatedly restating facts or questions to a caregiver as well as compulsive behaviours, such as rigid adherence to routines and needing things to be done in a particular way. These features have been described as compulsive features of the disorder and have important similarities with a wide range of other disorders [e.g. obsessive–compulsive disorder (OCD), Prader–Willi syndrome (PWS)]. ASD is also characterized by association symptoms including aggression, self-injury, irritability, mood instability, anxiety, and poor impulse control.

Divalproex is FDA-approved for the treatment of epilepsy, migraine, and bipolar disorder. Recent studies have shown that anticonvulsants such as divalproex may be effective in the treatment of psychiatric disorders with impulsive and compulsive features such as compulsive gambling (Pallanti et al., 2002), cluster B and borderline personality disorders (Hollander et al., 2003, 2005), binge eating (McElroy et al., 2004), alcohol abuse (Johnson et al., 2003), and OCD (Hollander, 1999). For example, anticonvulsants may be useful in augmenting SSRI interventions in treatment-refractory OCD patients with comorbid neurological impairments (Hollander, 1999). The clinical usefulness of divalproex in treating disorders with impulsive, compulsive, and/or neurological features suggests that divalproex could conceivably also be helpful in treating symptoms of autism, a disorder with repetitive behaviours, mood instability, impulsivity, and neurological impairment. We evaluated the utility of divalproex on various symptom domains of ASD in an open label trial (Hollander et al.,

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2001). Improvements in repetitive behaviours, social relatedness, aggression, and mood lability were reported. The present study is a follow-up to this open study, and is the first randomized, double blind, placebo-controlled trial of divalproex sodium in individuals with ASD. Based on the findings of previous trials with divalproex in compulsive-impulsive disorders, we hypothesized that treatment with divalproex sodium would result in improvement in repetitive behaviours in ASD.

Although the mechanism of action is not fully known, it has been suggested that valproate may exert its effect in a number of ways, including blocking voltage-gated sodium ion channels; enhancing GABA; inhibiting glutamate; acting on serotonin and norepinephrine systems; as well as via limbic kindling (Hollander et al., 2002; Soderpalm, 2002). An epigenetic mechanism involving GAD67 and reelin gene expression has also been implicated (Costa et al., 2003).

Methods

Subjects

Patients were recruited and screened for the presence of ASDs at the Seaver and New York Autism Center of Excellence. Twenty-five subjects were screened. Thirteen subjects were randomized, had at least one post-treatment outcome measure, and were included in the intent-to-treat (ITT) group. One subject dropped out in week 5 due to lack of efficacy (on medication) and 12 subjects completed the trial.

The average age of subjects was 9.5 yr (12 were child/adolescents with an age range 5–17 yr, and one was an adult, age 40 yr). Eight of the subjects were Caucasian, two were African American, two were Asian and one was Hispanic. Baseline assessments included comprehensive psychiatric, diagnostic, psychological, and medical evaluations. Diagnoses were established using DSM-IV criteria, Autism Diagnostic Interview – Revised (ADI-R), and Autism Diagnostic Observation Schedule (ADOS). Ten of the participants were diagnosed with autistic disorder, two were diagnosed with Asperger's disorder and one was diagnosed with pervasive developmental disotherwise specified (PDD-NOS).

Psychological testing included measures of cognitive functioning and adaptive behaviour. The sample represents the moderate to low functioning end of the autism spectrum. IQ scores for the majority of participants were in the mild to moderate mental retardation range, with a mean IQ score of 60 (range = 30–104). Scores on the Vineland Adaptive Behaviour Scale fell in the moderately to severely impaired range of functioning (mean = 44, standard deviation = 22).

Inclusion criteria for the study included subjects meeting DSM-IV and ADI-R criteria for an ASD and scoring as moderately ill on Clinical Global Impression Scale for Autistic Disorder (CGI-AD) rating. Patients were not selected on the basis of levels of repetitive or aggressive behaviours on study measures. Exclusion criteria included medical illnesses (with the exception of stable seizure disorder), past history of psychotic disorders, and recent or current use of divalproex, terfenadine (Seldane), or astemizole (Hismanal). Subjects using any psychoactive medication were allowed to participate in the trial only if the dose remained stable for at least 3 months prior to and during the trial. Only one participant was on a stable dose of risperidone prior to the study and continued throughout the 8 wk of the study. No other participant was on concomitant medications. This study was approved by the Mount Sinai Institutional Review Board. All participants provided informed consent prior to participation.

Study design

The study used a double-blind, placebo-controlled design, with nine subjects randomized into the treatment group and four subjects randomized in the placebo group. The randomization schedule had a goal of establishing a 2:1 ratio of patients in the active vs. placebo groups to increase the number of possible subjects who might show an effect and to facilitate recruitment.

Patients were evaluated weekly for the first 4 wk and bi-weekly for the next 4 wk in a double-blind fashion by the treating physician. Patients had divalproex sodium blood levels drawn every 2 wk until a therapeutic dose was reached. Complete blood count (CBC) and liver function was tested every 4 wk to monitor for side-effects.

