An Open Trial of Divalproex Sodium in Autism Spectrum Disorders

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Background: Autism spectrum disorders are characterized by core deficits in social interaction and speech/communication skills, repetitive behaviors, and restricted interests. Other abnormalities include seizures, electroencephalographic (EEG) abnormalities, affective instability, impulsivity, and aggression. Divalproex sodium is indicated as both an anticonvulsant in epilepsy and a mood stabilizer in bipolar illness and thus might be useful for these complicating symptoms in autism.

Method: A retrospective pilot study was conducted to determine whether divalproex sodium was effective in treating core dimensions and associated features of autism. Fourteen patients who met DSM-IV criteria for autism, Asperger's disorder, or pervasive developmental disorder not otherwise specified, both with and without a history of seizure disorders or EEG abnormalities, were openly treated with divalproex sodium. Improvement was assessed via the Clinical Global Impressions-Improvement scale.

Results: Of 14 patients who completed a trial of divalproex sodium, 10 (71%) were rated as having sustained response to treatment. The mean dose of divalproex sodium was 768 mg/day (range, 125–2500 mg/day), and it was generally well tolerated. Improvement was noted in core symptoms of autism and associated features of affective instability, impulsivity, and aggression.

Conclusion: Divalproex sodium may be beneficial to patients with autism spectrum disorders, particularly those with associated features of affective instability, impulsivity, and aggression as well as those with a history of EEG abnormalities or seizures. Of note, all patients with an abnormal EEG and/or seizure history were rated as responders. However, these findings must be interpreted with caution, given the open retrospective nature of the study. Controlled trials are needed to replicate these preliminary findings.

(J Clin Psychiatry 2001;62:530–534)

Received March 21, 2000; accepted Sept. 6, 2000. From the Department of Psychiatry and Seaver Autism Research Center, Mt. Sinai School of Medicine, New York, N.Y.

Supported in part by grants from the Seaver Foundation, New York, N.Y., Abbott Laboratories, Abbott Park, Ill., and a fellowship from the National Alliance for Autism Research (NAAR), Princeton, N.J.

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Autism is a developmental disorder characterized by impairments in social interaction, speech, and communication skills and the presence of repetitive behaviors and narrow restricted interests. Social deficits include poor eye contact, limited facial expressiveness, lack of social and emotional reciprocity, as well as a failure to develop peer relationships. Communication deficits include repetitive and stereotyped speech often containing echolalia and neologisms. Language development is usually delayed, or in many cases, speech does not develop at all. Behaviors include rigid routines and rituals, stereotypic body and hand movements, and a need for uniformity.[1] These 3 core symptom dimensions are often complicated by epilepsy, electroencephalographic (EEG) abnormalities, affective instability, impulsivity, and aggression.

Epilepsy develops in approximately one fifth[2] to one third[3] of autistic individuals. Seizures tend to peak either in early childhood prior to age 5 years[4] or in adolescence.[2,3] Various types of seizures occur in autism, including infantile spasms, complex partial seizures, absence seizures (typical and atypical), generalized tonic-clonic seizures, and myoclonic seizures.[2,5] In addition to the high rate of seizures, approximately half of autistic patients have abnormalities on EEG.[6] These EEG abnormalities are nonspecific, including focal slowing, generalized slowing, focal or centroparietal spikes, bilateral or multifocal spikes, and generalized spikes.[4]

Divalproex sodium is approved by the U.S. Food and Drug Administration (FDA) for the treatment of epilepsy. Case studies have reported improvement of autistic symptoms in patients treated with divalproex sodium for seizure disorders. Childs and Blair[7] described dramatic improvement in language and social skills in 3-year-old autistic twins with absence seizures who were treated with valproic acid. Difficult behavior and regression of skills were anecdotally associated with periods of breakthrough seizures.

