# Divalproex Treatment of Disruptive Adolescents: A Report of 10 Cases

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***Background:*** To report an open trial of divalproex sodium in 10 adolescents with chronic temper outbursts and mood lability.

***Method:*** Ten adolescents meeting screening criteria for chronic temper outbursts and mood lability were followed for 5 consecutive weeks on open divalproex sodium treatment. Temper outburst frequency and mood swings severity at pretreatment and posttreatment were compared by using paired t tests. Subjects continued to be followed to judge persistence of response.

***Results:*** All subjects showed clear improvement at 5 weeks and maintained it during follow-up while taking medication. Rapid relapse and recovery occurred in 5 of 6 patients who discontinued and then resumed medication.

***Conclusion:*** Divalproex sodium may be helpful in teenagers who have explosive tempers and severe mood swings, and benefits may generalize to school and family life.

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The disruptive disorders of childhood and adolescence (attention-deficit/hyperactivity disorder [ADHD], oppositional/defiant disorder, conduct disorder)[1] describe heterogeneous problem youngsters at high risk for substance abuse, criminality, and developmental failure. Yet only ADHD links diagnosis to treatment. Pharmacology of oppositional/defiant disorder and conduct disorder is limited to target symptoms (e.g., aggression, transient hallucinations) or comorbid diagnoses (dysthymia, substance abuse).[2] This well-recognized limitation of the current classification[3] motivated us to explore another possible syndrome-treatment link, i.e., that between irritable mood and temper outbursts on the one hand and treatment with anticonvulsant/mood stabilizers on the other.

Such a connection seemed theoretically plausible because mood stabilizers (valproic acid, carbamazepine, lithium) have antiaggressive properties.[4–7] Furthermore, intermittent explosiveness has been linked to limbic epileptoid activity,[8] and carbamazepine and valproic acid are also anticonvulsants. Motivated by these observations, we interviewed teachers, pediatricians, and substance abuse professionals, asking if explosive youngsters have irritable mood swings and if irritable, moody adolescents are explosive.

We learned this link is common and drafted screening criteria to tentatively define these youngsters. We hypothesized their symptoms would improve with an anticonvulsant/mood stabilizer and chose divalproex sodium because it is widely used in pediatric populations, is easy to monitor, and addresses both mood and epileptoid etiologies.

## METHOD

### Referral Patterns

The study was conducted at four New York metropolitan outpatient clinics. From January to July 1995, our request for adolescent subjects with temper outbursts and mood swings yielded 14 referrals. Twelve families signed informed consent and 2 patients subsequently dropped out. Ten adolescents completed at least 5 weeks of open treatment. Seven were referred by teachers, 2 by adolescent medicine physicians, and 1 by a substance abuse counselor. Completers ranged from 15 to 18 years of age and were of diverse social class and ethnicity (Table 1).

### Subjects

DSM-III-R diagnoses of treatment completers are listed in Table 1. Although every subject met criteria for either oppositional/defiant disorder or conduct disorder, as discussed above, this was neither necessary nor suffi-