Divalproex sodium and placebo were distributed in identical forms in a double-blind fashion. Dosage started with 125 mg/d and was increased by 125 mg every 4 d during the first 2 wk of treatment. The dose and titration schedule of study drug for each patient was determined by their investigator and was based on treatment response and tolerability. The recommended divalproex serum level was 50–100 μg/ml by week 2, and the maximum dose was 30 mg/kg . d. Trough serum concentrations of divalproex (samples collected prior to dosing) were determined at weeks 2, 4, 6, and 8. An unblinded person reported serum divalproex levels of $<50\,\mu$g/ml or $>100\,\mu$g/ml to the

investigators so that the dose of study drug could be adjusted appropriately. In order to preserve the study blind, sham divalproex levels were reported for selected placebo patients.

Outcome measures

The primary outcome measures in this study were the Children's Yale–Brown Obsessive Compulsive Scale (C-YBOCS), Compulsion subscale. The C-YBOCS Compulsion subscale (Goodman et al., 1991) assesses the symptom domain of compulsivity and has moderate to strong psychometric properties. The measure is used to provide important information regarding the core symptom domain of compulsivity in ASD. The C-YBOCS is a is a five-item clinician-rated questionnaire which rates on a 5-point scale the time spent, distress, interference, resistance and control in relation to compulsions. Ratings were based upon interviews with the patient and/or parent when the patient was unable to provide information for the ratings.

Statistical analysis

An ITT analysis was used including the 13 randomized subjects with evaluable data ($n=13$). Baseline differences on descriptive variables and C-YBOCS were evaluated with t tests. Analysis of the main effect was conducted using a t test on change scores from week 0 and week 8.

Results

The mean dose at end-point was 822.92 ± 326.21 mg/d (range = 500–1500 mg/d). The mean trough serum level of divalproex at end-point was 58.23 ± 21.63 μg/ml.

There were no group differences in total C-YBOCS compulsion scores or descriptive variables at baseline assessment ($t=-1.721$, $p=0.113$). Figure 1 shows total C-YBOCS Compulsion subscale scores for the drug and placebo groups over time. There was a statistically significant group difference on C-YBOCS change scores across the 8-wk trial such that repetitive behaviour scores improved on divalproex sodium and worsened on placebo ($t=2.37$, d.f. = 11, $p=0.037$). A large effect size was found ($d=1.616$). An analysis that included only child/adolescent subjects (i.e. without the single adult in the sample) was also conducted. Although decreasing the sample size reduced statistical power, the analysis still revealed significant group differences ($t=2.22$, d.f. = 11, $p=0.05$) and a large effect size ($d=1.53$).

Additional analyses were conducted to evaluate differences in response rates on divalproex vs. placebo.

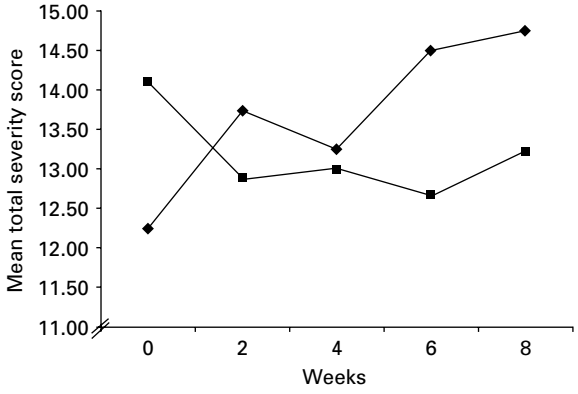

Figure 1. Average change from baseline C-YBOCS score in patients with autism spectrum disorders. –◆–, Placebo ($n=4$); –■–, divalproex ($n=9$). Drug × time interaction ($t=2.37$, d.f. = 11, $p=0.037$).

Descriptive data show that none of the participants in the placebo group maintained or improved repetitive behaviour severity scores on the C-YBOCS while 77% of the divalproex group maintained or improved C-YBOCS scores at end-point. The divalproex group had an average improvement of 0.889 points on C-YBOCS scores, compared to an average worsening of 2.5 points for the placebo group.

An exploratory analysis of C-YBOCS Compulsion subscale items was also conducted to evaluate whether results are related to specific or global improvements in C-YBOCS total severity scores. The analysis indicated a significant and positive correlation between changes in item 6, which assesses amount of time spent engaging in repetitive behaviours, and changes in total C-YBOCS scores ($r=0.762$, $p=0.002$). No other individual item had significant correlations with changes in total severity, indicating that results may be strongly related to reductions in time spent engaged in repetitive behaviours.

