# Divalproex Sodium for the Treatment of Conduct Disorder: A Randomized Controlled Clinical Trial

Hans Steiner, M.D.; Maya L. Petersen, B.A.; Kirti Saxena, M.D.; Sekou Ford, M.D.; and Zakee Matthews, M.D.

***Background:*** New treatments for conduct disorder are sorely needed. We aimed to test the efficacy of divalproex sodium for the treatment of conduct disorder.

***Method:*** Seventy-one youths with conduct disorder according to DSM-IV criteria were enrolled in a randomized, controlled, 7-week clinical trial. Subjects were all adolescent males with at least 1 crime conviction. Subjects were randomized into high- and low-dose conditions and were openly managed by a clinical team. Subjects and independent outcome raters were blinded to condition. Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) ratings, Weinberger Adjustment Inventory ratings, and staff ratings of behavioral privilege were used to assess outcome.

***Results:*** Intent-to-treat analyses showed significant associations between assignment to the high-dose condition and ratings on the CGI-S ($p = .02$) and CGI-I ($p = .0008$). Self-reported weekly impulse control was significantly better in the high-dose condition ($p < .05$), and association between improvement in self-restraint and treatment condition was of borderline statistical significance ($p < .06$). Parallel analyses comparing outcome by blood drug level achieved strengthened the results, as expected.

***Conclusion:*** This preliminary study in a most difficult population suggests a role for divalproex sodium in the treatment of conduct disorder. Divalproex sodium improved self-reported impulse control and self-restraint, variables shown to be predictive of criminal recidivism. Studies are needed of longer-term impact and side-effect profiles. This is one of few controlled psychopharmacologic studies of conduct disorder.

*(J Clin Psychiatry 2003;64:1183–1191)*

*Received May 31, 2001; accepted March 17, 2003. From the Division of Child Psychiatry and Child Development, Stanford University School of Medicine, Stanford, Calif.*

*This research was supported by grants from Abbott Pharmaceuticals, Chicago, Ill., the California Wellness Foundation, Los Angeles, Calif., and the California Youth Authority, Sacramento, Calif. (Dr. Steiner).*

*Dr. Steiner has received grant/research support and honoraria from and has served on the speakers or advisory board for Abbott.*

*Corresponding author and reprints: Hans Steiner, M.D., Stanford University School of Medicine, Division of Child Psychiatry and Child Development, 401 Quarry Road, Stanford, CA 94305-5719 (e-mail: steiner@stanford.edu).*

*"You know, doc, the staff used to ask me to count to 8 before I hit someone, and maybe I would get to 2. Now I can count to 8."*

—16-year-old delinquent boy
delivering nonstandardized outcome rating

Conduct disorder (CD) is one of the most common psychopathologies referred for psychiatric evaluation.[1] Its lifetime course is chronic,[2] and outcome is generally poor, whether measured by clinical assessment or criminal recidivism rates.[1] Until recently, reports reviewing the efficacy of various interventions were highly pessimistic about the potential to effect positive, lasting change.[3] Although recent expert panel reports have been more optimistic, outlining several preventive intervention successes,[4] treating CD remains problematic.[1]

Psychopharmacologic interventions represent one promising, but relatively unexplored, treatment modality. There is a paucity of controlled psychopharmacologic trials in which CD is the primary recruitment diagnosis and the trial is conducted with standardized instruments and according to a strict, randomized, double-blind, placebo-controlled design.[5] There are only a few trials with CD youths that have designs adequate to test agent efficacy.[6–14] Multiple drugs are currently used to treat aggression in the context of other juvenile psychopathology, but most are supported only by exploratory and open-label studies.

The scarcity of adequate psychopharmacologic studies is partly explained by population characteristics that make CD youths difficult subjects.[15] These characteristics include dishonesty, scarce social supports, unstable lifestyle, concurrent street drug use, and poor physical health. In addition, much of this population is handled by juvenile justice systems that do not view delinquency as a psychiatric disorder and so believe that medication for the problem is inappropriate. We wanted to contribute to the sparse knowledge of psychopharmacologic treatments for CD and to investigate the novel application of a well-established medication (divalproex sodium) to this intractable behavioral target. Aggressive delinquents were chosen as subjects because of the severity of their symptoms and their clear need for treatment.

Divalproex sodium, an enteric form of valproate sodium and valproic acid, has been used extensively in juve-



© Copyright 2003 Physicians Postgraduate Press, Inc.

niles of all ages for the treatment of seizure disorders, with high success rates and a favorable side effect profile. Successful use of divalproex sodium has also been reported in the management of panic disorder, mania, and the maintenance phase of bipolar disorder.[16–20] For psychiatric applications in underage populations, the majority of studies have been neither blind nor controlled; nevertheless, the medication is extensively prescribed, off-label, in youths of all ages for psychiatric targets such as aggression.

Some empirical evidence is available to support the efficacy of divalproex in the management of maladaptive aggression and related psychopathology. Several studies suggest that divalproex reduces agitation in bipolar or borderline patients.[21,22] Further preliminary reports support its efficacy in managing aggressive behavior, mood lability, and agitation in patients with organic brain syndromes[23] and in adolescent psychiatric inpatients.[24,25] Two recent reviews specifically suggest that antikindling agents are effective in the treatment of aggression in adults,[26] particularly those who have intellectual disabilities.[27]

We postulated that treatment with divalproex at doses effective for seizures would (1) reduce severity of disorders and result in clinical improvement at the end of a 7-week trial, with minor side effects; (2) reduce subjectively experienced distress, leading to increased levels of self-restraint; and (3) reduce verbal and behavioral manifestations of anger and aggression, as judged by institutional staff. To test these hypotheses, a 7-week, double-blind, randomized, controlled trial was undertaken.

