Neuropsychopharmacology (2010) 35, 990–998

www.neuropsychopharmacology.org

Divalproex Sodium *vs* Placebo for the Treatment of Irritability in Children and Adolescents with Autism Spectrum Disorders

Eric Hollander*[1,5], William Chaplin[2], Latha Soorya[3], Stacey Wasserman[3], Sherry Novotny[3], Jade Rusoff[3], Nicole Feirsen[3], Lauren Pepa[3] and Evdokia Anagnostou[4,5]

[1]Department of Psychiatry, Montefiore Medical Center University Hospital for Albert Einstein College of Medicine, Child Psychiatry Annex, Bronx, NY, USA; [2]Department of Psychology, St John's University, Jamaica, NY, USA; [3]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA; [4]Department of Pediatrics, Bloorview Kids Rehab, University of Toronto, Toronto, ON, Canada

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by social and language deficits and by repetitive behaviors and interests. Irritability/aggression is a significant comorbid symptom in this population, which greatly impacts burden of care. This study examined the effect of divalproex sodium for irritability/aggression in children and adolescents with ASD. This was a 12-week randomized, double-blind, placebo-controlled trial. All efficacy measures were obtained by an independent evaluator blinded to randomization condition and side effects. A total of 55 subjects gavetheir consent and 27 were randomized in a 1 : 1 manner (mean age 9.46 ± 2.46, mean nonverbal IQ 63.3 ± 23.9). Two subjects from the active group and one subject from the placebo group discontinued the study because of either a lack of efficacy or side effects (increased irritability). Primary outcome measures were Aberrant Behavior Checklist-Irritability subscale and Clinical Global Impression-Improvement, which focused on irritability. Overall, 62.5% of divalproex subjects *vs* 9% of placebo subjects were responders (CGI-irritability OR: 16.7, Fisher's exact $p = 0.008$). A statistically significant improvement was also noted on the ABC-Irritability subscale ($p = 0.048$). There was a trend for responders to have higher valproate blood levels compared with nonresponders. This study suggests the efficacy of divalproex for the treatment of irritability in children and adolescents with ASD. Larger sample follow-up studies are warranted.
Neuropsychopharmacology (2010) **35,** 990–998; doi:10.1038/npp.2009.202; published online 9 December 2009

Keywords: ASD; irritability; divalproex; children; adolescents

INTRODUCTION

Autism spectrum disorder (ASD) refers to a group of developmental disorders (Autistic disorder, Asperger's syndrome and pervasive developmental disorder not otherwise specified) affecting social and communicative functions and characterized by repetitive behaviors/restricted interests (American Psychiatric Association, 1994).

Impulsivity, self-injury, and other-directed aggression are common features in patients with ASD, and have a major impact on the care of affected individuals. For this reason, this domain has been the target of clinical trials, mostly focused on the use of atypical antipsychotics, (McCracken *et al*, 2002), and also of early studies of anticonvulsants, such as valproate, psychostimulants, and α- and β-adrenergic agonists.

Valproate has received FDA indications for the treatment of epilepsy (10 years and older), bipolar disorder (adult), and migraine prophylaxis (adult). Its mechanism of action is not well understood but may include the following: It potentiates GABA inhibitory effects in the CNS (Soderpalm, 2002) and is likely to have epigenetic effects, as it is a histone deacetylase inhibitor (Göttlicher, 2004). These two mechanisms are of specific interest in ASD, given theories of decreased inhibitory control in autism (Casanova *et al*, 2003), high frequency of seizures, and epileptiform EEGs in this population, especially in individuals with lower IQs (Amiet *et al*, 2008), and the increasing evidence to support a role of gene expression abnormalities in the pathophysiology of multiple neuropsychiatric disorders (Szyf, 2009). Other mechanisms that may or may not be relevant to the treatment of irritability include functional blockade of voltage-sensitive sodium channels, attenuation of NMDA-mediated excitation, influences on serotonin and norepinephrine function, effects on second messenger systems, and potential neuroprotective effects (Manji and Chen, 2000; Yasuda *et al*, 2009; Chen *et al*, 1999).

*Correspondence: Dr E Hollander, Department of Psychiatry, Montefiore Medical Center University Hospital for Albert Einstein College of Medicine, Child Psychiatry Annex, 111 E. 210th Street, Bronx, NY 10467-2490, USA, Tel: +1 718 696 3035, Fax: +1 914 698 4696, E-mail: eholland@montefiore.org
[5]These authors contributed equally to this work.
Received 31 July 2009; revised 21 October 2009; accepted 9 November 2009

In adults, valproate has shown to have some efficacy at reducing aggressive behaviors across diagnostic groups, and controlled trials have documented a reduction in irritability in cluster B personality disorders (Hollander *et al*, 2003, 2005). There are case reports and case series suggesting the efficacy of valproate for aggression in children and adults with mental retardation and associated comorbidities (Mattes, 1992; Kastner *et al*, 1993; Sovner, 1989; Donovan *et al*, 1997; Damore *et al*, 1998). In an open-label study, we found that valproate reduces irritability and aggression in children with ASD (Hollander *et al*, 2001). Hellings *et al* (2005) conducted a double-blind, placebo-controlled trial of divalproex for aggression in ASD, which did not demonstrate efficacy in reducing aggression. However, the authors felt this might reflect high intersubject variability, small sample size, and a large placebo effect, and recommended further evaluation.

