

Divalproex Sodium Reduces Overall Aggression in Youth at High Risk for Bipolar Disorder

Kirti Saxena, M.D., Meghan Howe, M.S.W., Diana Simeonova, B.S.,
Hans Steiner, M.D., and Kiki Chang, M.D.

ABSTRACT

Introduction: The psychopharmacology of aggression in youth is relatively unexplored, even though such maladaptive aggression manifests across many different diagnoses.

Methods: This study was a 12-week, open-label trial with divalproex sodium (DVPX) in 24 bipolar offspring 6–18 years of age (mean age = 11.3 years; 17 boys) with mixed diagnoses of major depression, cyclothymia, attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD). The Overt Aggression Scale (OAS) was used to measure aggression in 4-week intervals. We measured serum gamma-butyric acid (GABA) and glutamate levels at baseline and week 12.

Results: Seventy-one percent of evaluable subjects were considered responders to DVPX treatment by the OAS. There was a significant correlation between the Young Mania Rating Scale (YMRS) and OAS scores at week 0 ($p = 0.036$) and week 12 ($p = 0.025$). Serum DVPX level did not correlate with treatment response.

Conclusions: These youths who are at high risk for bipolar disorder experienced an overall decrease in aggressive behavior in response to DVPX. Age or gender did not predict a positive response to DVPX. This study is the first report of treatment efficacy of a mood stabilizer for aggression in youth at high risk for bipolar disorder.

INTRODUCTION

THE PSYCHOPHARMACOLOGY of aggression in youth is relatively unexplored, even though such maladaptive aggression manifests across many different diagnoses (Steiner et al. 2003). It is first important to delineate the subtype of aggression that the youth is exhibiting in order to identify whether the form of aggression may be amenable to psychopharmacological interventions. Subtypes of aggression include PIPP- (Proactive, Instrumental,

Planned, and Predatory) and RADI- (Reactive, Affective, Defensive, and Impulsive) type aggression (Steiner et al. 2003). PIPP aggression refers to the planful execution of aggression, where the anticipated outcome to the individual is positive, and the emotions accompanying this form of aggression are those of happiness and interest.

RADI-type aggression, however, is unplanned and is accompanied by negative emotions, such as fear, anger, and irritability. RADI-type aggression is often a prominent

Stanford University, School of Medicine, Department of Psychiatry and Behavioral Sciences, Division of Child Psychiatry and Child Development, Stanford, California.

These data were presented, in part, at the American Academic of Child and Adolescent Psychiatry (AACAP) 2003.

feature in children and adolescents with bipolar disorder (BD). Children of parents with BD who have subsyndromal symptoms of BD themselves also have been reported to have high levels of RADI-type aggression (Dienes et al. 2003). Although not meeting *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV; American Psychiatric Association 1994) criteria for bipolar I or II disorder, these children can present with irritability, rapid mood shifts, and aggression, warranting psychopharmacological intervention. As it is possible that these children are prodromal for fully developed BD, it would seem efficient to utilize an agent that could treat symptoms of both aggression and BD (Chang et al. 2003a).

Divalproex has evidence of efficacy for both BD and aggression in youth (Steiner et al. 2003). Divalproex has been shown, in controlled studies, to be effective in adult mania (Bowden et al. 2000; Bowden et al. 1994) and in open studies to be effective in pediatric mania (Wagner et al. 2002; Kowatch et al. 2000; Pavuluri et al. 2005). Regarding aggression, Donovan et al. demonstrated the efficacy of divalproex in decreasing aggressive symptoms in youths with conduct disorder (CD) and/or oppositional defiant disorder (ODD) in both open (1997) and controlled (2000) studies. Therefore, divalproex appears to be a reasonable candidate for the treatment of symptoms of both BD and aggression in children and adolescents.

We previously reported open divalproex to be effective in treating manic and depressive symptoms in a cohort of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms (Chang et al. 2003b). In this previous study, general improvement in the Clinician's Global Impression—Improvement scale and improvement in manic and depressive symptoms were primary and secondary outcome measures. However, we also collected data measuring change in RADI aggression, using the Overt Aggression Scale—Modified (OAS-M; Coccaro et al. 2000). Furthermore, we collected serum gamma-butyric acid (GABA) and glutamate levels pre- and post-treatment, owing to the theorized effects of valproate on brain GABA and studies correlating high aggres-

sion to low serum GABA levels (Bjork et al. 2001). We also wished to study effects on serum glutamate, as GABA is the major inhibitory, and glutamate the major excitatory, neurotransmitter in the brain (Lujan et al. 2004). Therefore, in this study, we wished to re-examine our data to include improvement in aggression as an outcome measure and to correlate both mood and aggression symptom improvement to changes in serum GABA levels. We hypothesized that treatment with divalproex would lead to a decrease in aggression in bipolar offspring with mood and behavioral symptoms, and improvement in aggression and mood symptoms would be correlated with increases in serum GABA and decreases in serum glutamate levels.