## METHOD

### Subjects

This protocol was approved by the California Youth Authority (CYA; Sacramento, Calif.) and the Stanford University Panel on Medical Human Subjects. The protocol called for active, informed consent by the subject and for notification of subjects' parents to provide them with an opportunity to object to participation. A neutral independent ombudsman was provided throughout the study to discuss with subjects any concerns that they might have and to expedite any requests for withdrawal. All research files were inaccessible to CYA staff.

One hundred seventy-five male adolescents were initially screened for participation. Inclusion criteria, in addition to fulfilling DSM-IV criteria for CD, were as follows: (1) ability to give active consent; (2) absence of parental denial; (3) absence of acute psychoses, homicidality, suicidality, mental retardation, and active medical illness; (4) no currently needed additional medication; (5) history of at least 1 offense against persons; and (6) ability to complete screening instrument (Weinberger Adjustment Inventory [WAI]) with an adequate validity score (at least 3.667).

Of the initial 175 screened, 71 subjects fulfilled all inclusion criteria, were eligible for participation, and consented. Sixty-one subjects completed the treatment course and received exit evaluations from at least 1 evaluator. Fifty-eight received exit evaluations from 2 raters and completed all measures. They constitute the sample for this article.

Of the original 71 subjects, 7 subjects discontinued the study due to institutional reasons (5 were transferred to other institutions and 2 were paroled early). Three subjects were discontinued by us: 1 began taking medication for treatment of tuberculosis, and 2 had persistent, mild alkaline phosphatase elevation of uncertain significance and without symptoms but were removed from the study as a precautionary measure.

Sixty-six percent (N = 38) had a violent committing offense ranging from manslaughter, robbery, and rape to assault with a deadly weapon. Thirty-three percent (N = 19) had a technical offense as their committing offense, which brought them into the institution, most commonly violation of parole conditions. If their committing offense was not classified as "against persons," they had to have had at least 1 prior offense against persons in their crime history. The mean number of prior offenses against persons was 1.04, ranging from 0 to 5 offenses. There were about 1.6 prior offenses against property, with a range of 0 to 6. There was a mean of 0.2 prior drug offenses, with a range of 0 to 1. There was a mean of 0.7 prior technical offenses, with a range of 0 to 3. The mean number of total prior offenses, without the committing offense, was 3.5, with a range of 0 to 11. These youths' crime profiles thus are more severe than the average in the CYA, because they were specifically recruited on the basis of having committed crimes against persons.

Study participants were all males from 1 particular campus, which tends to treat the youngest offender group in the CYA. Our subjects were comparable to the general population in the CYA, on which we have reported in prior studies,[28,29] in age (mean ± SD age = 15.9 ± 1.1 years; range, 14–18 years) and length of anticipated commitment (about 24 months). The mean length of stay at time of participation in the study was 3 months (range, 1–20 months). Our subjects differed from the general CYA population in ethnicity (more whites, fewer minorities) despite special efforts by the diverse team of researchers to include minorities (Table 1).

### Instruments: Self Report

***Achenbach Youth Self Report (YSR).*** The YSR is a well-known standardized clinical screening survey assessing 8 dimensions of psychopathology, as well as 3 superordinates: internalizing, externalizing, and total psychopathology. Clinical and borderline ranges are available. The instrument has good psychometric properties.[30] This screen is widely employed in underage populations to identify risk for psychopathology. Previous use in the CYA with large samples has yielded satisfactory re-

Table 1. Subject and California Youth Authority (CYA) Population Characteristics

| Variable | Subjects | CYA Population |
|---|---|---|
| Age, mean ± SD, y | 15.9 ± 0.83 | 15.9 ± 1.1[a] |
| WAI dimension score at screening, mean ± SD | | |
| Distress | 2.7 ± 0.6 | 2.7 ± 0.7[a] |
| Self-Restraint | 2.5 ± 0.7 | 3.4 ± 0.8[a] |
| Race/ethnicity, N (%) | | |
| White | 23 (37.7) | 381 (15)[b] |
| Latino | 23 (37.7) | 1170 (46.7)[b] |
| African American | 10 (16.4) | 738 (29.8)[b] |
| Asian | 2 (3.3) | 127 (5.5)[b] |
| Other/unspecified | 3 (5.5) | 77 (3.0)[b] |

[a]Data from Steiner et al.[28,29]
[b]Data from CYA 1997 census.
Abbreviation: WAI = Weinberger Adjustment Inventory.

sults in terms of the youths' ability to complete the survey and comprehend its content.

***Weinberger Adjustment Inventory.*** The WAI is a 62-item questionnaire measuring subjective distress (anxiety, depression, low well-being, low self-esteem) and self-restraint (impulse control, suppression of aggression, responsibility, consideration for others).[31] Previous studies have shown good psychometric properties and convergent validity with the Minnesota Multiphasic Personality Inventory.[32] There is also discriminant (psychopathology vs. normal controls)[33] and predictive validity in populations of both delinquents and nondelinquents.[34,35]

The instrument was given in 2 versions in this study. At screening and at entry, subjects completed a version reporting on the past year or longer. For assessments during the study, instructions were changed to reflect weekly assessments.

## Observer Ratings

***Best estimate diagnoses.*** At entry, all participants were examined by the managing clinician (Z.M.), a board-eligible child psychiatrist with 4 years of experience in the CYA population, with full access to all clinical information about each subject, including medical, criminal, and social histories; CYA case reports; and previous psychiatric evaluations. Using DSM-IV criteria, the clinician generated a "best estimate" of current psychiatric diagnoses for each participant. As a minimum, a subject was required to fulfill CD criteria by DSM-IV.