Most research into maladaptive behaviors in ASD has focused on the use of atypical antipsychotics (Jesner *et al*, 2007), with early data also potentially supporting the use of mood stabilizers, stimulants, and α- and β-adrenergic agonists (Aman, 2004). However, neuroleptic medications are associated with side effects, such as weight gain, which may increase the likelihood of diabetes and cardiovascular disease, with sedation and extrapyramidal symptoms, and not all patients exposed are responders. Lithium has documented efficacy for the treatment of irritability and aggression in several other disorders and early data may support its use in ASD (Kerbeshian *et al*, 1987; Teingard and Biederman, 1987; Craft *et al*, 1987), although, given the narrow therapeutic index of lithium, it is unlikely to be widely used in children with ASD. Other mood-stabilizing anticonvulsants, such as lamotrigine and levetiracetam, had promising early open-label data to support their use in ASD (Vebrant and Bauziene, 1994), but follow-up randomized controlled data failed to support this claim (Belsito *et al*, 2001; Wasserman *et al*, 2006).

Given the side effect profile of atypical antipsychotics, limited data to support efficacy for other compounds, conflicting early data for the use of divalproex in ASD, as well as the frequent occurrence of epileptiform EEG in patients with ASD, a further study of this compound in this population is warranted. This study examines the effect of divalproex sodium in the treatment of irritability/aggression in children with ASD, by means of a 12-week, double-blind, placebo-controlled trial, and explores the effect of baseline epileptiform activity on treatment response for irritability.

PATIENTS AND METHODS

The study was registered at clinicaltrials.gov (NCT00211757).

Study Participants

Inclusion criteria. Subjects were children aged 5–17 years, outpatients, who met DSM-IV-TR diagnostic criteria for autistic disorder, full diagnostic criteria on the ADI-R and autism spectrum criteria on the ADOS-G. Subjects had to be at least moderately ill (CGI-Severity score of at least '4') to justify exposure to this medication. The population was also stratified for significant irritability/aggression difficulties at baseline, such that children had an Overt Aggression Scale-Modified (OAS-M) score of at least 13 or an Aberrant Behavior Checklist (ABC)-Irritability score of at least 18 (raw scores) to qualify.

Exclusion criteria. We excluded sexually active and pregnant females and nursing mothers; subjects with overall adaptive behavior scores below the age of 2 years on the Vineland Adaptive Behavior Rating Scale; subjects with active or unstable epilepsy, other Axis I disorders, unstable medical illness, genetic syndromes, or congenital infections associated with autism-like syndromes, prematurity; subjects treated within the previous 30 days with any drug known to have a well-defined potential for toxicity or with any psychotropic drugs; subjects with clinically significant abnormalities in laboratory tests or physical examination; subjects with a history of hypersensitivity or severe side effects associated with the use of divalproex sodium or other ineffective previous therapeutic trial of divalproex sodium (serum levels within the range of 50–100 μg/ml for 6 weeks); and subjects who have begun any new nonmedication treatments, such as diet, vitamins, and psychosocial therapy, within the previous 3 months. A detailed clinical interview with parents by an expert clinician, followed by a physical examination and blood test, was used to ensure that subjects did not meet any of the exclusion criteria.

Study Design

This was a 12-week randomized double-blind, placebo-controlled trial. The study was approved by the institutional review board of the Mount Sinai School of Medicine. Informed consent was obtained after a complete description of the study to the subjects and as per the Helsinki agreement and local IRB guidelines. Participants responded to advertisements placed in newspapers, websites, and so on. If they passed a phone screen by the research assistant, they were invited to come in and sign the consent. Assent was obtained whenever possible. After consent was signed, inclusion/exclusion criteria were determined on the basis of diagnostic and adaptive functioning testing, clinical interview, physical examination, and blood test. Participants were randomized to divalproex *vs* placebo and the dose was titrated up according to body weight (see Table 1),

Table 1 Titration Schedule

	< 40 kg	**⩾ 40 kg**
Week	Dose	Dose
Week 0, days 1–4	125 mg po QHS	250 mg po QHS
Week 0, days 5–7	125 mg po BID	250 mg po BID
Week 1, days 1–4	125 mg po QAM, 250 mg po QHS	250 mg po QAM, 500 mg po QHS
Week 1, days 5–7	250 mg po BID	500 mg po BID
Weeks 2–3	Titrated to therapeutic drug level[a]	Titrated to therapeutic drug level[a]
Weeks 4–12	Maintained on therapeutic dose	Maintained on therapeutic dose

[a]Based on clinical response in conjunction with minimum valproate level (50 μg/ml).

therapeutic blood level (a minimum valproate blood level of 50 μg/ml, as is the established minimum for epilepsy), and ultimately treatment response. All clinicians involved in efficacy or safety assessments were blinded to the randomization condition. Efficacy measures were administered every 2 weeks by an independent evaluator, who was an experienced clinical psychologist blinded to side effects. Side effects were monitored by study physicians, who are experienced in treating children with ASD and using valproic acid formulations. The dose was titrated on the basis of feedback from a nonblinded physician who independently monitored blood. This clinician had no contact with the participants. All valproate levels and safety blood results were forwarded to him by the laboratory. He then instructed the study physicians to decrease, maintain, or increase the dose. Feedback on subjects randomized to placebo was based on a blocked schedule, so that all study clinicians remained blinded to the condition of randomization.

Baseline Measures

Autism diagnostic interview-revised (ADI-R). The ADI-R is a semi-structured psychiatric interview designed for the study of ASD and related disorders, typically administered to the subject's primary caretaker/family members (Rutter *et al*, 1994).

Autism diagnostic observation schedule-generic (ADOS-G). This instrument was developed as a companion instrument for ADI-R. It is a standardized protocol for the observation of social and communicative behavior in children, adolescents, and adults (Lord *et al*, 1998).

