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A Double-Blind, Placebo-Controlled Study of Valproate for Aggression in Youth with Pervasive Developmental Disorders

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ABSTRACT

Objective: **The aim of this study was to study valproate efficacy and safety for aggression in children and adolescents with pervasive developmental disorders (PDD).**

Methods: **In this prospective double-blind, placebo-controlled study, 30 subjects (20 boys, 10 girls) 6–20 years of age with PDD and significant aggression were randomized and received treatment with valproate (VPA) or placebo (PBO) for 8 weeks as outpatients. Mean VPA trough blood levels were 75.5 mcg/mL at week 4 and 77.8 mcg/mL at week 8.**

Results: **No treatment difference was observed statistically between VPA and PBO groups. The Aberrant Behavior Checklist—Community Scale (ABC-C) Irritability subscale was the primary outcome measure (p = 0.65), and CGI—Improvement (p = 0.16) and OAS (p = 0.96) were secondary outcome measures. Increased appetite and skin rash were significant side effects. Only 1 subject was dropped from the study owing to side effects, notably a spreading skin rash, which then resolved spontaneously. Two subjects receiving VPA developed increased serum ammonia levels, one with an associated parent report of slurred speech and mild cognitive slowing. Poststudy, of 16 VPA and PBO subjects receiving VPA, 10 subjects demonstrated sustained response, 4 of whom later attempted taper, with significant relapse of aggression.**

Conclusion: **The present negative findings cannot be viewed as conclusive, partly owing to the large placebo response, subject heterogeneity, and size of the groups. Larger studies are needed to expand upon these findings.**

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INTRODUCTION

Aggression is the most-common form of serious problem behavior in persons with developmental disabilities (for review, see Murphy 1997). By definition, aggression encompasses a spectrum of dangerous and destructive behaviors, with links to multiple neurotransmitter systems (Fava 1997). Various classifications exist, principally separating predatory types of aggression from impulsive and affective types (Moyer 1968; Wasman and Flynn 1962). Cognitive, communication, and neurological impairments increase aggression rates, as does a history of sexual or physical abuse, or psychiatric illness, such as psychosis or mania (Lewis et al. 1988). Often, an aggressive individual has several such risk factors. Safe and efficacious treatments for severe aggression are still under investigation.

Several studies have investigated atypical antipsychotic medications, particularly risperidone for aggression in mental retardation (MR) (Aman et al. 2002; Hellings et al. in press; Snyder et al. 2002; Zarcone et al. 2001) and autism (RUPP 2002). However, weight gain, the metabolic syndrome, and Type II diabetes are serious risks associated with risperidone treatment in this population (Hellings et al. 2004; Hellings et al. 2001). Few studies have evaluated the efficacy and safety of medications with links to the gamma-aminobutyric acid (GABA) system, such as valproic acid.

Valproate (VPA) has significant antiaggressive properties in animal models of aggression (Rayevsky and Kharlamov 1983). The inhibitory neurotransmitter GABA may be significantly involved in the different types of aggressive behavior studied in the laboratory, such as mouse-killing by rats and aggression induced by shock and isolation in mice. Earley and Leonard (1977) showed that aggressive responses were inversely related to GABA concentration in certain brain regions of isolated mice. It is suggested that VPA changes the emotional reactivity of the animals, possibly by decreasing the aversiveness of a noxious stimulus. There is also some preliminary reported efficacy of VPA for nonaffective aggression in man. The actual mechanism of the antiaggressive action of VPA in humans has yet to be elucidated; however, the drug is already in widespread use for nonseizure and off-label indications in the population with MR and pervasive developmental disorders (PDDs).

While preliminary open studies continue to support the general antiaggressive effect of VPA, conclusions remain limited until more controlled trials are available (Lindenmayer and Kotsaftis 2000). Several preliminary open clinical trials and case series support the efficacy of VPA for aggression in persons with developmental disabilities. Mattes (1992) reported two cases of VPA efficacy in nonaffective aggression in adults with mental retardation (MR as add-on therapy. Two case series (Kastner et al. 1993; Sovner 1989) reported significant improvement in approximately 80% of 23 patients, as measured by frequency counts and clinical impressions. In Kastner's series, irritability and behavioral cycling improved the most, though aggression and self-injurious behavior (SIB) also improved significantly. Donovan et al. (1997) published an open trial of divalproex (DVP) in 10 outpatient adolescents with explosive outbursts, mood lability, and associated fights or property destruction. Subjects with mild MR were included in this study, though autistic disorders were not reported.