While in some ways structured interviews for diagnosis would have been preferable, we felt that in this study we needed to preserve our subject's limited capacity for adhering to the protocol. To add structured interviews would have been an additional burden of 2 to 4 hours, which we felt would not be beneficial, as there is evidence that best estimate diagnoses are in many ways comparable to structured interviews. In other studies, authors have reported on the validity of best estimate diagnoses. Fennig et al.[36] reported on the short-term diagnostic stability of psychotic disorders. Patients were interviewed at baseline and after 6 months with the Structured Clinical Interview for DSM-III-R. A best estimate diagnosis was made at both timepoints. Affective psychosis and schizophrenic disorders were relatively stable broad diagnostic categories over the 6-month period, with 86.5% to 88.9% of the patients remaining in the same category. Simpson et al.[37] concluded that good interrater reliability for bipolar II disorder can be achieved when the interviews and best estimate diagnoses are done by experienced psychiatrists. Not all reports are positive, though. Taiminen et al.[38] compared clinical and best estimate research DSM-IV diagnosis in a Finnish sample of first-admission patients with psychosis and severe affective disorder. They concluded that hospital diagnoses were not reliable in first-episode patients. As none of our subjects were psychotic, we still felt that our current strategy was defendable, if not optimal.

The managing clinician also provided 2 Clinical Global Impressions scale (CGI) ratings at entry into and at exit from the study: CGI-Severity of Illness (CGI-S) at entry and exit and CGI-Improvement (CGI-I) at exit. The scales described by Guy[39] were used. For severity, the anchors "not at all ill" (0) to "among the most extremely ill" (6) were used. For improvement, the range was "very much improved" (1) to "very much worse" (7).

***Blinded clinician exit interview for target symptom ratings and clinical global ratings.*** At exit from the study, a second blinded clinician (H.S.), a board-certified child psychiatrist with 15 years of experience in the CYA population, examined subjects and rated them according to the CGI-S.[39] Additionally, the blinded clinician also estimated how improved the subjects were compared with their severity at entry into the study. In the course of the 1-hour examination, descriptions by the subjects of original levels of symptoms were elicited and allowed the blinded clinician to make some judgment as to the degree of improvement in the core symptoms of CD that occurred in the subject compared with their severity at the beginning of the study. This improvement was expressed along the usual CGI-I dimension of very much improved (1) to very much worse (7). This clinician was blinded to assessment and treatment status, criminological and clinical histories, and subjects' weekly self-reported progress. He did not participate in any other structured assessment of the subjects and met them during their last week in the study for a single examination to generate the CGI rating. Discussion focused on target symptoms (anger, aggression, and impulsivity). Final CGI-S and CGI-I scores were based on this discussion.

***Privilege level.*** Case management in the CYA involves assigning each ward a privilege level of 1 through 4, on the basis of the ward's weekly behavior and progress. The score is arrived at by consensus and is re-

**Table 2. Diagnoses by Managing Clinician in a Sample of Youths With Conduct Disorder (N = 58)**

| Diagnosis | Frequency N (%) |
|---|---|
| Conduct disorder | 58 (100) |
| Substance abuse disorder | 51 (88) |
| Learning disability | 35 (60) |
| Dysthymia/depression | 31 (54) |
| Attention-deficit/hyperactivity disorder | 30 (52) |
| Posttraumatic stress disorder | 13 (22) |
| Antisocial personality disorder | 4 (7) |
| Major depressive disorder | 2 (4) |
| Pedophilia | 2 (4) |
| Pyromania | 1 (2) |

**Table 3. Psychopathology as Assessed by the Youth Self Report (YSR) in Youths With Conduct Disorder (N = 58)**

| YSR Dimension | Clinical Psychopathology N (%) | Borderline Psychopathology N (%) |
|---|---|---|
| Withdrawal | 8 (13.7) | 17 (29.3) |
| Somatic complaints | 14 (24.13) | 16 (27.5) |
| Anxious/depressed | 19 (32.75) | 34 (58.62) |
| Social problems | 4 (6.89) | 21 (36.20) |
| Thought problems | 6 (10.34) | 18 (31.03) |
| Attention problems | 8 (13.79) | 44 (75.86) |
| Delinquency | 15 (25.86) | 13 (22.41) |
| Aggression | 19 (32.75) | 35 (60.34) |
| Internalizing | 18 (31.03) | 8 (13.79) |
| Externalizing | 34 (58.62) | 6 (10.34) |
| Total psychopathology | 26 (44.82) | 12 (20.90) |

viewed at least every 6 days by a team that includes the parole agent, a teacher, and a counselor. Subjects' privilege levels were recorded throughout the study. Subjects in special confinement receive no privileges, expressed as 0 in our system.

### Protocol

Following enrollment in the study, subjects spent 1 week in washout. During that week, the managing clinician conducted clinical evaluations of all participants and completed best estimate diagnoses.

Participants were randomized into either a high-dose (between 500 and 1500 mg/day or therapeutic plasma levels for seizure control between 50 and 120 μg/mL) or low-dose (up to 250 mg/day) condition. Open clinical management sought to minimize any risk or side effects, aiming for as low a dose as possible in either condition. Assignment to the high-dose condition resulted in a modal oral dose of 1000 mg/day, and assignment to the low-dose condition resulted in a modal oral dose of 125 mg/day. Both groups were started at 125 mg/day and both reported only mild side effects (sleepiness, transient gastrointestinal upset). Those in the high-dose condition were gradually titrated up to blood levels of 50 to 120 μg/mL. Dosages, response, side effects, and blood levels were monitored by the clinical team (H.S., Z.M.).