Leiter international performance scale-revised (Leiter-R). The Leiter-R is a nonverbal measure of intelligence and cognitive abilities. As it is nonverbal, it is especially suitable for children and adolescents who are cognitively delayed or autistic, as well as for those who are nonverbal, non-English speaking, ESL, or speech-, hearing-, or motor impaired. It has been used extensively in pharmacological studies of children with ASD (Roid and Miller, 1995,1997).

Primary Outcome Measures

We evaluated efficacy using the Clinical Global Impression-Improvement Scale (CGI-I) focusing on irritability, and the irritability subscale of the Aberrant Behavior Checklist (ABC).

The clinical global impression-improvement (CGI-I). The CGI-I is a 7-point improvement scale. Ratings of 1 or 2 (responders) indicate a substantial reduction in symptoms, so that a treating clinician would be unlikely to readily change the treatment regimen. A rating of 3 (minimally improved) on the CGI is defined as a slight symptomatic improvement that is not deemed clinically significant; patients with such an improvement were not considered responders. We used two versions of this test, one focused on irritability (primary outcome measure) and a general version CGI-I-autism focused on all symptoms including core symptom domains. The CGI-I irritability took into consideration the scores from the ABC-Irritability subscale, the OAS-M aggression and irritability subscales and information from open-ended questioning related to the degree of interference, nature, and range of behavioral problems at school and at home (Guy, 1976).

The aberrant behavior checklist (ABC)-community version (Irritability subscale). ABC-community version is the community version of the original residential version. It is designed to objectively identify five behavior subscales through observation by the primary caregiver: irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech. The ABC was filled out by parents (Aman *et al*, 1985).

Secondary Outcome Measures

The Overt Aggression Scale-Modified (OAS-M). The OAS-M is an instrument developed on the basis of an earlier version (the original Overt Aggression Scale, OAS), as well as on the basis of the Schedule for Affective Disorders and Schizophrenia (SADS) (Coccaro *et al*, 1991). It has been previously used in pediatric studies (Buitelaar *et al*, 2001), although the psychometric data for the scale was originally determined in adults.

The Child–Yale–Brown Obsessive-Compulsive Scale (CYBOCS). CYBOCS was used as a secondary measure to examine the effect of divalproex sodium on repetitive behaviors. The Child–Yale–Brown Obsessive-Compulsive Scale rates, on a 5-point scale, the time spent, distress, interference, resistance, and control in relation to obsessions and compulsions. It has been shown to be a reliable and valid scale in ASD populations, and in measuring change in treatment studies of ASD (McDougle *et al*, 1995).

Exploratory Outcome Measures

Vineland Adaptive Behavior Scale. This is a semistructured informant interview that assesses the daily functioning of subjects. The scale has been normed for the autistic population. Items are classified under four major adaptive domains: communication, daily living skills, socialization, and motor skills (Sparrow *et al*, 1984).

Young Mania Rating Scale (YMRS). It is a checklist of 11 items that was designed to measure the severity of manic symptoms and to gauge the effect of treatment on mania severity. Youngstrom *et al* reported on the scale's psychometric properties in children. The scale was administered as a parent report (Young *et al*, 1978; Youngstrom *et al*, 2003).

Electroencephalogram (EEG). A sleep-deprived EEG was attempted in all participants. No sedation was used. The EEGs were reviewed by an experienced neurologist and were classified as epileptiform if spike activity was noted, abnormal but not epileptiform if other nonspecific abnormalities were noted, or normal. Given the small number of EEGs, no attempt was made to discuss the localization of epileptiform abnormalities or specific patterns.

Safety Measures

A physical examination was conducted at baseline and end visits. Blood monitoring of hematopoietic, liver, and renal function was carried out at baseline, weeks 2 and 4, and at end visit. Weight, height, and BMI were recorded at baseline and at end visit and vital signs were taken at baseline, weeks 2 and 4, and at end visit. Adverse event monitoring took place every week for the first 4 weeks and every 2 weeks thereafter. Questioning was focused on known side effects of divalproex sodium, followed by open-ended questioning. The side effects specifically elicited included nausea, vomiting, stomachaches, appetite changes, dizziness, tremors, confusion, headaches, hair loss, and weight changes.

Statistical Methods

Baseline characteristics. Independent samples *t*-tests were used to determine whether there were baseline differences between treatment groups on the following potential covariates: age, intelligence level, and baseline severity (ABC and OAS-M irritability subscales).

Outcome measures. CGI-I (χ^2analysis). Consistent with intent-to treat principles, for those subjects missing the week-12 ratings, we imputed their value on the CGI at week 12 using mixed regression models based on the available values from all subjects and all seven time points. The predicted scores were then used to classify the subjects as responders or nonresponders at week 12 on the basis of the following: CGI $\leqslant 2$ (responders) or CGI >2 (nonresponders). χ^2 test was used to compare the response between groups.

ABC, OAS-M, CYBOCS, VINELAND, YMRS (Mixed Model Analysis). Data sets were evaluated for skewness and outliers, and winsorized if necessary. In these analyses, we used all available data across all time points and fit a four-parameter mixed effects regression model to evaluate the weeks *x* effect. We specified an unstructured covariance ('MANOVA') matrix to obtain the error terms in the analyses.

RESULTS

Participant Disposition

A total of 55 children signed consent for this trial. Of them, 27 were randomized and were included in the safety and efficacy analysis. Nonrandomized subjects either did not meet the criteria for ASD or for adaptive functioning more than 2 years ($n=23$) or withdrew their consent before randomization ($n=13$). A total of 16 subjects were randomized to active treatment and 11 to placebo. Three subjects withdrew from the study before week 12 (two on active compound and one on placebo). Only one patient on active compound discontinued because of side effects (Figure 1).