METHODS

The sample for this study was drawn from an ongoing phenomenology study of bipolar offspring. Families were recruited from the Stanford Bipolar Disorders Clinic (for adults), the Stanford Pediatric Mood Disorders Clinic, and from the surrounding community within Stanford, California. Oral and written, informed consent was obtained from at least 1 parent, and oral and written assent was obtained from subjects after an explanation of possible adverse effects and alternatives to study participation. This study was approved by the Stanford University Administrative Panel on Human Subjects.

Subjects were evaluated by either a child psychiatrist or a trained research assistant who was aware of parental status. Inter-rater reliability was established by rating videotaped interviews, observing trained rater interviews, and performing interviews with observation by a trained rater, as described by Geller et al. (1998). Both the parents and children were interviewed. Symptoms were positively rated if endorsed by either parent or child, based on interviewer decision (e.g., if a child seemed to be exaggerating a symptom, the interviewer had the option to use the parent's report instead). Diagnostic decisions were ultimately made by a child psychiatrist (KC), based on review of the structured-interview data, clinical

history, and videotapes of the interview if the research assistant performed the interview. The OAS-M was performed by a masters-level research assistant who was trained by observing at least four rater interviews. Inter-rater reliability was not done, as there was only one rater for the OAS-M. Inter-rater reliability on the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) was established by rating videotaped interviews, observing trained rater interviews, and performing interviews with observation by a trained rater, as described by Geller et al. (1998). The children's diagnoses were lifetime.

Inclusion criteria required a parent with bipolar I or II disorder by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al. 1995) and the subject with a current diagnosis of at least one of the following: Major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), dysthymic disorder (DVS), or cyclothymic disorder (CYC). Subjects also had to have at least mild affective symptoms, as determined by a score of at least 12 on the Young Mania Rating Scale (YMRS) and 26 or 12 on the 28-item Hamilton Rating Scale for Depression (HAM-D).

We studied 24 bipolar offspring 6–18 years of age (mean age = 11.3 years; 17 boys/7 girls) with mixed diagnoses of MDD (21%), CYC (29%), ADHD (58%), and ODD (8%) (Chang et al. 2003b). Sixty-point-zero-nine percent of subjects had mothers with BD. The mean percent of first- or second-degree relatives with a mood disorder was 52% (SD = 15%). Any psychotropic medications being currently taken were discontinued for at least five half-lives before the study. Divalproex was begun at 125–250 mg/day and increased by 125–250 mg/day every 4–7 days to reach a target serum level between 50 and 120 μ /mL by week 4. Dosage increase was slowed or halted if symptoms improved or adverse effects limited tolerability. Titration continued past week 4, if necessary, based on clinical response and serum level. No additional psychotropic medications were allowed.

Subjects were assessed with the parent-report version of the Child Behavior Checklist

(CBCL; Achenbach 1991) at baseline. The YMRS (Young et al. 1978) and the HAM-D (Hamilton 1960) were used to assess the subjects at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, and 12. The OAS-M (Coccaro et al. 2000) was completed at baseline and at week 12. The OAS-M is a clinician-administered scale, measuring frequency and degree of verbal assaults and assaults against objects, others, or self over the previous week. The OAS-M also measures subjective and overt irritability and suicidal tendencies. We considered a positive response for aggression in this study to be at least a 50% decrease in scores on the OAS-M.

Serum was drawn from each subject at baseline and again at week 12. Samples were taken in the morning, all between 7 and 10 a.m. Blood samples were obtained by venipuncture of the antecubital vein, using 15-mL round bottom tubes provided by the Nathan S. Kline Institute (Orangeburg, NY). The blood was centrifuged and the plasma removed and placed into a cryotube and kept frozen in a nonfrost freezer at -70°C until assayed. The samples were transferred without thawing on dry ice to the Analytical Psychopharmacology Laboratory (Nathan S. Kline Institute) for processing GABA and glutamate levels. To our knowledge, normal levels for serum GABA or glutamate levels have not been established for children and adolescents.