**Table 4. Youth Self Report (YSR) Scores at Entry and Exit (N = 58)**

| YSR Dimension | Entry Score Mean ± SD | Exit Score Mean ± SD | $\chi^{2a}$ |
|---|---|---|---|
| Withdrawal | 5.2 ± 2.9 | 4.2 ± 2.8 | 2.8 |
| Somatic complaints | 4.0 ± 3.8 | 2.2 ± 3.4 | 10.0* |
| Anxious/depressed | 8.8 ± 6.8 | 7.9 ± 7.1 | 0.6 |
| Social problems | 4.7 ± 2.8 | 4.1 ± 2.9 | 1.3 |
| Thought problems | 3.8 ± 2.5 | 3.4 ± 3.1 | 1.8 |
| Attention problems | 6.7 ± 3.5 | 6.8 ± 3.6 | 0.03 |
| Delinquency | 9.5 ± 4.0 | 8.4 ± 4.2 | 1.7 |
| Aggression | 14.1 ± 6.4 | 14.4 ± 8.0 | 0.003 |
| Internalizing | 17.3 ± 11.6 | 13.8 ± 11.3 | 2.5 |
| Externalizing | 23.6 ± 9.3 | 22.8 ± 11.5 | 0.3 |
| Total psychopathology | 65.5 ± 29.0 | 59.1 ± 31.2 | 0.9 |

[a]Comparison by Kruskal-Wallis chi-square approximation (df = 1).
*$p < .001$.

The 2 subgroups were comparable on all background variables discussed in the sample description, as we would expect from randomization.

### Statistics

All statistical analyses were performed using SAS (Statistical Analysis System, [version 8e]). Variables were found to be non-normally distributed, and Cronbach alpha, Spearman correlation, Kruskal-Wallis, Wilcoxon, and Fisher exact tests were thus used as appropriate. Linear regression of privilege level and WAI scores collected throughout the study were used to estimate each subject's mean change in privilege status and in all dimensions assessed by the WAI. Regression equations employed as many data points as were available for each subject (mean ± SD = 6.2 ± 1.7; range, 2–8).

## RESULTS

### Descriptive Characteristics of the Sample

Table 2 summarizes the best estimate diagnoses of the sample. All subjects were diagnosed with CD. In addition, entry diagnoses revealed significant comorbidity: the mean number of diagnoses per subject was 3.9 ± 1.2, median = 4; range, 1–6). Youth Self Report scores indicated psychopathology along multiple dimensions (Table 3). Nearly 70% of participants were clinical or borderline clinical externalizers (N = 40), approximately half were clinical or borderline clinical internalizers (N = 26), and approximately two thirds were in the clinical or borderline clinical range for total psychopathology (N = 38), as assessed by the YSR. These results are comparable to results found in much larger samples in the same population.[11] Twenty-four subjects were randomized to the low-dose condition, and 34 were randomized to the high-dose condition.

There was considerable stability of dimensional psychopathology during the study, reflected in high correlations between entry and exit levels of YSR scores (mean

Table 5. Blind Clinical Global Impressions-Severity of Illness (CGI-S) Ratings at Exit According to Dosing of Divalproex

| | CGI-S Rating | | | | |
|---|---|---|---|---|---|
| Condition | Borderline Mentally Ill N (%) | Mildly Ill N (%) | Moderately Ill N (%) | Markedly Ill N (%) | Severely Ill N (%) |
| High dose, 1000 mg[a,b] (N = 34) | 18 (53) | 7 (21) | 5 (15) | 1 (3) | 3 (9) |
| High blood drug level, > 45 μg/mL[c,d] (N = 32) | 17 (53) | 7 (22) | 4 (13) | 1 (3) | 3 (9) |
| Low dose, 125 mg[b] (N = 24) | 4 (17) | 4 (17) | 6 (25) | 4 (17) | 6 (25) |
| Low blood drug level, < 45 μg/mL[d] (N = 26) | 5 (19) | 4 (15) | 7 (27) | 4 (15) | 6 (23) |

[a]Comparison of 2 conditions using chi-square Fisher exact test ($\chi^2$ = 11.3, df = 4, p = .02).
[b]Analysis based on intent to treat.
[c]Comparison of 2 conditions using chi-square Fisher exact test ($\chi^2$ = 10.5, df = 4, p = .03).
[d]Analysis based on blood drug level achieved.

Spearman ρ = .62; range, .44–.73) and lack of any significant difference between mean scores at entry and exit for all but 1 dimension (Table 4).

### Correlation of Diagnoses, Dimensional Psychopathology, and Observer CGI Ratings

Cronbach alpha scores were high for all self-report instruments used (mean α = .80; range, .69–.95).

Spearman rank correlations were used to correlate the managing clinician's entry diagnoses with self-reported psychopathology scores on the YSR to examine convergence of clinician and self-reported results. The number of diagnoses given by the clinician correlated significantly with the subject's total psychopathology score on the YSR (Spearman ρ = .36, p = .005). Other comorbid diagnoses of interest also showed expected relationships to the YSR subscale scores. The clinical diagnosis of attention-deficit/hyperactivity disorder correlated significantly with the attention subscale score of the YSR (score = 0.26, p = .04) and the externalizing broadband score of the YSR (score = 0.28, p = .03), as would be expected. The diagnosis of posttraumatic stress disorder (PTSD) correlated significantly with the anxiety subscale score (score = 0.29, p = .03) and the internalizing broadband score of the YSR (score = 0.33, p = .01). On the other hand, the third most commonly encountered comorbid condition, dysthymia/depression, did not significantly correlate with any YSR scale scores. Substance abuse and learning disability, 2 other common diagnoses in this sample, have no equivalent on the YSR, and the remaining disorders listed in Table 2 were too infrequent to yield meaningful results.

The managing clinician's CGI-S ratings at entry were distributed as follows: 1 subject (1.6%) was rated as borderline ill; 6 (10%), as mildly ill; 16 (26%), as moderately ill; 18 (30%), as markedly ill; 15 (25%), as severely ill; and 5 (8%), as extremely ill. The CGI-S ratings by the managing clinician correlated significantly (Spearman ρ = .36, p = .005) with the total psychopathology score of the YSR.