Treatment-emergent adverse events were measured each week for the first 4 wk and every 2 wk thereafter by the study psychiatrist who examined the child and queried the parent for any adverse events (Table 1). There were no statistically significant differences between the numbers or types of adverse events reported by patients on divalproex vs. placebo. Reported adverse events in the divalproex vs. placebo groups included irritability (33% vs. 25%), weight gain (22% vs. 25%), anxiety (11% vs. 25%) and aggression (11% vs. 0%). No subjects in either the divalproex or placebo groups dropped out due to adverse events. One patient, in the divalproex group, terminated early due to lack of treatment efficacy, but did not report any adverse events.

Table 1. Treatment emergent adverse events occurring in >10% of patients in any treatment group

	Placebo ($n=4$)	Divalproex ($n=9$)
Any adverse event	2 (50%)	7 (77%)
Anxiety	1 (25%)	1 (11%)
Irritability	1 (25%)	3 (33%)
Weight gain	1 (25%)	2 (22%)
Aggression	0	1 (11%)

Discussion

This study provides preliminary support for the use of divalproex sodium in the treatment of repetitive behaviours in individuals with ASD. Since divalproex sodium has been shown to be effective in the treatment of mood lability and irritability (Hollander et al., 2003), we explored the possibility that the present results may reflect a reduction in the distress, irritability, or other negative reactions associated with preventing or inhibiting compulsions. However the exploratory analysis of C-YBOCS items suggested that improvements in repetitive behaviours were driven by a reduction in time spent engaged in repetitive behaviours; not by reductions in the level of distress associated with prevention of repetitive behaviours.

In addition to improvements in the treatment group, results suggest that there was a worsening on placebo from baseline levels of repetitive behaviours. Although no statistically significant differences were noted in baseline C-YBOCS scores, none of the four subjects in the placebo group maintained or improved their baseline levels of functioning. In comparison, 77% of the divalproex group had stable or improved responding as measured by the C-YBOCS. Given the double-blind nature of the study, the trend is difficult to explain by threats to internal validity such as experimenter bias or social desirability effects. It is possible that the placebo group experienced a true increase in symptom scores in the absence of treatment, particularly if behaviours were self-stimulatory.

Results also suggest that future studies should explore patient-specific factors that contribute to treatment response. Of interest, the patients with the most robust responses (i.e. improvement of over 30% on total C-YBOCS scores) in the divalproex group also had maximum scores on ADI items measuring higher-order, compulsive behaviours (mean = 6, standard deviation = 1.41). These robust responders had relatively lower scores on ADI items measuring lower-order, stereotyped behaviours such as hand flapping (mean = 2.5, standard deviation = 2.1). In contrast, no differences in ADI items measuring higher-order vs. lower-order compulsive behaviours were found in patients with moderate or stable responses in the divalproex group. Future studies could stratify patient populations based on the presence of higher-order vs. lower-order repetitive behaviours to evaluate treatment response.

The mechanism by which divalproex sodium exerts its effects on repetitive and stereotyped behaviours is still unresolved, but animal studies may be informative. Yang et al. (2000) found that both single and repeated doses of divalproex immediately prior to methylphenidate (MPH) administration reduced sensitization effects of MPH on stereotyped, repetitive motor movements in rats. The authors hypothesize that stimulating GABA activity with divalproex reduces dopamine release and inhibits its effects, which results in a reduction in compulsive-like behaviours.

Research in PWS may also provide some insight into the mechanisms by which divalproex ameliorates repetitive behaviours in ASD. In a study of PWS, treatment with topiramate, which affects both GABA and glutamate, resulted in reductions in self-abusive behaviour (i.e. skin picking) and compulsive eating in children with PWS (Smathers et al., 2003). The links between PWS and ASD are of interest given the similarity of genetic and medication treatment findings in these disorders. Both disorders have been associated with abnormalities on chromosome 15q and have overlapping symptom patterns. Patients with PWS exhibit a higher prevalence rate of 25.3% of ASD than the general population (Veltman et al., 2004). Therefore, hypotheses about the molecular, chemical, and behavioural foundations for the repetitive behaviours in PWS may be germane to ASD investigations. Dimitropoulous et al. (2000) suggested that GABA might play a central role in the repetitive behaviours found in PWS, citing evidence that the GABA-A receptors are located in 15q. According to Dimitropoulous et al. (2000), GABA might reduce repetitive behaviours in PWS, as in OCD, through its inhibitory effect on serotonin and dopamine neurons in the fronto-striatal system. The findings suggest a need for basic science research to clarify the direct or indirect action of GABA on the fronto-striatal systems in PWS and ASD to better understand the relationship between GABA and repetitive behaviours.

While results of this study suggest a promising link between divalproex and the compulsive-like behaviours associated with ASD, the small, heterogeneous sample and the short-term administration of divalproex are important limitations. Studies with larger

sample sizes and longer durations are needed to confirm efficacy. Future studies are also needed, as suggested above, to identify correlates of treatment response including dosing, metabolism, and patient characteristics such the nature of repetitive behaviours (e.g. lower-order self-stimulatory behaviour vs. higher-order compulsions), irritability, and/or aggression.

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Statement of Interest

Dr Hollander has served on an advisory board of Abbott Laboratories.

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