Case studies have also described improvement with valproic acid in autistic children with abnormal EEGs but no history of seizures. Plioplys[8] described 3 cases of autistic children (aged 3–5 years) with epileptiform findings on EEG who significantly improved with valproate treatment. Each child improved in language and social skills to such an extent that they were described as no longer technically qualifying for the diagnosis of autism. Autistic epileptiform regression, characterized by epileptiform EEG and regression of language and social skills, may be a variant of Landau-Kleffner syndrome.[9] In the Landau-Kleffner syndrome, verbal auditory agnosia and comorbid autistic symptoms are temporally related to seizure/abnormal EEG activity. Traditionally, the Landau-Kleffner syndrome has been treated with anticonvulsant medication. This supports the use of divalproex sodium in the treatment of autism, particularly in young children with epileptiform EEGs or regression of skills. However, there are gaps in our knowledge about the use of divalproex sodium in older children, adolescents, and adults, as well as patients without epilepsy or EEG abnormalities.

Comorbid affective disorders are common in patients with autism spectrum disorders. A review of 17 published cases of autism found 35% to have affective disorders.[10] Among patients with Asperger's disorder, 24% were found to have affective disorders. There is also a higher rate of affective illness (major depression and bipolar disorder) in first-degree relatives of autistic probands (35%) compared with controls (Down's syndrome probands) (17.3%).[11] Divalproex sodium is approved by the FDA for manic episodes associated with bipolar illness and has also been shown to be helpful for its variants including secondary mania,[12,13] mixed or dysphoric mania,[14,15] and nonresponders to conventional therapy.[16]

Impulsivity[17] and aggression[18] are also common symptoms in autism. Ando and Yoshimura[19] reported that among 47 autistic children, 36% had hyperactivity and 43% were self-injurious. Divalproex sodium has been reported to reduce impulsivity, aggression, and affective instability across different disorders. Preliminary open and controlled studies with divalproex sodium in borderline personality disorder suggest improvement in impulsivity, aggression, and mood instability.[20–22] This has also been reported in adolescents with mood swings and explosive temper outbursts[23] and in patients with organic brain syndromes with aggression.[15] Thus, divalproex sodium may be potentially useful in the treatment of core autistic dimensions as well as associated features of mood lability, impulsivity, and aggression, particularly in patients with seizure disorders, EEG abnormalities, or language regression.

METHOD

This open, retrospective study examines the efficacy of divalproex sodium in the treatment of 14 consecutive patients with autism spectrum disorder. The data are presented in a descriptive fashion.

Subjects

Consecutive patients with autistic disorder or an autism spectrum disorder (Asperger's disorder or pervasive developmental disorder not otherwise specified [PDD-NOS]) who were treated with divalproex sodium were included. Diagnoses were made by DSM-IV criteria through patient and parent interviews as well as all other available clinical information, including neuropsychological tests and teacher reports. Patients were evaluated by a board certified psychiatrist with expertise in the diagnosis and treatment of autism spectrum disorders and recruited from the authors' office-based practices or clinical programs specializing in the treatment of autism. The presence of comorbid psychiatric illness or seizures did not preclude inclusion in the study.

Subjects included 12 males and 2 females, of which 10 were children/adolescents and 4 were adults. Their ages ranged from 5 to 40 years, with a mean age of 17.93 ± 10.24 years. Patient IQ scores ranged from 20 to 105, with a mean score of 69.1 ± 20.7 and thus, on average, were in the deficient range of intellect. Ten patients met DSM-IV criteria for autism, 2 for Asperger's disorder, and 2 for PDD-NOS. Of the 14 patients in the study, 12 had comorbid diagnoses including anxiety disorders (N = 7), impulse-control disorders (N = 5), mood disorders (N = 4), attention-deficit/hyperactivity disorder (N = 3), and psychotic disorder (N = 1). Three of the 14 patients had a history of seizures, including complex partial seizures (subject 4), febrile seizures (subject 12), and unspecified (subject 7). Of the 9 patients who had an EEG completed, 5 had normal results, and 4 had abnormal readings including gross abnormalities (subject 7), several mild discrete left hemisphere sharp waves (subject 8), excessive bilateral theta activity and rare generalized spikes (subject 9), and asymmetrical sleep pattern suggesting left hemisphere dysfunction (subject 4) (Table 1). Ten patients took concomitant medications during the study, including selective serotonin reuptake inhibitors, other antidepressants, atypical neuroleptics, benzodiazepines, and α_1 agonists (Table 2). All concomitant medications were kept at stable doses throughout divalproex sodium treatment.