The blinded clinician's CGI-S ratings at exit from the study, which served as one of the primary outcomes, were distributed as follows: No subjects were rated as not ill; 22 subjects (38%) were rated as borderline ill; 11 (19%), as mildly ill; 11 (19%), as moderately ill; 5 (9%), as markedly ill; and 9 (16%), as severely ill. None were in the extremely ill group. The CGI-S ratings by the blinded clinician correlated significantly with the total psychopathology scores on the YSR (ρ = .23, p = .04, 1-tailed) and the nonblinded CGI-S rating at exit from the study by the managing clinician (ρ = .23, p = .04, 1-tailed).

CGI-I ratings by the blinded clinician served as another primary outcome measure. CGI-I ratings by the blinded clinician and managing clinicians agreed significantly (Spearman ρ = .44; weighted κ = .37; 95% confidence interval = 0.18 to 0.57; Fisher exact test p < .01). There was no significant difference in the magnitude of the CGI-I ratings between managing clinician (mean score = 2.03 ± 0.82) and blinded outcome rater (mean score =2.13 ± 0.85). Both results indicate acceptable rater concordance on the improvement ratings.

The managing clinician's CGI-S ratings at exit and CGI-I ratings correlated significantly (ρ = .55, p = .0001). The blinded clinician's CGI-S and CGI-I ratings at exit correlated significantly (ρ = .76, p = .0001). Both results support the 2 raters' consistency.

### Efficacy by Intent to Treat

In these analyses, we used random assignment to condition as a factorial to examine the effects of the differential dosing. A Fisher exact test showed a significant ($\chi^2$ = 11.3, df = 4, p = .02) differentiation of severity of disorder at exit from the study by blinded clinician CGI-S ratings as a function of being in one treatment condition versus the other (Table 5). Of the 22 subjects rated as borderline ill, 18 (82%) were in the high-dose condition. In

Table 6. Blind Clinical Global Impressions-Improvement (CGI-I) Rating at Exit According to Dosing of Divalproex

| Condition | CGI-I Rating: Very Much or Much Improved N (%) | Minimally Improved N (%) | No Change or Minimally Worse N (%) |
|---|---|---|---|
| High dose, 1000 mg[a,b] (N = 34) | 18 (53) | 10 (29) | 6 (18) |
| High blood drug level, > 45 μg/mL[c,d] (N = 32) | 18 (56) | 9 (28) | 5 (16) |
| Low dose, 125 mg[b] (N = 24) | 2 (8) | 10 (42) | 12 (50) |
| Low blood drug level, < 45 μg/mL[d] (N = 26) | 2 (8) | 11 (42) | 13 (50) |

[a]Comparison of 2 conditions using chi-square Fisher exact test ($\chi^2$ = 13.5, df = 2, p = .0008).
[b]Analysis based on intent to treat.
[c]Comparison of 2 conditions using chi-square Fisher exact test ($\chi^2$ = 16.1, df = 2, p = .0003).
[d]Analysis based on blood drug level achieved.

the mildly ill group, 64% (N = 7) were in the high-dose condition. The pattern then reverses in the moderately to severely ill ratings: between 55% and 80% (moderately ill: N = 6 of 11; markedly ill: N = 4 of 5; severely ill: N = 6 of 9) of the subjects in each group were in the low-dose condition, indicating that those who were given low doses of the medication also were judged to be more severely ill by the blinded clinician.

Additionally, CGI-I ratings produced significant results. A Fisher exact test revealed a significant association between the CGI-I rating by the blinded clinician at exit and the assigned treatment condition (high or low dose) of the subjects. Subjects in the high-dose condition were more likely to receive markedly improved (clustering very much improved and much improved levels) CGI-I ratings ($\chi^2$ = 13.5, df = 2, p < .001), compared with ratings of minimal improvement, no change, or slight worsening (Table 6). Changes in secondary efficacy measures during the course of the study were compared between treatment groups using Kruskal-Wallis tests. Changes in privilege level awarded by staff did not differ significantly between the 2 groups. Improvement in self-reported impulse control on the WAI was significantly greater in the therapeutic group (p < .05), and improvement in self-reported restraint was suggestively greater (p < .06) (Table 7).

### Efficacy by Blood Drug Level Achieved

The mean blood drug level was 71.2 ± 22.8 μg/mL in the high-dose condition and 13.8 ± 5.12 μg/mL in the low-dose condition. Thirty-four of the subjects completing the study were initially assigned to the high-dose group; of these, 32 achieved therapeutic blood levels. Two subjects assigned to the high-dose group did not approach therapeutic blood drug levels, probably due to noncompliance. Since assignment to the high-dose group did not ensure therapeutic dosage, we repeated the above intent-to-treat analyses using a code based on peak valproate level reached (> 45 μg/mL), expecting that the results would remain the same or even be strengthened.

As above, a Fisher exact test revealed a highly significant association between blind CGI-S rating and therapeutic drug level ($\chi^2$ = 10.5, df = 4, p < .02) (Table 5). Furthermore, an additional Fisher exact test revealed a highly significant association between CGI-I rating and therapeutic drug level ($\chi^2$ = 16.1, df = 2, p < .001) (Table 6). Analysis of secondary efficacy measures also supported results from the intent-to-treat analysis. As above, change in privilege level over the course of the study did not differ significantly between the 2 groups. Self-restraint and impulse control were the only WAI measures to show significantly greater improvement in the group that achieved therapeutic blood drug levels (p < .05) (Table 7).