Baseline Characteristics

All children met ASD criteria on both ADI-R and ADOS-G. Four of the 27 children had no phrase speech delay and were therefore classified as having Asperger's disorder (see Table 2 for subject characteristics). There were no significant differences in baseline characteristics, except for IQ: the placebo group had a significantly higher mean full-scale IQ ($t=2.57$, df $=23$, $p=0.017$). Thus, we evaluated the effects of treatment using full-scale IQ score as a covariate in the analyses. No subjects had epilepsy and none were on anticonvulsant medications. Eight subjects met our *a priori* OAS-M aggression entry criteria but not the ABC-Irritability entry criteria, likely reflecting children with significant aggressive outbursts but low levels of irritability throughout the day. In addition, a total of seven children had previous exposure to risperidone.

Efficacy Analysis

Primary. CGI-I for Irritability. On the basis of intent-to treat analyses, 10 of the 16 active treatment subjects (62.5%) showed a response tn irritability, whereas only one of the placebo subjects (9.09%) showed a response (OR $=16.66$). This effect is significant by Fisher's exact test ($p=0.008$). The odds ratio indicates that subjects receiving treatment with divalproex sodium are over 16 times more likely to respond to treatment than subjects receiving placebo. To control for the IQ differences between groups, we reanalyzed the data using a logistic regression model, with IQ as a continuous variable. The effect remains significant ($p=0.045$).

ABC-Irritability subscale. There is a significant weeks *x* condition interaction ($t=-2.09$, df $=22.71$, $p=0.048$), suggesting that the active group showed a drop of more than 0.53 points per week compared with the placebo group on the ABC parent irritability ratings (Figure 2). The significant condition *x* weeks interaction remains significant and indeed the effects seem somewhat stronger after controlling for IQ differences ($t=-2.28$, df $=20.38$, $p=0.033$). The mean irritability scores at baseline and at end point were the following: $\text{divalproex}_{\text{baseline}}$ 22 (7.81), $\text{divalproex}_{\text{end}}$ 14.5 (6.67), $\text{placebo}_{\text{baseline}}$ 20.30 (7.36), $\text{placebo}_{\text{end}}$ 17.70 (7.94), effect size $d=0.44$ (moderate effect size).

Secondary. OAS-M Irritability subscale. For two of the time points (weeks 0 and 8), the scale has a negative skew $>|1.0|$. On the basis of both winsorized ($t=-1.09$, df $=23.44$, $p=0.28$) and nonwinsorized ($t=-1.37$, df $=24.01$, $p=0.181$) data, no statistically significant improvement in this measure was noted in subjects receiving divalproex *vs* placebo. Controlling for the IQ differences did not change these conclusions. The mean irritability scores at baseline and end point were the following: $\text{divalproex}_{\text{baseline}}$ 6.43 (1.41), $\text{divalproex}_{\text{end}}$ 5.42 (2.17), $\text{placebo}_{\text{baseline}}$ 5.36 (2.2), $\text{placebo}_{\text{end}}$ 6.25 (1.28).

CYBOCS. Mixed model analysis was used to examine the effect of divalproex sodium *vs* placebo on repetitive behaviors as measured by CYBOCS. There were no statistically significant differences between groups ($p=0.748$).

Exploratory Analysis

Vineland adaptive behavioral scale, YMRS. There were no statistically significant differences between groups in either the Vineland domains (communication: $p=0.865$, daily living: $p=0.77$, socialization: $p=0.119$) or the YMRS ($p=0.987$). Controlling for IQ did not change these findings.