**Table 1. Divalproex Sodium Response in 10 Cases of Explosive Mood Disorder***

| Patient | Demographics: Age (y) | Sex | Ethnicity | DSM-III-R Diagnosis | Ratings[a]: Baseline | Wk 5 | Follow-Up[b] |
|---|---|---|---|---|---|---|---|
| 1 | 15 | Male | Latin | Mar Dep<br>CD | Outburst/wk = 12<br>Lability = 4<br>GAF = 28 | 0<br>1<br>51 | 34 wk; medication use erratic after Wk 20; symptoms partly back at Wk 26; GAF = 60 |
| 2 | 17 | Male | White | Mar Dep<br>CD | Outburst/wk = 5<br>Lability = 4<br>GAF = 35 | 0<br>2<br>55 | 30 wk; outbursts rare; mood stable; stopped medication Wk 8–10 and relapsed in 5 days; worked past summer; wants to graduate; GAF = 70 |
| 3 | 15 | Female | White | Mar Ab<br>CD | Outburst/wk = 13<br>Lability = 4<br>GAF = 40 | 1<br>1<br>55 | 22 wk; outbursts very rare; mood stable; peer group not completely drug free; GAF = 63 |
| 4 | 17 | Male | Black | Mar Ab<br>CD | Outburst/wk = 10<br>Lability = 4<br>GAF = 40 | 0<br>0<br>75 | 23 wk; was working and GAF was 80 at Wk 19 when stopped medications and relapsed in 3 wk; GAF = 60; realized need for medication |
| 5 | 16 | Male | White | Mar Ab<br>CD | Outburst/wk = 2<br>Lability = 3<br>GAF = 35 | 0<br>0<br>61 | 20 wk; no outbursts; mood stable; legal problems resolved; in school and drug program; private physician treating; GAF = 71 |
| 6 | 16 | Male | White | Mar Ab<br>CD | Outburst/wk = 2<br>Lability = 4<br>GAF = 35 | 0<br>0<br>75 | 13 wk; working; stopped medication Wk 9, relapsed Wk 11; realized need for medication; back in school after year's truancy; GAF = 75 |
| 7 | 15 | Male | White | ADHD | Outburst/wk = 10<br>Lability = 4<br>GAF = 35 | 0<br>0<br>80 | 12 wk; stopped medication Wk 6, relapsed wk 7; resumed, stopped again Wk 9, relapsed Wk 10; realized need for medication; GAF = 71 |
| 8 | 15 | Male | Black | ODD | Outburst/wk = 5<br>Lability = 4<br>GAF = 35 | 0<br>0<br>65 | 12 wks; doing much better in school and at home; GAF = 75 |
| 9 | 15 | Male | White | Mar Dep<br>Alc Ab<br>CD | Outburst/wk = 1<br>Lability = 4<br>GAF = 35 | 0<br>0<br>65 | 12 wk; in drug treatment; stopped medication Wk 9, partial relapse Wk 11; situation detected and medication restarted before GAF declined; GAF = 71 |
| 10 | 18 | Female | White | Mar Ab<br>ODD | Outburst/wk = 5<br>Lability = 3<br>GAF = 55 | 0<br>1<br>75 | Lost to follow-up; Wk 5 ratings are the last ones; GAF (same as Wk 5) = 75 |

*Abbreviations: Ab = abuse; ADHD = attention-deficit/hyperactivity disorder; Alc = alcohol; CD = conduct disorder; Dep = dependence; Mar = marijuana; ODD = oppositional/defiant disorder.
[a]Assessment units: temper outbursts are number of outbursts in previous week. Lability in the previous week is rated 0–4; increasing numbers imply greater frequency, duration, and autonomy of mood swings. GAF is the Global Assessment of Function scale score for the previous week, with anchors as described in DSM-III-R Axis V. See text for further details.
[b]Weeks = weeks since baseline assessment.



cient to describe the clinical picture. What these adolescents shared as a group was a low threshold/high amplitude for dyscontrol especially when in an irritable mood, and shifts from normal to irritable mood without any clear precipitant. While the dyscontrol was fairly predictable once they were irritable, the shift into an irritable state was unpredictable. The irritability was evident behaviorally as either a sudden, withdrawn grouchiness or a boisterous intrusiveness. Most subjects showed both behaviors at different times, but no referred patient had ever had a manic or unequivocal hypomanic episode. See Table 2 for inclusion/exclusion screening criteria.

The symptoms were chronic (at least 2 years' duration) with onset in prepuberty or peripuberty, and they led directly to school, legal, or family problems. Although many smoked large amounts of marijuana, the temper and mood symptoms antedated substance use by at least 1 year by both teenager and parent reports.