### Tolerability

Divalproex was well tolerated by all study participants. Generally, the side effect profile was mild and in accordance with previous studies,[17,25] consisting of gastrointestinal upset and sleepiness and decreasing rapidly over time. Six individuals reported experiencing increased sleepiness, and 1 individual experienced nausea and an isolated instance of vomiting. In general, side effects disappeared within 3 to 4 weeks. There were no instances of the serious side effects that have been reported elsewhere.[18]

## DISCUSSION

This trial provides preliminary evidence for the short-term efficacy of divalproex for the treatment of CD. This was a fully controlled, double-blind, randomized study with a substantial sample size, the first of such studies to investigate the potential of divalproex in the treatment of severe CD. All self-rating instruments used appeared to function reliably and had good alpha scores for all dimensions. CGI ratings by managing and blinded clinicians supported each other and correlated with YSR scores from the subjects as well.

The medication resulted in significant clinical improvement, as rated by the blinded clinician, and concomitant weekly gradual improvement of restraint and impulse control, as reported by the subjects. Both self-reported WAI measures (distress and self-restraint) affected have been shown to be predictive of future criminal recidivism in a prospective study.[29] This study is particularly significant given the paucity of controlled, randomized studies of divalproex for targets other than mood and seizure control.

The medication resulted in differential improvement between high- and low-dose conditions, but several sub-

Table 7. Change in Privilege Level and Weinberger Adjustment Inventory (WAI) Scores[a]

| Item | Intent to Treat[b] | | | Blood Drug Level Achieved[c] | | |
|---|---|---|---|---|---|---|
| | High Dose/High Blood Drug Level Mean ± SD | Low Dose/Low Blood Drug Level Mean ± SD | $\chi^2$ | High Dose/High Blood Drug Level Mean ± SD | Low Dose/Low Blood Drug Level Mean ± SD | $\chi^2$ |
| Change in privilege level | .008 ± .21 | .05 ± .17 | 0.38 | .008 ± .23 | .05 ± .16 | 0.28 |
| Change in WAI dimension scores | | | | | | |
| Distress | –.04 ± .10 | –.02 ± .05 | 0.38 | –.05 ± .10 | –.02 ± .05 | 0.60 |
| Low self-esteem | –.02 ± .16 | –.05 ± .09 | 2.3 | –.03 ± .16 | –.05 ± .09 | 1.8 |
| Low well-being | –.06 ± .17 | .001 ± .09 | 1.13 | –.06 ± .17 | .001 ± .09 | 1.1 |
| Anxiety | –.02 ± .10 | –.008 ± .07 | 0.05 | –.03 ± .09 | –.008 ± .07 | 0.19 |
| Depression | –.07 ± .10 | –.02 ± .08 | 3.07 | –.07 ± .11 | –.02 ± .08 | 2.55 |
| Self-restraint | .04 ± .09 | –.008 ± .08 | 3.44 | .04 ± .09 | –.008 ± .06 | 4.0* |
| Consideration for others | .04 ± .16 | –.03 ± .10 | 1.4 | .05 ± .16 | –.03 ± .10 | 1.7 |
| Responsibility | .06 ± .16 | –.002 ± .07 | 1.7 | .06 ± .15 | –.002 ± .07 | 2.3 |
| Impulse control | .03 ± .08 | –.009 ± .08 | 5.22* | .03 ± .07 | –.009 ± .08 | 4.7* |
| Suppression of aggression | .02 ± .08 | .005 ± .10 | 0.35 | .02 ± .08 | .005 ± .10 | 0.63 |

[a]Comparison using Kruskal-Wallis chi-square approximation (df = 1).
[b]Analysis based on intent to treat.
[c]Analysis based on blood drug level achieved.
*p < .05.

jects receiving a high dose did not respond to therapeutic levels of the medication. It is also clear from our initial results that divalproex will not lead to improvement for all youths with CD; in fact, only a portion of the total sample responded to either low or high doses of divalproex sodium (N = 32).

In addition, 2 subjects in the low-dose condition showed marked improvement. It is possible that a subgroup of CD youths may exist that respond to relatively small doses of divalproex; however, this study design does not allow us to distinguish such a population from individuals improving due to either a placebo effect or factors external to the study. In both conditions there were also a significant number (N = 10 each) who were rated as minimally improved. It is possible that these individuals might have responded to higher doses with marked improvement.

Our study suggests that divalproex increases self-reported restraint significantly, albeit modestly in the span of 7 weeks of treatment, and did so more in the high-dose condition. A subjective increase in restraint was substantiated by informal commentary on the treatment provided by study participants (see quote at beginning of article). Three of the high-dose subjects specifically reported a delay in aggressive or angry response following their reaction to a stressor.

Contrary to our expectations, treatment condition was not found to be associated with a differential reduction in distress, a finding particularly interesting in light of the literature reporting the profound effects of divalproex on mood stabilization.[16,19,20] Instead, subjective distress decreased equally in both treatment groups. Several potential explanations exist for this result. First, it is possible that distress is not affected by divalproex, and the reduction in distress observed in both conditions was due to a general therapeutic effect of study participation and the associated increase in services. Alternately, divalproex could be effective at reducing distress even at low doses, with the magnitude of the effect observed not significantly increased with increasing dose, at least in the short run. Another possible explanation is that the construct of distress as measured by the WAI is related to, but not synonymous with, mood and affective dysregulation, as usually found in mood disorders, and thus would not be differentially affected by a mood stabilizing medication in therapeutic doses.

The study had several limitations, which need to be fairly acknowledged. We only studied boys, and it is an open question as to whether similar results would be obtained in girls. We did not study diagnoses by structured interviews, and thus there is some uncertainty as to the full range of comorbidities in this sample. Blind CGI ratings were made at a single point in time, i.e., at exit. Secondary standardized outcome measures were mostly by self-report. We lacked measures that accurately and sensitively reflect performance-related criteria, in particular, verbal and behavioral manifestations of anger and aggression within the institution.