Statistical analyses

SPSS version 13 was used to perform the statistical analysis, including the descriptive statistics. Spearman's correlations were performed for the following: Correlation between baseline CBCL subscales and baseline OAS-M scores, correlation between percent change GABA and percent change in OAS-M, and a correlation between percent change glutamate and percent change OAS-M. In addition, we used paired *t* test analyses to measure changes in OAS subscales over 12 weeks.

RESULTS

Subject demographics are given in Table 1. The dose of divalproex ranged from 375 to

TABLE 1. SUBJECT DEMOGRAPHICS

Subject	Age (years)	Gender	Diagnosis
1	8	M	ADHD
2	16	F	CYC
3	17	F	CYC
4	6	M	ADHD
5	18	M	CYC
6	6	M	ADHD
7	11	M	ADHD, ODD
8	9	M	ADHD
9	7	M	ADHD, ODD, CYC
10	17	F	MDD, GAD
11	9	M	ADHD
12	12	M	ADHD
13	8	M	DYS
14	10	M	CYC, ADHD
15	7	F	MDD
16	10	M	ADHD
17	16	M	MDD
18	16	M	CYC
19	10	M	ADHD
20	9	M	ADHD
21	7	F	DYS
22	16	M	MDD, ADHD
23	12	F	CYC, ADHD
24	8	F	MDD

M = Male; F = Female; ADHD = attention-deficit/hyperactivity disorder; CYC = Cyclothymia; ODD = oppositional defiant disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder; DYS = Dysthymia.

1500 mg/day, with a mean final dose of 821 ± 280 mg/day. Serum levels of divalproex were targeted to 50–120 µg/mL, with a mean final serum level of 79.0 ± 26.8 µg/mL. Seventy-one percent of subjects were Caucasian, 13% Hispanic, 13% Asian, and 4% African-American. One subject (male) withdrew from the study

before week 3 because of a lack of perceived improvement symptoms.

As previously reported, 78% of our subjects were considered responders by mood criteria (a decrease over the study of at least 50% in HAM-D or YMRS scores) (Chang et al. 2003b). Mean HAM-D scores were 12.97 ± 8.2 at baseline (range = 1–26) and 5.6 ± 5.3 at week 12 (range = 1–24). Mean YMRS scores were 15.3 ± 8.0 (range = 0–27) at baseline and 4.9 ± 4.6 at week 12 (range = 0–23).

Seventy-one percent of evaluable subjects were considered responders to treatment by the OAS-M. Neither gender (*p* = 0.79) nor age (*p* = 0.78) predicted response. Neither the final dose nor final serum level of DVPX correlated with treatment response (*p* = 0.51). There was a significant correlation between YMRS scores and OAS scores at week 0 (*r* = 0.67; *p* = 0.004) and week 12 (*r* = 0.77; *p* = 0.001), indicating that the more severe the manic symptoms, the more severe the aggression, and vice versa, at entry and at exit from the study.

Mean OAS scores decreased significantly from week 0 (50.4 ± 67.7) to week 12 (26.2 ± 42.7; *t* = 1.96, *p* = 0.005). Using paired *t* test analyses of OAS subscales at weeks 0 and 12, mean scores of Assault Against Others (18.2 ± 29.5 to 2.5 ± 3.8; *p* = 0.001) and Irritability (5.1 ± 2.6 to 2.1 ± 2.0; *p* = 0.008) all decreased significantly. Subscales that did not change were Assault Against Objects (6.3 ± 6.0 to 1.3 ± 1.7; *p* = 0.82) and Assault Against Self (0.86 ± 3.2 to 0.23 ± 0.83; *p* = 0.82). The one subscale that showed a significant increase was Verbal Aggression (20.2 ± 13.2 to 36.0 ± 31.1; *p* = 0.04).

The mean serum glutamate level at baseline was 90.3 ± 71.8 µM/L and at 12 weeks was

TABLE 2. SUBJECT DEMOGRAPHICS

Mean ± SD age	Gender	Diagnoses	VPA mean final dose	VPA mean final serum level	Ethnicity
11.3 ± 3.9 years	17 boys/7 girls	Major depression, cyclothymia, ADHD, ODD, DYS	821 mg/day ± 280 mg/day	79.0 µg/mL ± 26.8 µg/mL	Caucasian: 71% Hispanic: 13% Asian: 13% African-American: 4%

SD = standard deviation; VPA = valproic acid; ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; DYS = dysthymia.