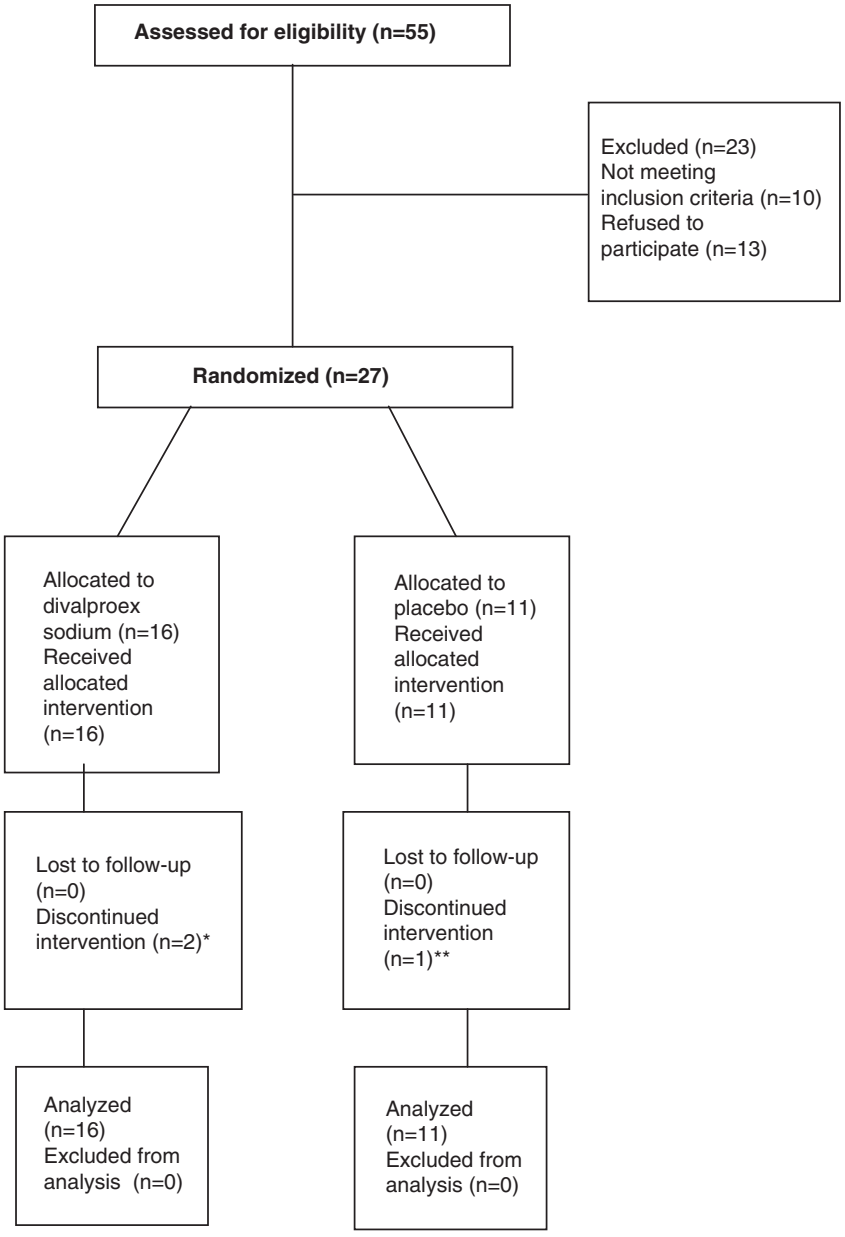

Figure 1 Consort diagram. *One subject withdrew because of side effects, one subject withdrew for nonefficacy. **One subject withdrew because of side effects.

CGI-I autism. There were only two responders, both from the divalproex group. As such, 12.5% of divalproex subjects responded at week 12, whereas 0% of the placebo group responded. The small number of responders, with none in the placebo group, only allowed for the computation of a Fisher's exact probability to test the relationship of response to treatment. This relationship is not significant ($p = 0.499$).

Relation of EEG, Blood Levels and Treatment Response

Relation of IQ to EEG findings. In our sample, the mean nonverbal IQ was higher for subjects with epileptiform abnormalities than for those with no epileptiform abnormalities (92.75 *vs* 65.9).

Relation of response to EEG findings. We were able to obtain a sleep-deprived EEG at baseline for 19 of the 27 children. Of these, 17 EEGs included interpretable records and 10 of those were within the active group. Given the small sample size, the data are exploratory but intriguing, given the paucity of data regarding the effect of epileptiform abnormalities on treatment response in ASD. Table 3 suggests that subjects with abnormal/epileptiform EEGs (2/3), especially those with epileptiform EEGs (2/2), may be more likely to respond to divalproex sodium than subjects with normal EEG records (4/7).

Relation of response to valproate levels and mean dose. We examined whether valproate blood levels or dose correlated with improved outcomes in this sample. This analysis includes only the active group ($n = 16$). Responders tended

Table 2 Subject Characteristics

Characteristic	Total sample ($n=27$)	Placebo ($n=11$)	Divalproex sodium ($n=16$)
Gender *n* (%)			
Male	23 (83.6)	10 (90.1)	13 (81.3)
Female	4 (16.4)	1 (9.9)	3 (18.7)
Age (years)			
Mean (SD)	9.46 (2.65)	8.97 (2.8)	9.66 (2.64)
Range	4.85–14.92	4.85–14.05	5.31–14.92
Ethnicity n (%)[a]			
White nonhispanic	8 (29.6)	4 (36.4)	4 (25)
Hispanic	6 (22.2)	1 (9.1)	5 (31.3)
Black	6 (22.2)	2 (18.2)	4 (25)
Asian	3 (11.1)	3 (27.3)	0
Other	2 (7.4)	1 (9.1)	1 (6.3)
More than one race	2 (7.4)	0	2 (12.5)
Diagnosis n (%)			
Autistic disorder	23	9	14
Asperger's syndrome	4	2	2
Baseline severity			
CGI-S-Irritability mean (SD)	4.96 (0.65)	4.73 (0.47)	5.13 (0.72)
OAS-M Irritability mean (SD)	6 (1.82)	5.36 (2.2)	6.43 (1.41)
ABC-Irritability mean (SD)	21.29 (7)	20.77 (7.64) $n=9$	22 (7.46) $N=7$
IQ full-scale[b]			
Mean (SD)	63.3 (23.9)	76.1 (26.45)	52.92 (18.5)
Range	30–126	41–126	30–89
Vineland			
Mean (SD)	39.24 (16.34)	42.4 (17.21)	37.13 (15.9)
Range	20–68	20–68	20–68

[a]Ethnicity data was collected to assure that we do not recruit subjects from a single racial group. The categories were predefined by the investigator, and the subjects classified themselves.
[b]All baseline differences are not significant except for IQ ($t=2.57$, df $=23$, $p=0.017$).

to have higher mean valproate blood levels compared with nonresponders: 89.77 (31.7) *vs* 64.33 (59.3), respectively. Subjects with therapeutic valproate levels between 87 and 110 mcg/ml had a 100% response rate on the CGI-Irritability Scale, whereas subjects with levels <87 had a 60% response rate and subjects with levels >110 had a response rate of 33%. Valproate dose had a moderate effect on improvement scores: responders 25.5 (8.58) mg/kg *vs* nonresponders 22.7 (0.83) mg/kg.