Ruedrich et al., in a retrospective chart review, described efficacy of DVP for aggression and self-injury in 28 adults, 20–63 years of age, with MR. Improvement on the CGI—Severity was 71% of patients rated much or very much improved, and 20% minimally improved (Ruedrich et al. 1999). In a significant number of cases, other psychotropic medications could be discontinued (46%), or the dosage reduced (39%). Another open retrospective review of divalproex for 14 persons with ASD and an IQ between 20 and 105, 11–40 years of age found a sustained response to treatment in 64% (Hollander et al. 2001). The most common symptoms observed to improve were impulsivity, aggression, and mood lability.

Thus, the antiaggressive effect appears greatest in patients with mood lability, bipolar disorder, or organic disorders, such as dementia or brain injury, though a nonspecific efficacy has been described in open studies. See Lindenmayer and Kotsaftis (2000) for a critical review.

We examined the efficacy and safety of VPA versus placebo (PBO), targeting aggression in 30 children and adolescents with PDDs 6–20 years of age. This was a randomized, controlled trial of 8 weeks duration. Following the controlled trial, the option was given to continue VPA, stay off medication in the case of PBO responders, or try other medications.

METHODS

Subjects

This study was approved by the Human Subjects Committee of the University of Kansas Medical Center (Kansas City, KS). We obtained written, informed consent from each parent or guardian and assent from subjects when feasible. Recruitment was through the University of Kansas MR/Autism outpatient specialty clinic and through advertising in newspapers, in schools, and on the Internet.

Inclusion criteria were an age of 6–20 years, significant aggression to self, others, or property at least three times per week, and the presence of a PDD. All comorbid *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) (American Psychiatric Association, 1994) Axis I diagnoses, except Tourette's Disorder, were allowed.

Exclusion criteria were a previous adequate VPA trial for any indication or clinical seizures within the past year. Other exclusion criteria were a history of degenerative neurological changes or metabolic disorders, Tourette's Disorder, a history of thrombocytopenia, hepatitis, pancreatitis, pregnancy, or polycystic ovarian syndrome. Concomitant psychotropic or antiseizure medications were not allowed. Stimulant medications were required to be stopped the day before PBO run-in commenced; washout for the 2 subjects receiving tricyclics was 2 weeks and for all other psychotropic medications was 4 weeks.

Baseline measures

Baseline measures included a DSM-IV-based interview with recording of any diagnosable comorbidity, the Autism Diagnostic Inventory—Revised (ADI-R; Lord et al. 1994), and the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 1989). Physical and neurological examinations were performed by the principal investigator PI (J.H.). Each subject's weight, height, blood pressure, and pulse were checked at baseline and at every visit. Screening laboratory tests obtained were CBC (complete blood count) and platelet count, chemistry (10 basic indices, including electrolytes, glucose, aspartate transaminase, urea, and creatinine), alanine transaminase, and plasma ammonia. Baseline measures of the rating scales detailed below were filled out. Intelligence (IQ) was retested, if not updated within the previous 3 years, using the Weschler Intelligence Scale for Children— Revised (WISC-R; Wechsler 1991) or the Stanford Binet, and the Vineland Scales of Adaptive Behavior (Sparrow et al. 1984).

Response and side-effect measures

Treatment response was measured by having the subject's parent and teacher rate the Aberrant Behavior Checklist—Community scale (ABC-C) weekly (Aman et al. 1995) as the primary outcome measure. Parents and teachers were also asked to fill out the description of each aggressive outburst as it occurred on the Overt Aggression Scale (OAS; Yudofsky et al. 1986). Aggression recurring after 30 minutes of nonaggressive behavior was documented as a separate episode. The OAS and Clinical Global Impressions—Improvement Subscale (CGI-I; Guy 1976) were secondary outcome measures.

The ABC-C is a 58-item checklist developed as a measure of treatment effects and for assessing general behavior problems in people with MR in the community. The scale items are divided into five subscales, which were factor analytically derived: (1) Irritability (15 items); (2) Lethargy (16 items); (3) Stereotypic behavior (7 items); (4) Hyperactivity (16 items); and (5) Inappropriate speech (4 items). The ABC, on which the ABC-C is based, has been used extensively in drug research (Aman et al. 1995) in children, adolescents, and adults with MR. The Irritability subscale comprises 15 items rating aggression, including verbal and physi-

cal aggression, property destruction, and self-injury from 0 (not at all) to 3 (frequent).