TABLE 3. BASELINE AND OUTCOME MEASURES OF OAS-M, SERUM GABA, AND GLUTAMATE

	Baseline	12 weeks	<i>p</i> -value
OAS-M	50.4 ± 67.7	26.2 ± 42.7	0.005
Serum GABA	19.3 ± 12.7 μM/L	17.6 ± 8.3 μM/L	0.43
Serum glutamate	90.3 ± 71.8 μM/L	104.5 ± 54.3 μM/L	0.46

GABA = gamma-butyric acid; OAS-M = Overt Aggression Scale—Modified.

104.5 ± 54.3 μM/L, a nonsignificant difference ($p = 0.46$). Response to divalproex in aggression was not correlated with change in serum GABA ($p = 0.43$) or glutamate ($p = 0.28$). However, response to divalproex in mood symptoms was negatively correlated with a decrease in serum glutamate levels over the course of the study ($p = 0.02$). Change in serum GABA levels were not correlated with mood response ($p = 0.40$).

DISCUSSION

Aggression in youth commonly occurs in the context of mood and other psychiatric disorders and is often the major targeted symptom for treatment. In this study, severity of aggression occurring in a population of children and adolescents at high risk for development of BD was found to lessen with divalproex monotherapy.

We measured aggression using the OAS, which, preferentially, measures RADI-type aggression. This type of aggression has been consistently reported in cohorts of children and adolescents with bipolar disorders, as well as children with early forms of bipolar disorder (Dienes et al. 2002). Therefore, although we saw significant decreases in RADI-aggression in our subjects, we cannot comment on the effects of divalproex on PIPP-type aggression.

As divalproex has been shown in other studies to increase serum and brain GABA (Johannessen and Johannessen 2003; Loscher 1999; Loscher 2002; Petroff et al. 1999), we had hypothesized that improvement of aggression symptoms would be correlated with increases in serum GABA and, conversely, decreases in serum glutamate. Previous studies have suggested that an increase in GABA activity usu-

ally results in increased impulse control, hence decreasing RADI aggression (Swann et al. 2002; Brown et al. 1990). For example, Bjork et al. (2001) found that in subjects selected for having a first-degree relative with primary unipolar depressive disorder, plasma GABA was negatively correlated with aggressiveness. These data suggest that low GABA levels may correlate with some aspects of aggressiveness and may be genetically regulated. Bjork et al. (2001) found that in subjects selected for having a first-degree relative with primary unipolar depressive disorder, plasma GABA was negatively correlated with aggressiveness. These data suggest that low GABA levels may correlate with some aspects of aggressiveness and may be genetically regulated. This was not found to be the case in regard to our subjects with aggression. However, improvement in mood was found to be correlated with a decrease in serum glutamate levels. It is, therefore, possible that although mood mechanisms may be linked to changes in the GABA/glutamate system, aggression may be dependent on other systems, such as serotonin. However, serum neurotransmitter levels may not be accurate indicators of brain levels, which are more relevant to behavioral and mood changes, and so our findings cannot be conclusive. Future studies could better examine the role of GABA and glutamate in aggression by measuring levels in the brain through magnetic resonance spectroscopy.

Because we did not include a healthy control group, we do not know if the baseline serum levels of GABA in our subjects were lower than normal, as has been reported in other studies. Prosser et al. (1997) measured plasma GABA (pGABA) concentrations in 115 inpatients (7–17 years of age) with child psychiatric disorders. Group mean pGABAs were

compared for 38 patients with mood disorders only, 29 with behavior disorders only, 48 with comorbid mood and behavior disorders, and 14 normal controls (14–17 years of age). No patient in the behavior disorders group or control group had pGABA below 100 pmol/mL, but low pGABAs were found in 15% of patients with mood disorders (who had no behavior disorder) and in 16% of patients with comorbid mood and behavior disorders.

In our sample, 71% of evaluable subjects were considered responders to divalproex treatment by the OAS-M. Mean overall OAS-M scores decreased significantly from week 0 to week 12. Of the OAS-M subscales, Overall Aggression, assault against others and irritability all decreased over the 12-week trial. Scores of assault against objects and assault against self did not decrease significantly. This could be because these children had more severe psychiatric impairment, were more impulsive, and possibly need to be treated for a longer period to see decrease in these subtypes of aggression. Interestingly, verbal aggression increased significantly over the trial. It is not clear that this was a clinically significant increase, but it is also possible that with divalproex treatment, more physical acts of aggression were “traded” for less physical and more verbal acts.