Safety Analysis

Divalproex sodium was well tolerated within this group. Most side effects were mild to moderate in severity and most resolved with small changes in dosing and did not require a discontinuation of medication. Table 4 lists all reported side effects that were different from baseline. The only treatment emergent side effect that was cited as a reason for discontinuation was a paradoxical increase in irritability associated with insomnia on just 250 mg of active compound in one participant. The side effect resolved with tapering off of the medication. No serious adverse events were reported in this cohort. Increased aggression was reported as a side effect in two subjects in the active group and in one subject in the placebo group. No cases of altered mental status were reported and no abnormalities in systolic/diastolic blood pressure or heart rate were noted at any visits for any of the subjects. There were no clinically meaningful elevations of liver function tests, no suppression of blood lines, and no cases of pancreatitis. There were no significant differences in weight gain between groups (weight $\text{gain}_{\text{placebo}} = 2.95 \pm 3.37$ lbs, weight $\text{gain}_{\text{active}} = 3.02 \pm 6.41$ lbs), but one subject in the active group had a clinically significant weight gain ($>7\%$ of starting weight). This subject had a trough valproate level of 104 μg/ml. Given that we had only one subject with such weight gain in the active group, we cannot reach any conclusion regarding the relationship between significant weight gain and blood levels. Unfortunately, height measurements proved to be very difficult and were tolerated by only a small number of children.

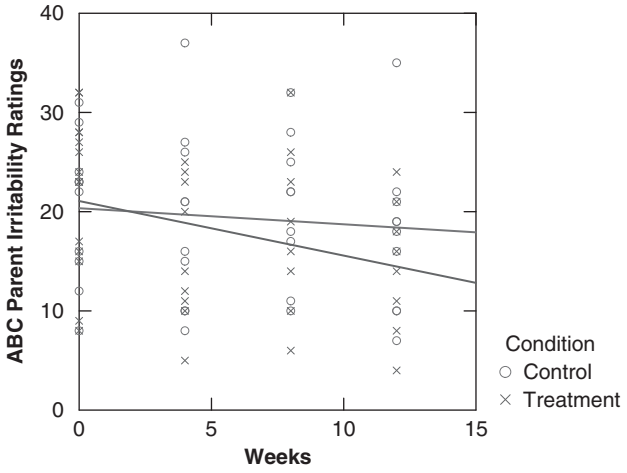

Figure 2 Improvements in ABC-Irritability subscale in divalproex *vs* placebo-randomized subjects over 12 weeks. There is a significant weeks *x* condition interaction ($t=-2.09$, df $=22.71$, $p=0.048$), suggesting that the active group showed a drop of more than 0.53 points per week compared with the placebo group. Note that the scatter plot includes all subjects, but the symbols correspond to ABC values. Some subjects had identical scores and are therefore reflected in a single overlapping symbol.

DISCUSSION

This study suggests that valproate may be effective in the treatment of irritability in ASD. There are several reasons why this may be the case. First, the GABA-enhancing mechanism of valproate may be relevant to both the pathophysiology of aggression and that of ASD (Bjork *et al*, 2001; Casanova *et al*, 2003). Second, the documented ability of valproate to inhibit kindling has been proposed as

Table 3 CGI-Irritability Treatment Response Based on Drug Status and EEG Results

Divalproex responders[a]			Placebo responders[a]		
62%			9%		
Abnormal EEG[b]: 2/3 (66.6%)	Epileptiform 2/2 (100%)	Normal 4/7 (57%)	Abnormal EEG[b] 0/3 (0%)	Epileptiform 0/3 (0%)	Normal 1/4 (25%)

[a]% of sample randomized to each condition that was classified as 'responder'.
[b]Epileptiform and non epileptiform abnormalities.

Table 4 Adverse Events[a]

Divalproex	Placebo
Insomnia (mild): 1[b]	Insomnia (mild): 1
Insomnia (severe): 1	Insomnia (moderate): 1
Weight gain (moderate): 1	Weight gain (moderate): 1
Headache (mild): 1	
Rash (mild, viral): 2	
Polyuria (mild): 2	
Agitation (mild): 1	Agitation (mild): 1
Agitation (severe): 1	
	Hypersomnolence (mild): 3
Infections (viral): 2	Infection (viral): 3

[a]Within the active group, five participants experienced more than one side effect whereas within the placebo group two participants experienced more than one side effect.
[b]Number of subjects presenting with the adverse event.

an additional mechanism that may explain its effectiveness in treating mood lability, and as such, may be particularly important in the treatment of irritability (Soderpalm, 2002). Third, the treatment of underlying epileptiform abnormalities may contribute to behavioral response. This theory, although controversial, is supported by our very preliminary data that showed that children randomized to divalproex sodium with epileptiform EEGs were classified as responders. This hypothesis is further supported by a report by Stoll *et al* (1994), who reviewed 115 bipolar and schizoaffective lithium-refractory patients and found that those with a seizure or head injury history and abnormal EEG findings were much more likely to have a robust response to valproate (70%). Of interest, our sample had a mean nonverbal IQ below 70 and a systematic review of the literature has suggested that children with IQs under 70 are more likely to have seizures and epileptiform EEGs (Amiet *et al*, 2008). However, the usual pattern did not hold true, with the mean IQ actually being higher in children with epileptiform abnormalities than in children with nonepileptiform EEGs. Thus, our small sample does not support this well-documented phenomenon, but is limited by a small sample size.

We would also like to make note of our preliminary findings suggesting that therapeutic blood levels of valproate are associated with better response. Such results are congruent with data from a large study of valproate in adults with acute mania, in which it was reported that subjects with valproate blood levels of 87 mcg/ml or higher had improvement that was twice the effect size compared with subjects with blood levels less than 87 mcg/ml (Allen *et al*, 2006). Although our sample size did not allow for proper dose response and blood level response analysis, it is suggestive enough to highlight the need for a larger study designed and powered to address this issue.

The results of this study are not congruent with the report from the previous small randomized study of this drug in ASD (Hellings *et al*, 2005). As previously mentioned, the authors reported high intersubject variability and a large placebo effect, and recommended further evaluation. We would like to suggest that our strategy of stratifying for irritability severity at baseline and enrolling only those subjects with significant difficulties in this domain may be responsible for decreased intersubject variability and increased power in this study.