The OAS is a behavioral frequency and intensity single-incident measure of four categories of aggressive behaviors: Verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against other people. While documenting the aggressive episode, the rater checks one of four weighted severity levels. The weighted scores for each aggression subcategory are then totaled for the total OAS score. While the OAS has not been fully validated in the MR or autistic outpatient population, a preliminary study is available with findings of significant correlation between the OAS and ABC-C Irritability in 8 of the present subjects (Hellings et al. 2005).

In addition, treatment response was rated weekly by the PI using the CGI—Improvement subscale (CGI-I). This is a 7-point Likert Scale; scores range from 1 (Very Much Improved) to 7 (Very Much Worse). In this study, the PI was not completely blinded to side-effect information. Adverse effects of VPA were rated by the study nurse using a checklist derived from the PDR (Physicians' Desk Reference 1997). The unblinded coinvestigator monitored all laboratory results and the PI was blinded to these.

Study design

The study design comprised an 8-week trial of two parallel groups of subjects, randomized to liquid VPA or PBO by the study pharmacist. The investigators, parents, and teachers were blinded regarding medication or PBO status. A second board-certified child and adolescent psychiatrist (D. E. and then S. C.), not involved in ratings, was responsible for VPA dosage adjustment to obtain trough blood levels between 70 and 100 mcg/mL after measurement at the end of weeks 2 and 4, without breaking the blind to parents. We informed parents at the time of consent that in some, but not all, cases they would receive a telephone call with an order to adjust the dose to be given. This would be no indication of whether their child was receiving active drug or placebo, however. Mock dosage adjustment was made for the placebo group, using a randomized system by patient number, determined before the start of the study. Blood level of VPA was also obtained at the end of the study, week 8. Isolated doses of rescue medications (diphenhydramine) were allowed if parents first contacted the study nurse and PI.

All subjects received a 1-week PBO lead-in, followed by a random assignment to receive VPA or PBO in liquid form for 8 weeks. The purpose of the placebo run-in was to exclude placebo responders and those noncompliant with the study liquid. For subjects in the active drug group, VPA liquid (250 mg/5ml) was gradually introduced from day 1 of the active phase, by adding 250 mg every 3rd day, replacing the equivalent amount of PBO liquid, to achieve a dosage of 20 mg/kg/day. At the end of the study, parents were offered the options of continuing VPA treatment, an open trial of VPA if their child had been on PBO, switching to a different medication, or trying without medication treatment.

Statistical methods

All statistical analysis was conducted using SAS Version 8.02 (SAS Institute Inc.; Cary, NC). All p values are based on two-sided tests. A significance level of 0.05 was set prior to the study. A descriptive analysis comparing baseline demographic data for differences between the VPA and PBO groups was performed using a Wilcoxon rank sum test for continuous variables, such as age. Fisher's exact tests were used to compare categorical variables. These were gender, current placement, whether aggression was the worst presenting problem, and parent marital status.

For the power analysis, we used an expected medium to large effect size and a correlation of 0.4 between the measures, for a final sample size of 30 subjects (15 per treatment group). This provided estimated power of at least 0.80 for the proposed analysis. The primary analysis was performed using a Wilcoxon rank sum test, comparing drug and PBO groups on the ABC-C Irritability subscale score difference between the end of the PBO run-in (as baseline) and post-treatment. For post-treatment scores, we used means of the scores obtained

at weeks 6, 7, and 8, as aggression is highly variable over time and also affected by external triggers, which could vary from week to week. This data analysis was based on intent to treat, and, for subjects completing at least 1 week, but fewer than 8 weeks of treatment, the last score was carried forward as the post-treatment score. Parents filled out the ABC-C at each weekly visit. Teacher ratings of the ABC-C were less systematic, and even less so for the OAS. Therefore, only parent ratings were used in the data analysis.

We also analyzed the data in two additional ways: (1) using completing subjects only and (2) using a repeated measure analysis of variance (ANOVA) with a multiple imputation procedure to impute missing data. All three methods yielded similar results. To analyze the secondary measures, notably OAS and CGI—Improvement, we again used the Wilcoxon rank sum test on the difference between initial and post-treatment scores. To evaluate VPA side effects, the Fisher's exact test was used to compare side effects occurring in at least 10% of subjects for significance between the VPA and PBO groups.