Disappointingly, the sole measure of behavioral performance used, staff privilege rating, did not prove significantly different between treatment groups. One potential explanation lies in the occurrence of a gang-related group disturbance during the study, affecting some 20 subjects and resulting in a universal reduction in privilege level for all present on the premises. As this incident revealed, privilege level is too vulnerable to institutional demands to serve as an adequate measure of behavioral performance, and future studies should establish an independent objective assessment of aggression and impulse control.

Future study, involving a larger population and a wider range of assessment instruments, is necessary to correct

some of these shortcomings and clearly elucidate the processes by which divalproex affects change in severe CD.

Nevertheless, our study also has some strengths, which are worth emphasizing. It is one of few with a difficult-to-study population. The milieu in which the study was conducted is not ordinarily associated with carrying out clinical trials with standardized protocols. Usually in this milieu, subjects' motives, intentions, and behaviors are closely monitored. Additionally, in this study, performance along dimensions measured can be linked to increased privileges and, ultimately, freedom. Although participants were assured that their responses to self-report instruments and interviews were anonymous and lacked any personal ramifications, there probably still was not complete trust in the study administrators and their intentions. Still, we obtained what seemed to be honest, meaningful, and substantially different responses. Our study produced interesting results, which converge with other, similar studies of mood stabilizers and maladaptive aggression.[7,25,40]

Our study directs us to some interesting leads regarding the role of mood stabilizers in the treatment of severe CD. One of the processes that could be affected by these medications is the link between PTSD, CD, and maladaptive aggression. Such a link has been postulated by Post et al., especially for chronic PTSD.[41] From previous studies, we know that incarcerated juvenile delinquents have high rates of both PTSD[28,29] and affectively driven aggression[42] problems that have been demonstrated to be linked.[41] From an empirical point of view, there is some evidence that 2 antiepileptic agents, carbamazepine[34] and divalproex,[43,44] are effective in the treatment of PTSD. Divalproex could potentially reduce reactive aggression in incarcerated delinquents by interfering via specific pathways linking negative affective arousal and reduced restraint.[45] The drug could achieve this by inhibiting contagion between affective arousal and aggressive behavior (through inducing restraint) via action on the γ-aminobutyric acid (GABA)-ergic and/or the serotonergic neurotransmitter system, both of which have been shown to be affected by divalproex sodium.[46]

We would like to conclude on a final cautionary note. Despite its positive findings, this remains only a preliminary study of divalproex treatment of CD, and much work needs to be done. Although the sample size employed was large enough to demonstrate some efficacy, a larger sample is needed to confirm the findings and further elucidate the process by which the positive outcome occurs. The duration of the observed effects, as well as the potential for long-term compliance issues and side effects, also remains unclear. Long-term follow-up studies are required. Although it is highly unlikely that a single medication will be sufficient to significantly improve long-term outcome for all CD youths, divalproex seems to offer a potentially beneficial new tool to add to our treatment arsenal. With improved understanding of its effects in this population, it may be possible to incorporate divalproex in a multifaceted long-term treatment approach for CD.

*Drug names:* carbamazepine (Tegretol, Epitol, and others), divalproex sodium (Depakote), valproate sodium (Depacon and others), valproic acid (Depakene and others).

## REFERENCES


1. Steiner H, and the AAACAP Work Group on Quality Issues. Practice Parameters for the Assessment and Treatment of Children and Adolescents With Conduct Disorder. J Am Acad Child Adolesc Psychiatry 1997;36(suppl 10):122S–139S
2. Loeber R, Keenan K, Lahey BB, et al. Evidence for developmentally based diagnoses of oppositional defiant disorder and conduct disorder. J Abnorm Child Psychol 1993;21:377–410
3. Lipsey MW. Juvenile delinquency treatment: a meta-analytic inquiry into the variability of effects. In: Cook T, ed. Meta-Analysis for Explanation. New York, NY: Russell Sage Foundation; 1992:83–128
4. Loeber R, Farrington DP. Serious and Violent Juvenile Offenders: Risk Factors and Successful Interventions. The Report of the Study Group on Serious and Violent Juvenile Offenders. Office of Juvenile Justice and Delinquency Prevention (OJJDP): Washington, DC; 1998
5. Steiner H, Redlich A. Child psychiatry and juvenile justice. In: Lewis M, ed. Child Psychiatry. New York, NY: Williams & Wilkins; 2002: 1417–1425
6. Campbell M, Adams PB, Small AM, et al. Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. J Am Acad Child Adolesc Psychiatry 1995;34:445–453
7. Malone RP, Delaney MA, Luebbert JF, et al. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. Arch Gen Psychiatry 2000;57: 649–654
8. Sheard MH, Marini JL, Bridges CI, et al. The effect of lithium on impulsive aggressive behavior in man. Am J Psychiatry 1976;131:1409–1413
9. Campbell M, Small AM, Green WH, et al. Behavioral efficacy of haloperidol and lithium carbonate: a comparison in hospitalized aggressive children with conduct disorder. Arch Gen Psychiatry 1984;41:650–656
10. Rifkin A, Karajargi B, Perl E, et al. Lithium in adolescents with conduct disorder. Presented at the 29th annual meeting of the New Clinical Drug Evaluation Unit; May 5–11, 1989; Key Biscayne, Fla
11. Klein RG. Preliminary results: lithium effects in conduct disorders. In: CME Syllabus and Proceedings Summary of the 144th annual meeting of the American Psychiatric Association; May 11–16, 1991; New Orleans, La. Symposium 2:119–120
12. Silva RR, Campbell M, Golden RR, et al. Side effects associated with lithium and placebo administration in aggressive children. Psychopharmacol Bull 1992;28:319–326
13. Klein RG, Abikoff H, Klass E, et al. Clinical efficacy of methylphenidate in conduct disorder with and without attention deficit hyperactivity disorder. Arch Gen Psychiatry 1997;54:1073–1080
14. Malone RP, Bennett DS, Luebbert JF, et al. Aggression classification and treatment response. Psychopharmacol Bull 1998;34:41–45
15. Steiner H, Cauffman E. Juvenile justice, delinquency, and psychiatry. Child Adolesc Psychiatr Clin N Am 1998;7:653–672
16. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. Can J Psychiatry 1998;43:73–77
17. Woodman CL, Noyes R Jr. Panic disorder: treatment with valproate. J Clin Psychiatry 1994;55:134–136
18. Papatheodorou G, Kutcher SP, Katic M, et al. The efficacy and safety of divalproex sodium in the treatment of acute mania in adolescents and young adults: an open clinical trial. J Clin Psychopharmacol 1995;15: 110–116
19. Bowden CL. Predictors of response to divalproex and lithium. J Clin Psychiatry 1995;56(suppl 3):25–30
20. Bowden CL. Role of newer medications for bipolar disorder. J Clin Psychopharmacol 1996;16(suppl 1):48S–55S
21. Wilcox J. Divalproex sodium in the treatment of aggressive behavior. Ann Clin Psychiatry 1994;6:17–20