The safety profile of valproate in this study was very good. One should not assume though that the safety profile of a medication in a short-term study would be reflective of a long-term safety with this medication. Reported side effects of this medication include abdominal discomfort, nausea/vomiting, ataxia and tremor, hyperammonnemic encephalopathy, headaches, and weight gain. Serious side effects such as hepatic insufficiency and agranulocytosis have been rarely reported. One should consider the fact that the frequency of the rare side effects is much higher in children under the age of 2 years, and as such, the use of this medication in that age group remains controversial. There is also much controversy on the prevalence of polycystic ovarian syndrome, which is of concern to parents of high-functioning children in terms of its effects on fertility. Finally, although only one child in our cohort showed significant weight gain, such a side effect has been reported extensively in studies on other disorders, and follow-up studies will be critical in assessing the risk for cardiovascular and metabolic outcomes.

Limitations of our study include the relatively small sample size, which did not allow for a complete analysis of EEG and valproate blood level data. In addition, the absence of an EEG record at the end of the study makes it impossible for investigators to determine whether an improvement in EEG patterns correlated with treatment response. The choice of the ABC-Irritability subscale, although a validated measure in ASD, precludes us from making recommendations regarding specific types of aggression that may be responsive to divalproex. The fact that only seven children had previous exposure to an atypical antipsychotic also did not allow us to explore whether those with previous risperidone treatment were less responsive to valproate *vs* those without previous risperidone, and this remains a question for a future trial.

Of interest, there was no change in Vineland scores in this acute trial. The effect sizes of improvement noted in Vineland in the RUPP risperidone studies were small to medium and documented mostly at 6 months of treatment (Williams *et al*, 2006). In the acute phase and with our sample size, we did not have the power to detect

such effects. Qualitative reports of relief due to decreased aggression did not seem to affect the scores on Vineland. There was also no change in CGI-I autism, which is not surprising, given that core symptom domain severity was scored within this measure. Finally, OAS-M did not seem to be sensitive to the changes detected by ABC. OAS-M is not a validated measure in ASD and does not have pediatric psychometric data, and we identified conceptual issues related to how this scale is scored that make it difficult to obtain reliable information in this population. For example, a child with relatively benign repetitive hitting of her chest that was continuous throughout the day was likely to get worse scores than children with more rare but severe self-injury.

Although it is hard to compare the effect size of a pilot study with that of a multicenter trial, the effect size for improvement on the ABC-Irritability subscale is moderate, but less than what was reported in the RUPP risperidone trial (very large). A follow-up of larger trials will be required for an appropriate comparison between the two drugs in terms of effect size of response and safety. In addition, a larger sample study powered to address the question of whether the presence of epileptiform abnormalities, while controlling for IQ, affects differential treatment response to anticonvulsants compared with atypicals, and whether treatment response is mediated by improvements in epileptiform abnormalities is required.

ACKNOWLEDGEMENTS

We thank Dr Audrey King, Ms Karen Zagusrky, Ms Nadia Tanel, and Ms Stephanie Lee for their assistance with data collection. This project was funded by NINDS R21 NS4 3979-01, E Hollander, PI. Active medication and matching placebo were provided by Abbott Laboratories. In addition, this publication was made possible by Grant Number MO1-RR00071 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NCRR or NIH.

DISCLOSURE

Eric Hollander received consultation fees from Abbott, Neuropharm, Nastech, BMS, and Forest; received research grants from Abbott, and UBS Pharma; and has intellectual property related to oxytocin and memantine and ASD. Evdokia Anagnostou received a consultation fee by InteGragen. The rest of the authors have nothing to disclose.

CLINICAL TRIAL REGISTRATION

Clinicaltrials.gov
Title: Divalproex Sodium *vs* Placebo in Childhood/Adolescent ASD; ClinicalTrials.gov Identifier: NCT00211757; URL: http://clinicaltrials.gov/ct2/show/NCT00211757?term = ASD+and+divalproex&rank = 1.

REFERENCES

Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL (2006). Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry* **163**: 272–275.

Aman M, Singh N, Stewart A, Field C (1985). The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic* **89**: 485–491.

Aman MG (2004). Management of hyperactivity and other acting-out problems in patients with ASD spectrum disorder. *Semin Pediatr Neurol* **11**: 225–228.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR*, 4th edn. American Psychiatric Association: Washington, DC.

Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P *et al* (2008). Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. *Biol Psychiatry* **64**: 577–582.

Belsito KM, Law PA, Kirk KS, Landa RJ, Zimmerman AW (2001). Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *Journal of ASD and Developmental Disorders* **31**: 175–181.

Bjork JM, Moeller FG, Kramer GL, Kram M, Suris A, Rush AJ *et al* (2001). Plasma GABA levels correlate with aggressiveness in relatives of patients with unipolar depressive disorder. *Psychiatry Res* **101**: 131–136.

Buitelaar JK, van der Gaag RJ, Cohen-Kettenis P, Melman CT (2001). A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. *J Clin Psychiatry* **62**: 239–248.

Casanova MF, Buxhoeveden D, Gomez J (2003). Disruption in the inhibitory architecture of the cell minicolumn: implications for ASD. *Neuroscientist* **9**: 496–507.

Chen G, Huang LD, Jiang YM, Manji HK (1999). The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. *J Neurochem* **72**: 1327–1330.

Coccaro E, Harvey P, Kupsaw L, Herbert J, Herbert JL, Bernstein DP (1991). Development of neuropharmacologically based behavioral assessments of impulsive aggressive behavior. *J Neuropsychiatry Clin Neurosci* **3**: S44–S51.