RESULTS

Subjects were enrolled from 1998 to 2003. Of 139 patients screened, 36 child and adolescent outpatients were consented, after which 30 patients (20 boys and 10 girls), 6–20 years of age, proceeded in the study to receive VPA or PBO. Six subjects dropped out before randomization to study drug or placebo for the following reasons: Much improved (n = 1), lost to follow-up (n = 2), noncompliance with study liquid (n = 1), and serious worsening after attempted taper of stimulant medication (n = 2). All subjects met criteria for aggression and either Autistic disorder (AD), pervasive developmental disorder—not otherwise specified (PDD-NOS) (n = 1), or Asperger's disorder (n = 2). While subjects were initially required to have MR (n = 26), we later expanded recruitment to include subjects with borderline intellectual functioning (n = 2) or average intelligence (n = 1), or above-average intelligence (n = 1).

Thirty subjects proceeded beyond the PBO run-in week. There were 20 boys and 10 girls, of which 27 were Caucasian, 2 were African-American, and 1 was Hispanic. Mean age was 11.2 years (S.D. ± 4.2 years). Sixteen subjects received VPA, and 14 subjects received PBO. Twenty-seven subjects met criteria for Autistic disorder on ADI and ADOS. One subject (3%) was diagnosed with PDD-NOS and 2 subjects (7%) with Asperger's disorder. Levels of MR were mild (n = 7), moderate (n = 16), or severe (n = 1). The mean IQ of the sample was 54 (range, 20–137). Two subjects had average or above-average IQ, and 2 subjects had borderline intellectual functioning. Another 2 subjects had missing IQ data but had no expressive language and probable MR clinically. Thirteen of 16 subjects (81.2%) who received VPA, and 12 of 14 subjects (85.7%) who received PBO completed all 8 weeks of the study. One subject completed 7 weeks, 2 completed 3 weeks, 1 completed 2 weeks, and 1 completed 1 week. Data from subjects completing 3, 2, or 1 week(s) was used in the intent-to-treat analysis. All of the subjects who dropped out of the study before the last scheduled visit manifested dangerous aggression, except for one who was advised to discontinue the study after 3 weeks owing to a spreading skin rash. Isolated doses of diphenhydramine rescue medication were used in 3 subjects, 1 of whom was severely hyperactive and dropped out after 2 weeks. An additional 4 subjects received isolated doses (range, 1–8) of diphenhydramine for upper respiratory infections, and 1 subject received 2 doses for a transient skin rash. No other rescue medications were used. Of the 14 subjects who had received PBO in the blinded study, 6 subjects' parents elected to have them receive an open trial of VPA. None of the placebo-responders' parents elected to have them try the drug.

The mean VPA blood level at week 4 was 75.5 mcg/dL, and at week 8 was 77.7 mcg/dL (range, 58.6–101.1). Subject demographics are summarized in Table 1, which shows no demographic difference between drug and placebo groups. For treatment outcome, the Wilcoxon rank sum test did not show a statistically significant treatment difference between the VPA and PBO groups. Table 2 shows that this finding held for the primary measure of outcome,

TABLE 1. DEMOGRAPHICS OF SUBJECTS RANDOMIZED (n = 36)

	Placebo group	*Valproate group*	*p value*
Age, mean ± standard deviation	12.1 ± 4.8	10.3 ± 3.7	0.2343
Males, *n* (%)	14 (77.8)	12 (66.7)	0.4568
Current placement home, *n* (%)	18 (100)	18 (100)	1.0000
Day placement school, *n* (%)	18 (100)	16 (88.9)	0.4857
Years current placement, mean ± standard deviation	5.8 ± 4.5	5.0 ± 4.4	0.6175
Parents married, *n* (%)	11 (61.1)	10 (55.6)	0.7353
Aggression worst presenting, *n* (%)	10 (55.6)	8 (47.1)[a]	0.6152

Note: p values for categorical data are based on a two-sided Fisher's exact test.
p values for continuous data are based on a two-sided Wilcoxon rank sum test.
[a]Note one subject missing.

the ABC-C Irritability subscale (p = 0.65), as well as for the secondary outcome measures of CGI—Severity (p = 0.96), CGI—Improvement (p = 0.16), and parent-rated OAS Total Severity (p = 0.96). Analysis of the data comparing completing subjects only in the two groups, and using a repeated-measure ANOVA with imputation for missing data also did not reach significance.