Their temper outbursts were frequent and severe. Daily shouting was the rule, and several times a month they would destroy property or start a fight. Obvious mood shifts occurred at least several times a week, briefer oscillations daily. Though interpersonal problems were common, the mood and temper symptoms were not confined to one intense relationship.

All 10 had a history of school suspensions. Two had been arrested. Seven met conduct disorder criteria, typically by breaking curfews, lying, and committing minor thefts. All 10 lived in intact or single parent homes and not in institutions.

Five patients had psychostimulant treatment during grade school. Three parents said it was at best of marginal benefit. Two said it was "quite helpful." One boy continued methylphenidate into adolescence; his concentration improved but not his temper or mood swings. The other boy stopped showing any behavioral benefit. Five parents said psychostimulants were never recommended. Two patients had had temper outbursts and mood swings for 2 years, the rest had had these symptoms for more than 5 years.

**Table 2. Inclusion and Exclusion Criteria for Entrance Into the Pilot Study**

Inclusion
1. Age 13–20 years
2. Meets screening criteria for explosive mood disorder
   A. An explosive temper as evidenced by four or more outbursts of rage, property destruction, or fighting per month on minimal provocation
   B. Mood lability as evidenced by multiple, daily, distinct shifts from normal to irritable mood with withdrawn or boisterous behavior occurring without a clear precipitant
   C. Duration of at least 1 year when not treated
   D. Symptoms result in impairment in two or more areas including school, the law, family, substance use, peers, work
   E. Symptoms do not occur only during substance toxicity or withdrawal
   F. Symptoms not confined to a single setting or context
3. Parent willing to consent to study and supervise medication
4. Willingness of substance abusing adolescent to participate in treatment for the substance abuse

Exclusion
1. History of psychosis other than drug-induced
2. Seizure or other neurologic disturbance unless approved for the study by a pediatric neurologist
3. Pregnancy
4. Moderate-to-severe retardation
5. Sexually active females who refuse to use birth control
6. Physical examination or laboratory results with significant abnormalities
7. Active suicidal or homicidal ideation
8. Use of barbiturates
9. Unequivocal manic or hypomanic episode



After the study was completely described to the subjects, written informed consent was obtained from the custodial parent and written informed assent was obtained from the adolescent.

### Treatment

The dose of divalproex sodium was advanced in 250-mg increments to 1000 mg/day over 2 to 4 weeks. Blood levels were checked after the patients took 1000 mg of divalproex sodium for 1 week to ensure compliance. The mean divalproex sodium level was 75 μg/mL (range, 45–113). Patients were seen weekly for half hour sessions during which medication was adjusted, assessments performed, and supportive therapy provided. Two patients were also in substance abuse treatment programs.

### Assessments

Baseline assessments were completed prior to the initiation of treatment. Diagnoses (Table 1) were made by an experienced research child and adolescent psychiatrist. Since the subjects were older adolescents, we also used the Structured Clinical Interview for DSM-III-R (SCID) with supplemental questions.[9]

No standardized instruments were available to quantify the psychopathology these youngsters presented. The Modified Overt Aggression Scale[10] designed for inpatients under regular surveillance provided anchors for the definition of an outburst. Each week, the psychiatrist recorded the number of outbursts reported by the informants (subject, parent, school) and made a final estimate of the number for the previous week.

Ratings of mood lability were obtained weekly from all informants, and items were related to the frequency, amplitude, and autonomy of the mood swings. These items resemble bipolar items in the General Behavior Inventory,[11] and they yielded a global impression of the subject's mood lability during the previous week on a 0 to 4 scale.

We used multiple observers because our instruments were untested and adolescents and parents are known to give differing reports of psychopathology. Interrater agreement was good, although the goal of the interviews was to reach consensus about what occurred the previous week, and parents and children were often seen together. Teachers and counselors were contacted at least twice during the study for the same information. Each week the research psychiatrists made a best estimate on the basis of all the data on a subject for each category, and that became the final rating. General impairment was estimated using the Global Assessment of Functioning (GAF) scale.