Psychometric Instrument

Assessment of autistic symptom improvement was achieved through retrospective use of the Clinical Global Impressions-Improvement scale (CGI-I). This clinician-rated instrument was used to compare the patient's condition at baseline with his/her condition at the end of clinical treatment to determine global improvement. The scale ranges from 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse to 7 = very much worse.

Table 1. Demographics/Clinical Data in 14 Autism Spectrum Disorder Patients[a]

Subject	Age (y)	Sex	IQ	Main Diagnosis	Comorbid Diagnoses	Seizure Activity/EEG Abnormalities
1	11	M	105	Asperger's	OCD, learning disorder, eating disorder-NOS, ADD, hypotonia	No seizures; EEG: normal
2	13	M	60	PDD-NOS	ICD-NOS, ADHD, separation anxiety disorder	No seizures; EEG: normal (awake) in Feb 1998
3	10	M	87	Autism	OCD, ICD-NOS, mood disorder-NOS	No seizures; EEG: not done
4	15	M	74	Autism	IED	2 complex partial seizures at 5 years old after chicken pox; EEG: asymmetrical abnormality suggesting frontal lobe dysfunction
5	15	F	55	Autism	Bipolar disorder	No seizures; EEG not done
6	8	M	69	Autism	OCD, ICD-NOS	No seizures; EEG: normal (awake)
7	17	M	73	Asperger's	OCD	Seizure disorder; EEG: gross abnormalities
8	5	M	95	Autism	None	No seizures; EEG: initial EEG mildly abnormal, several discrete left hemisphere sharp waves (sleep deprived) at age 5. Follow-up EEG on divalproex sodium was normal.
9	15	M	68	Autism	OCD, psychotic disorder-NOS	No seizures; Initial EEG (awake) on clomipramine and perphenazine was abnormal with excessive bilateral theta activity and rare generalized spikes. Follow-up EEG (awake) on divalproex sodium showed no change; third EEG (awake) on divalproex sodium showed some change: infrequent discrete spike discharges in posterior quadrant of left hemisphere
10	40	M	66	Autism	None	No seizures; EEG: normal (24 h)
11	35	M	20	Autism	Bipolar disorder	No seizures; EEG: not done
12	15	M	47	Autism	ADHD	Febrile seizure at 1 year old; EEG: not done
13	23	M	75	PDD-NOS	OCD, IED, congenital deafness	No seizures; EEG: not done
14	29	F	74	Autism	Bipolar disorder-NOS	No seizures; EEG: normal EEG (sleep deprived)

[a]Abbreviations: ADD = attention-deficit disorder, ADHD = attention-deficit/hyperactivity disorder, EEG = electroencephalogram, ICD = impulse-control disorder, IED = intermittent explosive disorder, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, PDD = pervasive developmental disorder.

Table 2. Divalproex Sodium and Concurrent Medication Dosage[a]

		Divalproex Sodium Treatment			
Subject	Concurrent Medications (mg/d)	Treatment Length (mo)	Highest Dose Total mg/d	Final Dose Total mg/d	Maximum Valproate Level (μg/mL)
1	None	43	625	250	50
2	Fluoxetine 60 mg/wk, methylphenidate 35	10	750	750	85
3	Clonazepam 0.5	0.5	125	125	…
4	Fluoxetine 60, clonidine 0.4	10	1000	1000	82
5	Fluoxetine 20, alprazolam 1 prn	7	750	625	66
6	None	0.5	250	250	…
7	Fluvoxamine 300, clonazepam 1, buspirone 20, carbamazepine 400	17	1500	500	71
8	Venlafaxine 25	4	500	500	84
9	Olanzapine 2.5, fluvoxamine 300	20	1250	1000	85
10	None	3	500	500	85
11	Olanzapine 15, buspirone 30	27	2500	2500	92
12	Buspirone 60	2	750	750	65
13	Fluvoxamine 100	4	1000	1000	…
14	None	2	1000	1000	68

[a]Symbol: … = not available.