Table 3 shows mean baseline and post-treatment scores for all subjects on the parent-rated ABC-C Irritability subscale for the VPA and PBO groups, parent OAS-Total Severity scores, and investigator-rated CGI—Severity and CGI—Improvement scores. None of the measures reached significance for VPA over PBO. The CGI—Improvement trend may have reached significance with more subjects in each group. The variability in subject scores can be seen from this table. Thus, we did not find a significant difference between VPA and PBO groups in this study.

Side effects were mostly mild and tolerable. Only 1 subject dropped out of the study owing to side effects, notably a spreading skin rash on the trunk and extremities, for which the PI and unblinded child psychiatrist advised study discontinuation. The rash resolved spontaneously after (VPA) liquid discontinuation. The only side effect reaching significance was increased appetite (p = 0.03); skin rash approached significance (p = 0.06). Mean weight gain was 1.98 kg (S.D. ± 1.88) for VPA, and 1.1 kg (S.D. ± 1.10 for PBO) (see Fig. 1). Gastrointestinal complaints of nausea, vomiting, abdominal discomfort, constipation, and diarrhea, and other complaints, including drowsiness, lethargy, headache, chills, and fever, did not differ significantly between drug and PBO groups (see Table 4). Elevations in ammonia were observed above the normal range of 21–50 mcmol/L in 2 subjects receiving VPA. One subject's parent had reported cognitive slowing and slurred speech at times (ammonia level of 98 mcmol/L at the end of the study). No cognitive worsening was noted in the other subject with an ammonia level of 74 mcmol/L at week 8. Clinically significant elevations in transaminase liver enzymes (greater than 100 1U/L) and thrombocytopenia (under 100,000 platelets) did not occur.

TABLE 2. PRIMARY MEASURES

	Placebo group		*Valproate group*		
	Baseline	*End of treatment*	*Baseline*	*End of treatment*	*p value*
ABC Irritability	21.93 ± 11.59	15.45 ± 10.39	23.33 ± 8.58	18.17 ± 8.79	0.65
POAS Total	10.50 ± 11.91	5.72 ± 4.62	10.05 ± 8.25	5.86 ± 3.84	0.96
CGI–Severity	5.40 ± 0.74	4.50 ± 1.06	5.40 ± 0.64	4.50 ± 0.84	0.96
CGI–Improvement	3.64 ± 0.61	2.93 ± 0.93	3.72 ± 0.56	2.56 ± 0.73	0.16

ABC = Aberrant Behavior Checklist; POAS = Parent Overt Aggression Scale; CGI—Severity = Clinical Global Impression—Severity; CGI—Improvement = Clinical Global Impressions—Improvement.
Note: p values were based upon a two-sided Wilcoxon rank sum test.