Weekly interviews with patients and families were continued as long as possible beyond Week 5, and 9 patients are still being followed. GAF was assessed at Week 5 and at the last follow-up observation.

### Data Analysis

We computed the mean scores for temper outbursts, mood lability, and GAF rating for the 10 completers at baseline and at 5 weeks and used paired t tests to examine the statistical significance of changes.

## RESULTS

Pre- and post-scores for each patient are presented in Table 1. The sample's mean ± SD number of outbursts/week was 6.5 ± 4.4 at baseline and 0.1 ± 0.3 at Week 5 (paired t test = 4.75, df = 9, $p < .001$). The mean lability score (0–4 scale) was 3.8 ± 0.4 at baseline and 0.5 ± 0.7 at Week 5 (paired t test = 12.68, df = 9, $p < .000$). The mean GAF score was 37.8 ± 7.0 at baseline and 65.7 ± 10.2 at

Week 5 (paired t test = 10.22, df = 9, p < .000). At baseline, 0/10 patients had a GAF of 71 or more; at Week 5, 4/10; at last follow-up, 6/10. Scores above 71 indicate transient or no pathology.

During follow-up, 6 patients stopped taking medication on their own for at least 5 days. Five (Patients 2, 4, 6, 7, 9) quickly relapsed then recovered a few days after resuming medication (Patient 7 did this twice). Patient 1 took medication sporadically and remained well for 6 weeks before partial relapse set in.

Divalproex sodium was well tolerated by all patients. There were no serious side effects. Two patients noted mild sedation and transient nausea. Fatal hepatotoxicity is a major concern among pediatricians treating babies on multiple anticonvulsants. The risk declines with age, and on monotherapy after age 10 years, it may approach zero.[12] Nonetheless, liver function tests were monitored monthly, and no significant changes were detected.

## DISCUSSION

This pilot study raises the possibility that a specified subgroup of disruptive adolescents may improve on treatment with a particular medication. The first 10 patients who completed 5 weeks of treatment shared temper outbursts, mood swings, and a clear response to divalproex sodium. At Week 5, temper outbursts and mood lability were in or close to remission for almost all subjects. Follow-up suggested improvements may persist and may generalize to areas other than temper and mood (i.e., school, family life, and substance use) (Table 1).

Four possible explanations for this association of explosiveness, irritability, and divalproex sodium response come to mind. First, it could all be a coincidence, but this seems implausible. Referring professionals recognized the association of symptoms, the sample consisted of consecutive referrals, and the improvement on divalproex sodium treatment persisted until discontinuation, suggesting a true medication response.[13] Second, it could be an artifact in that if all behaviorally disturbed teenagers benefit from divalproex sodium, the symptom association would be nonspecific. It is difficult to see, however, why the premise should be true. Third, a frequent comorbidity between, for example, intermittent explosive disorder and a "variation" on cyclothymia may seem more reasonable, but it leaves unanswered where "variation" exceeds the diagnostic term's original meaning. Associated hypomanic symptoms, for example, could not be required, and the oscillations would have to be from normal to irritable mood, not from elation to depression. Fourth, a separate syndrome, implying a more or less single diathesis, is another possibility. Only family, longitudinal, biological, and double-blind medication studies can narrow down these alternative explanations.[14] Until the condition can be clarified, we propose, for communication purposes, to label the hypothetical condition identified by the screening criteria *explosive mood disorder*.

We recognize that this report has the limitations of an uncontrolled, open study with a small sample size. Nonetheless, in view of the obvious need to improve understanding and treatment of disruptive youngsters, we believe these preliminary findings merit further research.

*Drug names:* carbamazepine (Tegretol and others), divalproex sodium (Depakote), methylphenidate (Ritalin), valproic acid (Depakene and others).



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