Responders are patients who received a CGI-I score of 1 or 2 (very much or much improved). The ratings were completed by study psychiatrists who utilized all available chart data in determining CGI-I scores. The study psychiatrists had special interest in the 3 core autistic dimensions (social, communication, and repetitive behaviors) as well as impulsivity/aggression and mood lability, and, on each study visit, specifically queried patients regarding these symptoms. There was continuity in the study visits, as the same psychiatrist completed all study visits for each individual subject.

Medication Administration

Patients were started on low doses of divalproex sodium. At follow-up visits, patients and their parents were interviewed regarding potential side effects, blood valproate levels were determined, and doses were subsequently adjusted to minimize side effects, maximize improvement, and maintain the valproate level within a therapeutic range (50–100 mg/mL). Data from all 14 patients are included in this report.

Statistical Analysis

Responder and nonresponder groups were compared on valproate dose and blood level via nonparametric Mann-Whitney U tests.

Table 3. Clinical Improvement and Side Effects on Divalproex Sodium

Subject	CGI Score	Side Effects	Symptoms Improved
1	2[a]	Mood lability, agitation	Concentration, general functioning, efficiency, more pleasant
2	2[a]	Fatigue, dizziness	Irritability, aggression, obsessive-compulsive symptoms, social relatedness
3	5	Insomnia, anxiety, obsessive-compulsive symptoms	None
4	2[a]	Diarrhea	Frequency and intensity of violent outbursts, flexibility
5	1[a]	Sedation, weight gain	Agitation, insomnia, impulsivity, hyperactivity, manageability
6	5	Agitation, anxiety, disinhibition	None
7	1[a]	Increased appetite, weight gain (mild), hair loss	Obsessive-compulsive symptoms, irritability, mood, anxiety, social relatedness
8	1.5[a]	None	Language: vocabulary, articulation, and frequency of speech and mood lability; sleep; academics
9	1.5[a]	Weight gain, increased appetite, increased sleep	Organization, obsessive-compulsive symptoms, listening, awareness, academics, increased curiosity, responsibility
10	4	Difficulty waking in morning	None
11	1[a]	Elevated liver enzymes	Self-abusive behavior, impulsivity, mood lability, restlessness
12	1[a]	None	Aggression, impulsivity, less anger and fighting with others
13	2[a]	None	Impulsivity, explosiveness, mood lability, more predictable
14	4	Hair loss, sedation, weight gain, buccal numbness	None

[a]Responder on the Clinical Global Impressions scale (CGI), with a Global Improvement score of 2 = much improved or 1 = very much improved.

RESULTS

Subjects were treated with divalproex sodium for 10.7 ± 12.3 months (range, 0.5–43 months). The final dose of divalproex sodium was 768 ± 582 mg/day (range, 125–2500 mg/day), and the mean peak valproate level was 75.8 ± 12.6 μg/mL (range, 50–92 μg/mL). Side effects of divalproex sodium in this sample were predominantly mild to moderate and included fatigue/sedation (N = 5), behavioral activation (N = 3), digestive disturbances (N = 3), weight gain (N = 3), reversible hair loss (N = 2), mood lability (N = 1), and elevated liver enzymes (N = 1) (Table 3). Two patients experienced behavioral activation within the first 2 weeks of treatment of sufficient severity to be discontinued from medication treatment.

Ten (71%) of 14 patients were rated as sustained treatment responders, with final CGI-I scores of much improved (2) or very much improved (1). Overall, the mean CGI-I score was 2.36 ± 1.48. Symptoms of all 3 core dimensions of autism were noted to improve with divalproex sodium treatment. Four patients were noted to manifest improvements in the social dimension, including social relatedness, general pleasantness, awareness, and listening. Four patients manifested improvements in the repetitive dimension, including reduced obsessive-compulsive symptoms and increased flexibility. Only 1 patient demonstrated improvement in the language/communication dimension, including enhanced vocabulary, improved articulation, and increased frequency of speech.