Other factors, such as age and gender, did not predict aggression response. There was a significant correlation between YMRS scores and OAS scores at weeks 0 and 12, indicating that the higher the mania, the higher the aggression, and vice versa, at entry and at exit from the study. This finding may indicate that aggression symptoms improved owing to an improvement in mania, especially as divalproex has been suggested to be effective in the treatment of mania in children and adolescents (Wagner et al. 2002; Kowatch et al. 2000). Alternately, divalproex may affect aggression through mechanisms distinct from its actions on mania.

Divalproex has been shown to be effective in treating aggression in the context of other disorders in youth. Donovan et al. (2000) reported divalproex to be superior to placebo in treating 20 outpatient children and adolescents with a disruptive behavior disorder (ODD or CD)

who met the specific criteria for explosive temper and mood lability. Steiner et al. (2003) also studied the use of divalproex in youths with conduct disorder. Subjects in a high-dose condition were found to have significant improvements in impulse control and self-restraint, compared to subjects in a low-dose condition. These findings provide further evidence that divalproex may act in a global manner to decrease aggression symptoms across various psychiatric conditions in youth.

Limitations

The limitations of this study included a relatively small sample size of a diagnostically heterogeneous cohort. However, the subjects of the cohort were similar in having a strong family history of BD and fairly high levels of aggression before treatment. Furthermore, this was a retrospective analysis of data from an open trial, which is subject to rater bias. Finally, without a control condition, it is difficult to determine if improvements in aggression were from other factors, such as being seen frequently at a university clinic.

CONCLUSIONS

Nevertheless, to our knowledge, this is the first study examining the effect of divalproex on decreasing aggression in youth having a strong family history of BD. Aggressive behaviors in youth are present across various psychiatric diagnoses, including sub- and fully syndromal forms of BD. The importance of treating aggression cannot be emphasized enough, as it can cause significant dysfunction in all aspects of the youth's life. Further, controlled studies with larger samples are needed in this population.

REFERENCES

- Achenbach TM: Manual for Youth Self-Report and 1991 Profile. Burlington (Vermont), University of Vermont Department of Psychiatry, 1991.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington (DC), American Psychiatric Association, 1994.