Craft M, Ismail IA, Krishnamurti D, Mathews J, Regan A, Seth RV *et al* (1987). Lithium in the treatment of aggression in mentally handicapped patients: a double blind trial. *Br J Psychiatry* **150**: 685–689.

Damore J, Stine J, Brody L (1998). Medication-induced hypomania in Asperger's disorder. *J Am Acad Child Adolesc Psychiatry* **37**: 248–249.

Donovan SJ, Susser ES, Nunes EV, Stewart JW, Quitkin FM, Klein DF (1997). Divalproex treatment of disruptive adolescents: a report of 10 cases. *J Clin Psychiatry* **58**: 12–15.

Göttlicher M (2004). Valproic acid: an old drug newly discovered as inhibitor of histone deacetylases. *Annu Hematol* **83**(Suppl 1): S91–S92.

Guy W (1976). *ECDEU Assessment Manual for Psychopharmacology. Revised. NIMH Publication DHEW Publ No (adm.) 76-388*. National Institute of Mental Health: Bethesda, MD, 217–222.

Hellings JA, Weckbaugh M, Nickel EJ, Cain SE, Zarcone JR, Reese RM *et al* (2005). A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol* **15**: 682–692.

Hollander E, Dolgoff-Kaspar R, Cartwright C, Rawitt R, Novotny S (2001). An open trial of divalproex sodium in ASD spectrum disorders. *J Clin Psychiatry* **62**: 530–534.

Hollander E, Tracy KA, Swann AC, Coccaro EF, McElroy SL, Wozniak P *et al* (2003). Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacology* **28**: 1186–1197.

Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB (2005). Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am J Psychiatry* **162**: 621–624.

Jesner OS, Aref-Adib M, Coren E (2007). Risperidone for ASD spectrum disorder. *Cochrane Database Syst Rev* (1). Art. No. CD005040.

Kastner T, Finesmith R, Walsh K (1993). Long-term administration of valproic acid in the treatment of affective symptoms in people with mental retardation. *J Clin Psychopharmacol* **13**: 448–451.

Kerbeshian J, Burd L, Fisher W (1987). Lithium carbonate in the treatment of two patients with infantile ASD and atypical bipolar symptomatology. *J Clin Psychopharmacol* **7**: 401–405.

Lord C, Rutter M, DiLavre PC (1998). *ASD Diagnostic Observation Schedule-Generic (ADOS-G)*. Psychological Corp: San Antonio, TX.

Manji HK, Chen G (2000). Post-receptor signaling pathways in the pathophysiology and treatment of mood disorders. *Curr Psychiatry Rep* **2**: 479–489.

Mattes JA (1992). Valproic acid for nonaffective aggression in the mentally retarded. *J Nerv Ment Dis* **180**: 601–602.

McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG *et al* (2002). Research units on pediatric psychopharmacology autism network. Risperidone in children with autism and serious behavioral problems. *Engl J Med* **347**: 314–321.

McDougle CJ, Kresch LE, Goodman WK, Naylor ST, Volkmar FR, Cohen DJ *et al* (1995). A case-controlled study of repetitive thoughts and behaviors in adults with autistic disorder and obsessive-compulsive disorder. *Am J Psychiatry* **152**: 772–777.

Roid GH, Miller LJ (1995;1997). *Leiter International Performance Scale-Revised*. Stoelting Co.: Wood Dale, Il.

Rutter M, Lord C, LeCouteur A (1994). *ASD Diagnostic Interview-Revised (ADI-R)*, 3rd edn. Department of Psychiatry: University of Chicago.

Soderpalm B (2002). Antivonvulsants: aspects of their mechanism of action. *Eur J Pain* **6**(suppl A): 3–9.

Sovner R (1989). The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. *J Clin Psychiatry* **50**: 40–43.

Sparrow S, Balla D, Cicchetti DV (1984). *Vineland Adaptive Behavior Scales (Survey Form)*. American Guidance Service: Circle Pines, MN.

Stoll AL, Banov M, Kolbrener M, Mayer PV, Tohen M, Strakowski SM (1994). Neurologic factors predict a favorable valproate response in bipolar and schizoaffective disorders. *J Clin Psychopharmacol* **14**: 311–313.

Szyf M (2009). Epigenetics, DNA methylation, and chromatin modifying drugs. *Annu Rev Pharmacol Toxicol* **49**: 243–263.

Teingard R, Biederman J (1987). Lithium, responsive manic-like symptoms in two individuals with ASD and mental retardation. *J Am Acad Child Adolesc Psychiatry* **26**: 932–935.

Vebrant P, Bauziene R (1994). Intractable epilepsy in children. The efficacy of lamotrigine treatment including non-seizure-related benefits. *Neuropediatrics* **25**: 284–289.

Wasserman S, Iyengar R, Chaplin WF, Watner D, Waldoks SE, Anagnostou E (2006). Levetiracetam versus placebo in childhood and adolescent ASD: a double-blind, placebo-controlled study. *Int Clin Psychopharmacol* **21**: 363–367.

Williams SK, Scahill L, Vitiello B, Aman MG, Arnold LE, McDougle CJ *et al* (2006). Risperidone and adaptive behavior in children with ASD. *J Am Acad Child Adolesc Psychiatry* **45**: 431–439.

Yasuda S, Liang MH, Marinova Z, Yahyavi A, Chuang DM (2009). The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. *Mol Psychiatry* **14**: 51–59.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry* **133**: 429–435.

Youngstrom EA, Gracious BL, Danielson CK, Findling RL, Calabrese J (2003). Toward an integration of parent and clinician report on the Young Mania Rating Scale. *J Affect Disord* **77**: 179–190.