TABLE 3. SUBJECTS' BASELINE AND MEAN OUTCOME DATA

						CGI-S		CGI-I		P-ABC-I		POAS	
ID	*Group*	*Gender*	*Age*	*Weeks completed*	*Clinical response*	*Mean baseline*	*Mean end*	*Mean baseline*	*Mean end*	*Mean baseline*	*Mean end*	*Mean baseline*	*Mean end*
1	v	F	15	8	yes	6.5	4.67	3	1.67	43.0	30.67	220.0	74.33
2	p	M	19	8	yes	5.5	3.33	4	3.00	22.5	9.33	33.5	18.00
3	v	M	12	7	**no**	5.5	6.00	4	4.00	14.0	21.00	16.0	32.00
4	p	M	11	8	yes	6.0	4.00	3	2.67	23.0	14.33	103.0	46.33
5	p	F	10	8	yes	6.5	4.67	3	2.00	38.5	31.00	128.0	79.33
6	v	M	8	8	yes	5.0	4.33	4	2.33	19.5	12.67	104.0	6.00
7	v	M	7	8	yes	5.5	3.67	4	2.00	19.5	16.00	66.0	34.67
8	v	M	9	8	yes	5.5	3.00	4	2.33	17.0	4.67	30.00	18.00
9	p	M	6	2	**no**	6.0	6.00	4	4.00	29.5	20.00	n/a	n/a
11	p	F	19	8	yes	5.5	3.33	3	2.00	31.5	21.67	9.0	11.67
12	v	F	19	8	yes	4.5	4.67	3	3.00	32.5	29.00	13.0	9.67
13	v	F	8	8	**no**	6.5	5.67	4	3.67	37.0	23.00	37.0	41.00
14	p	M	14	8	yes	4.5	3.00	3	2.00	5.0	0.00	23.0	0.00
15	v	M	8	8	yes	5.5	5.00	4	2.33	21.5	22.67	27.0	45.00
16	p	F	6	8	**no**	5.5	4.67	3	3.00	21.5	22.00	30.0	29.00
17	v	F	12	5	yes	5.0	4.00	3	2.00	18.0	13.00	7.0	49.00
18	v	M	7	8	yes	6.0	4.67	4	2.33	34.0	19.33	32.0	3.33
20	v	F	17	8	**no**	4	5.00	2	3.00	8.0	3.33	16.0	8.00
21	p	M	9	8	**no**	6.0	6.33	4	3.67	38.0	25.67	n/a	n/a
22	p	M	9	8	**no**	4.0	5.67	4	4.00	10.5	17.00	25.0	29.33
24	p	M	20	8	yes	4.0	3.67	3	2.00	9.0	3.33	8.0	0.00
25	p	M	18	8	yes	5	4.00	4	2.00	1.5	0.33	184.0	56.00
26	v	M	8	8	yes	5.5	3.67	4	2.00	23.0	24.33	25.0	7.33
27	v	M	12	1	**no**	5.0	6.00	4	4.00	20.5	28.00	8.0	12.00
30	v	M	11	3	yes	5.0	4.00	4	2.00	16.0	11.00	45.0	18.00
32	p	M	8	8	yes	5.0	4.00	4	2.33	19.0	12.00	6.0	4.67
33	v	M	9	8	yes	5.5	3.67	4	2.00	17.5	6.67	38.5	38.33
34	p	M	6	3	**no**	5.5	6.00	4	5.00	38.0	31.00	7.0	37.00
35	v	M	7	8	yes	5.5	4.33	4	2.33	27.0	25.33	67.0	24.67
36	p	M	10	8	**no**	6.0	4.67	5	3.33	25.5	8.67	36.0	37.67

CGI-S = Clinical Global Impressions—Severity; CGI-I = Clinical Global Impressions—Improvement; P-ABC-I = Parent Aberrant Behavior Checklist Irritability Subscale; POAS: Parent Overt Aggression Scale Total Score; v = valproate; p = placebo; n/a = not available; mean baseline = mean of baseline and placebo week rating; mean end = mean of weeks 6, 7, and 8 ratings.

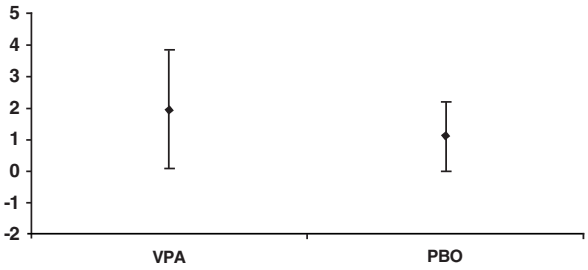

FIG. 1. Weight gain (kg) by group. VPA = valproate; PBO = placebo.

Of the subjects who had received PBO during the study (n = 14), 6 subjects entered an open trial of VPA after the study. An additional 10 subjects of the 16 who had received VPA in the study elected to continue an open-maintenance trial of it. Of the total 16 subjects proceeding to receive open-maintenance VPA, 10 demonstrated a sustained response. In four cases, gradual VPA taper was attempted by parents (in one case, several times) to see if their children still needed it, with ensuing relapse in irritability and aggression, and VPA treatment was resumed in each case.

DISCUSSION

In this double-blind, placebo-controlled 8-week study of VPA for the treatment of aggressive behavior, we did not find a significant difference between the VPA and PBO groups in children and adolescents with PDD. Adequate blood levels within the therapeutic range were achieved and maintained from at least week 4 to week 8. Neither the primary outcome measure, the ABC-C Irritability subscale, nor the secondary measures, including the OAS, CGI-S, and CGI-I showed significant differences between the baseline and post-treatment scores of the drug and placebo groups. High intra- and intersubject variability was found. The high intrasubject variability is shown by large differences in aggression frequency and severity for different weeks during the 8-week period. High intersubject variability is shown by the large standard deviations found for each of the measures (as shown in Tables 2 and 3). Such high variability weakens study power, and larger group sizes are needed to show significance in response difference.