  

22. Wilcox JA. Divalproex sodium as a treatment for borderline personality disorder. Ann Clin Psychiatry 1995;7:33–37
23. Horne M, Lindley SE. Divalproex sodium in the treatment of aggressive behavior and dysphoria in patients with organic brain syndromes [letter]. J Clin Psychiatry 1995;56:430–431
24. Deltito JA, Levitan J, Damore J, et al. Naturalistic experience with the use of divalproex sodium on an in-patient unit for adolescent psychiatric patients. Acta Psychiatr Scand 1998;97:236–240
25. Donovan SJ, Susser ES, Nunes EV, et al. Divalproex treatment of disruptive adolescents: a report of 10 cases. J Clin Psychiatry 1997;58:12–15
26. Davis LL, Ryan W, Adinoff B, et al. Comprehensive review of the psychiatric uses of valproate. J Clin Psychopharmacol 2000;20:1S–17S
27. Ruedrich S, Swales TP, Fossaceca C, et al. Effect of divalproex sodium on aggression and self-injurious behavior in adults with intellectual disability: a retrospective review. J Intellect Disabil Res 1999;43: 105–111
28. Steiner H, Garcia IG, Matthews Z. Posttraumatic stress disorder in incarcerated juvenile delinquents. J Am Acad Child Adolesc Psychiatry 1997; 36:357–365
29. Steiner H, Cauffman E, Duxbury E. Personality traits in juvenile delinquents: relation to criminal behavior and recidivism. J Am Acad Child Adolesc Psychiatry 1999;38:256–262
30. Achenbach TM. Manual for Youth Self-Report and 1991 Profile. Burlington, Vt: University of Vermont Dept of Psychiatry; 1991
31. Weinberger DA. Distress and self-restraint as measures of adjustment across the life span: confirmatory factor analysis in clinical and nonclinical samples. Psychol Assess 1997;9:132–135
32. Huckaby W, Kohler M, Garner EH, et al. A comparison between the Weinberger Adjustment Inventory and the Minnesota Multiphasic Personality Inventory with incarcerated adolescent males. Child Psychiatry Hum Dev 1998;28:273–285
33. Steiner H, Feldman S. Two approaches to the measurement of adaptive style: comparison of normal, psychosomatically ill, and delinquent adolescents. J Am Acad Child Adolesc Psychiatry 1995;34:180–190
34. Loof D, Grimley P, Kuller F. Carbamazepine found efficacious for some children, adolescents with PTSD. Special Report: Anxiety Disorders. Psychiatric Times 1995 Feb;12(2):23
35. Feldman SS, Weinberger DA. Self-restraint as a mediator of family influences on boys' delinquent behavior: a longitudinal study. Child Dev 1994;65:195–211
36. Fennig S, Kovasznay B, Rich C, et al. Six-month stability of psychiatric diagnoses in first-admission patients with psychosis. Am J Psychiatry 1994;151:1200–1208
37. Simpson SG, McMahon FJ, McInnis MG, et al. Diagnostic reliability of bipolar II disorder. Arch Gen Psychiatry 2002;59:736–740
38. Taiminen T, Ranta K, Karlsson H, et al. Comparison of clinical and best-estimate research DSM-IV diagnoses in a Finnish sample of first-admission psychosis and severe affective disorder. Nord J Psychiatry 2001;55:107–111
39. Guy W. ECDEU Assessment Manual for Psychopharmacology. 2nd ed. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
40. Steiner H, Saxena K, Chang K. Psychopharmacologic strategies for the treatment of aggression in juveniles. CNS Spectrums 2003;8:298–308
41. Post RM, Weiss SR, Smith M, et al. Kindling versus quenching: implications for the evolution and treatment of PTSD. Ann N Y Acad Sci 1997;821:285–295
42. Cauffman E, Feldman SS, Waterman J, et al. Posttraumatic stress disorder among incarcerated females. J Am Acad Child Adolesc Psychiatry 1998;37:1209–1216
43. Fesler FA. Valproate in combat-related posttraumatic stress disorder. J Clin Psychiatry 1991;52:361–364
44. Clark RD, Canive JM, Calais LA, et al. Divalproex in posttraumatic stress disorder: an open-label clinical trial. J Trauma Stress 1999;12: 395–401
45. Weinberger DA, Gomes ME. Changes in daily mood and self-restraint among undercontrolled preadolescents: a time series analysis of "acting out." J Am Acad Child Adolesc Psychiatry 1995;34:1473–1482
46. Loscher W. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Prog Neurobiol 1999;58:31–59