- Barratt ES, Stanford MS, Kent TA, Felthous A: Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. *Biol Psychiatry* 41:1045–1061, 1997.
- Bjork JM, Moeller FG, Kramer GL, Kram M, Suris A, Rush AJ, Petty F: Plasma GABA levels correlate with aggressiveness in relatives of patients with unipolar depressive disorder. *Psychiatry Res* 101:131–136, 2001.
- Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, Dilsaver SC, Davis JM, Rush AJ, Small JG, et al: Efficacy of divalproex versus lithium and placebo in the treatment of mania: The Depakote Mania Study Group. *JAMA* 271:918–924, 1994.
- Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG, Jr, Chou JC, Keck PE, Jr, Rhodes LJ, Swann AC, Hirschfeld RM, Wozniak PJ: A randomized, placebo-controlled, 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder: Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 57:481–489, 2000.
- Brown GL, Linnoila MI: CSF serotonin metabolite (5-HIAA) studies in depression, impulsivity, and violence. *J Clin Psychiatry* 51:31–41, 1990.
- Chang KD, Adleman N, Dienes K, Reiss AL, Ketter TA: Bipolar offspring: A window into bipolar disorder evolution. *Biol Psychiatry* 53:945–941, 2003a.
- Chang K, Dienes K, Blasey C, Adelman N, Ketter T, Steiner H: Divalproex in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. *J Clin Psychiatry* 64:936–942, 2003b.
- Coccaro EF, Harvey PD, Kupsaw LE, Herbert JL, Bernstein DP: Overt Aggression Scale—Modified (OAS-M). In: *American Psychiatric Association Task Force for the Handbook of Psychiatric Measures*. Washington (DC), American Psychiatric Association, 2000, pp 699–702.
- Dienes KA, Chang KD, Blasey CM, Adleman NE, Steiner H: Characterization of children of bipolar parents by parent report CBCL. *J Psychiatr Res* 36:337–345, 2002.
- Donovan SJ, Susser ES, Nunes EV, Stewart JW, Quitkin FM, Klein DF: Divalproex treatment of disruptive adolescents: A report of 10 cases. *J Clin Psychiatry* 58:12–15, 1997.
- Donovan SJ, Stewart JW, Nunes EV, Quitkin FM, Parides M, Daniel W, Susser E, Klein DF: Divalproex treatment for youth with explosive temper and mood liability: A double blind, placebo-controlled, crossover design. *Am J Psychiatry* 157: 818–820, 2000.
- First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington (DC), American Psychiatric Press, Inc., 1995.
- Geller B, Williams M, Zimmerman B, Frazier J: Washington University in St. Louis, Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). St Louis, (Missouri), Washington University, 1996.
- Geller BG, Warner K, Williams M, et al: Prepubertal and young adolescent bipolarity versus ADHD: Assessment and validity using the WASH-U-KSADS, CBCL, and TRF. *J Affect Disord* 51:93–100, 1998.
- Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 12:56–62, 1960.
- Johannessen CU, Johannessen SI: Valproate: Past, present, and future: *CNS Drug Rev* 9:199–216, 2003.
- Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, Emslie GJ, Weinberg WA, Rush AJ: Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 39:713–720, 2000.
- Loscher W: Valproate: A reappraisal of its pharmacodynamic properties and mechanisms of action. *Prog Neurobiol* 58:31–59, 1999.
- Loscher W: Basic pharmacology of valproate: A review after 35 years of clinical use for the treatment of epilepsy. *CNS Drugs* 16:669–694, 2002.
- Lujan R, Shigemoto R, Lopez-Bendito G: Glutamate and GABA receptor signalling in the developing brain. *Neuroscience* 130:567–580, 2005.
- Malone RP, Sheikh R, Zito JM: Novel antipsychotic medications in the treatment of children and adolescents. *Psychiatr Serv* 50:171–174, 1999.
- Malone RP, Delaney MA, Luebbert JF, Cater J, Campbell M: A double-blind, placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Arch Gen Psychiatry* 57:649–654, 2000.
- Mick E, Biederman J, Mick E, Biederman J, Pandina G, Faraone SV: A preliminary meta-analysis of child behavior checklist in pediatric bipolar disorder. *Biol Psychiatry* 53:1021–1027, 2003.
- Pavuluri MN, Henry DB, Carbray JA, Naylor MW, Janicak PG: Divalproex sodium for pediatric mixed mania: A 6-month prospective trial. *Bipolar Disord* 7:266–273, 2005.
- Petroff OA, Rothman DL, Behar KL, Hyder F, Mattson RH: Effects of valproate and other antiepileptic drugs on brain glutamate, glutamine, and GABA in patients with refractory complex partial seizures. *Seizure* 8:120–127, 1999.
- Prosser J, Hughes CW, Sheikha S, Kowatch RA, Kramer GL, Rosenbarger N, Trent J, Petty F: Plasma GABA in children and adolescents with mood, behavior, and comorbid mood and behavior disorders: A preliminary study. *J Child Adolesc Psychopharmacol* 7:181–199, 1997.

- Steiner H: The evaluation and management of aggression in juveniles. *New Dir Psychiatry* 22:355–369, 2002.
- Steiner H, Petersen ML, Saxena K, Ford S, Matthews Z: Divalproex sodium for the treatment of conduct disorder: A randomized, controlled clinical trial. *J Clin Psychiatry* 64:1183–1191, 2003.
- Steiner H, Saxena K, Chang K: Psychopharmacological strategies for the treatment of aggression in youth. *CNS Spectr* 8:298–308, 2003.
- Swann AC, Bjorn JM, Moeller FG, Dougherty DM: Two models of impulsivity: Relationship to personality traits and psychopathology. *Biol Psychiatry* 51:988–994, 2002.
- Wagner KD, Weller EB, Carlson GA, Sachs G, Biederman J, Frazier JA, Wozniak P, Tracy K, Weller RA, Bowden C: An open-label trial of divalproex in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 41:1224–1230, 2002.
- Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: Reliability, validity, and sensitivity. *Br J Psychiatry* 133:429–435, 1978.

Address reprint requests to:

Kirti Saxena, M.D.

Stanford University

School of Medicine

Department of Psychiatry and Behavioral Sciences

Division of Child Psychiatry and Child

Development

401 Quarry Road

Stanford, CA 94305-5719

E-mail: ksaxena@stanford.edu

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.