Our follow-up finding of 10 subjects showing a sustained response suggests that a sub-

TABLE 4. SIDE EFFECTS IN AN 8-WEEK TRIAL OF VALPROATE VERSUS PLACEBO (n = 30)

	Valproate (n = 16)		*Placebo (n = 14)*		p^b
Side effect[a]	*n*	%	*n*	%	
Any SE Present during the trial?	15	94%	11	78%	0.31
Nausea	4	25%	2	14%	0.66
Vomiting	4	25%	1	7%	0.34
Constipation	2	13%	3	21%	0.64
Diarrhea	4	25%	1	7%	0.34
Abdominal pain	4	25%	2	14%	0.66
Increased appetite	9	56%	2	14%	**0.03**
Headache	5	31%	3	21%	0.69
Drowsiness	3	19%	3	21%	0.99
Lethargy	3	19%	0	0%	0.23
Skin rash	6	38%	1	7%	0.06
Chills	3	19%	1	7%	0.60
Fever	4	25%	1	7%	0.34
Weight gain	7	44%	4	29%	0.46
Other	7	44%	4	29%	0.46

[a]Number and percent of subjects who ever reported the side effect during the time they were participating in the trial.

[b]p values were based upon the two-sided Fisher's Exact test.

group may show a response that could be demonstrated in a larger study. The most common symptoms showing improvement in the open trial by Hollander et al. (Hollander et al. 2001) were aggression, impulsivity, and mood lability. Thus, recruitment selection for a more homogeneous subgroup of subjects with aggression accompanied by mood lability or bipolar symptoms may have greater likelihood of demonstrating a VPA response.

Discussion of the study limitations must include the small group sizes, the large placebo effect, and intra- and intersubject heterogeneity. The large PBO response was even greater for the high-functioning subjects enrolled toward the latter part of the study. However, comparison of VPA and PBO groups of only MR subjects also failed to reach significance, although these numbers were most likely too small to have the power to reach significance. We also compared VPA and PBO groups using more homogeneous groups of only subjects with autistic disorder, again without finding significance.

It remains difficult to recruit subjects with autistic disorder and significant aggression into double-blind studies. Three common reasons potential subjects did not participate were: (1) behavioral worsening during taper of stimulants prior to study entry; (2) prior VPA treatment; and (3) current epilepsy. To help recruitment, later in the study we broadened the inclusion criteria to include subjects with PDD-NOS ($n = 1$) and Asperger's disorder ($n = 2$). While subject IQ of 70 or less had been required in the initial 4 years, 2 subjects with borderline intellectual functioning, and 1 with normal IQ and 1 with above-average IQ, were later included for the purposes of recruitment. This strategy may have weakened subject homogeneity.

Subject recruitment for future studies may be greater if the design utilizes multiple sites, and subjects stabilized on a stimulant for at least a month and held on a stable stimulant dose during the study are included. By utilizing multiple sites, subject recruitment could be achieved while maintaining greater subject homogeneity limited to subjects meeting criteria for MR and autistic disorder only. A longer PBO run-in, for possibly 4 weeks, may reduce placebo-responder enrollment.

Overall, side effects observed were mild in this 8-week study, apart from 1 subject's allergic skin rash, which remitted spontaneously after valproate discontinuation, and 1 subject's reported cognitive slowing and intermittent slurred speech was associated with an elevation in serum ammonia level. While some clinicians monitor ammonia levels closely in patients receiving VPA treatment, others do not routinely obtain ammonia levels. Precautions detailed in the PDR for VPA include ammonia monitoring for patients showing sedation or altered consciousness associated with VPA treatment. Our findings suggest that ammonia elevation may be associated with more subtle cognitive and speech changes in this population. Weight gain occurred in both drug and placebo groups; however, this was greater in the VPA group. During open follow-up our observation that 10 of the 30 subjects demonstrated a sustained response to VPA after the study, with relapse on tapering attempted in 4 subjects, suggests larger studies with further efforts to minimize placebo effects (e.g., longer placebo run-in) are warranted.

CONCLUSION

In summary, this study could not confirm open-label and case report findings of VPA efficacy for aggression in children and adolescents with ASD. Subject heterogeneity, small group size, and placebo response were problems in this study. It may be possible to define a subgroup of aggressive children and adolescents with ASD who respond to VPA. A larger, multisite study would be both feasible and worthwhile.

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