Improvements were also seen in the associated features of autism. Six patients manifested improvement in affective instability, 5 patients became less impulsive, and 4 patients were less aggressive. The 2 patients who had follow-up EEGs after divalproex sodium treatment revealed some improvement. One patient (subject 8) who had several discrete left hemisphere sharp waves at baseline, had normal results in a follow-up EEG after divalproex sodium treatment. Another patient (subject 9) initially showed excessive bilateral theta activity and rare generalized spikes and, on a follow-up EEG, showed only infrequent discrete spike discharges in posterior quadrant of left hemisphere.

Responder and nonresponder groups did not marginally or significantly differ in endpoint divalproex sodium dose (887.50 ± 619.28 vs. 468.75 ± 386.96 mg/day) or maximum valproate levels (75.61 ± 13.43 vs. 76.50 ± 12.02 μg/mL). Both groups had comorbid affective and impulsive disorders, but differed in comorbid seizure/EEG abnormalities. Among the 10 responders, 4 had an abnormal EEG, 4 had an impulse-control disorder, 4 had obsessive-compulsive disorder (OCD), 3 had attention-deficit/hyperactivity disorder, 3 had a history of seizure disorder, and 2 had bipolar disorder. Among the 4 nonresponders, 2 had impulse-control disorder, 2 had OCD, 1 had bipolar disorder, 1 had another mood disorder, but none had history of seizures or abnormal EEG (although 1 patient did not have an EEG done) (Table 1).

DISCUSSION

This pilot study provides preliminary evidence that divalproex sodium may be beneficial to individuals with autism spectrum disorders, particularly those with associated affective instability, impulsivity, or aggression, as well as those with EEG abnormalities or history of seizure disorder. Divalproex sodium was helpful in the treatment of mood instability, impulsivity, and aggression, as well as core dimensions of autism including social deficits and repetitive behaviors/restricted interests in both child/

adolescent and adult age groups. Divalproex sodium was generally well tolerated; however, there may be a small subset of patients who experience behavioral activation in response to the medication. Two patients in this trial needed to be discontinued within the first 2 weeks of treatment for this reason.

EEG abnormalities and seizure disorders are common in autism. In our sample, 4 of 9 patients who had baseline EEGs manifested abnormalities, and 3 of 14 patients had a history of seizure disorder. Of note, all patients with an EEG abnormality or seizure disorder were rated as responders to divalproex sodium treatment. This may be a particularly responsive subgroup of the autistic population, who are responsive in both core dimensions and associated features. Previous studies found divalproex sodium to be effective for autistic symptoms and language regression in young children who had autism spectrum disorders with accompanying seizure disorders and EEG abnormalities.[7,8] Findings in the present study supplement these earlier reports because our population is older (mean age = 17.93 ± 10.24 years) and includes subjects both with and without seizure disorder/EEG abnormality.

The current findings must be interpreted with caution, given the open, retrospective nature of the study. Furthermore, the small sample size and heterogeneous study population limit the conclusions that can be drawn. Nine of 10 of the responders were taking concomitant medications, and although these medications were kept at stable doses, it is possible that improvements were due to interaction effects between divalproex sodium and these medications. Furthermore, the inconsistent manner in which the EEGs were completed (i.e., some sleep deprived, some awake, some without follow-up) must be considered when interpreting the encouraging findings in this area. Future studies might obtain sleep-deprived or 24-hour EEGs systematically at baseline and endpoint, as well as exclude the use of concomitant medications.

Nevertheless, these positive preliminary findings of global improvement in 10 (71%) of 14 patients treated with divalproex sodium suggest that a double-blind, placebo-controlled trial in a more homogeneous group of autistic patients using state of the art diagnostic instruments and standardized outcome rating scales is warranted.

Drug names: alprazolam (Xanax and others), carbamazepine (Tegretol and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clonidine (Catapres and others), divalproex sodium (Depakote), fluoxetine (Prozac), fluvoxamine (Luvox), methylphenidate (Ritalin and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), valproic acid (Depakene and others), venlafaxine (Effexor).

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