Baseline Predictors of Response to Divalproex in Conduct Disorder

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Background: Successful treatment of conduct disorder remains difficult. On the basis of a positive response to divalproex among adolescent boys with conduct disorder, we conducted an analysis of the impact of baseline comorbid diagnoses and personality factors on the likelihood of treatment response to divalproex.

Method: Seventy-one adolescent boys with conduct disorder (DSM-IV) and a history of at least 1 offense against persons were randomly assigned to receive high- or low-dose divalproex for 7 weeks. Evaluations included best estimate diagnoses, the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I), the 62-item Weinberger Adjustment Inventory (WAI-62) assessment of distress and restraint, the Response Evaluation Measure assessment of immature and mature defenses, and the Achenbach Youth Self-Report assessment of overall psychopathology. All were conducted at study entry and exit, and the WAI-62 was conducted weekly throughout the 7-week study period. Treatment response was defined as a rating of much improved or very much improved on the CGI-I. Data were collected from June 1997 to April 1998.

Results: Fifty-eight subjects completed the study and were eligible for inclusion in the analysis. Plasma divalproex level ($p = .003$) and immature defenses ($p = .004$) were significant positive predictors of treatment response, while restraint ($p = .01$) and level and range of psychopathology ($p = .04$) were significant predictors of nonresponse. Comorbidities or distress ($p = .06$) were not significantly associated with treatment outcome.

Conclusion: Predictors of response to divalproex treatment for conduct disorder were identified, despite the small sample size in this study. The pattern of positive and negative predictors of response to divalproex, an antikindling agent, tends to support a model of kindling-reinforced reactive/affective/defensive/impulsive aggression among adolescent boys with conduct disorder. Additional studies are needed to identify more subtle predictors of treatment response and to clarify the mechanisms contributing to the development of conduct disorder.

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Conduct disorder is a relatively common psychopathology characterized by a chronic course (frequently evolving into antisocial personality disorder) and a generally poor prognosis.[1,2] Despite some evidence for successful interventions, both clinical assessments and criminal recidivism rates confirm the difficulty of effecting long-term positive outcomes.

A particularly challenging symptom cluster in conduct disorder is aggressive and violent behavior.[3] Aggression and violence in juvenile conduct disorder tends to be predominantly reactive in nature, frequently induced by high levels of agitation, dysphoria, and distress.[4–6] This behavior is consistent with a pattern of reactive/affective/defensive/impulsive (RADI) aggression, triggered by a real or perceived threat, and characterized by angry and/or anxious affect and the anticipation of a negative outcome unless aggressive (or violent) action is taken.[7–9] RADI aggression is distinguished from proactive/instrumental/premeditated/predatory (PIPP) aggression, which is based on acquisitiveness and is characterized by high levels of excitement and interest and anticipation of a positive outcome.[10]

Treatment selection for juveniles with conduct disorder as their principal diagnosis in the absence of psychosis, mental retardation, and pervasive developmental disorders is complicated by the relative scarcity of well-designed, controlled clinical trials of psychopharmacologic agents, which reflects to some extent the challenges involved in conducting such trials in this population.[11,12]

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Agents that have been evaluated, with varying degrees of success, include lithium,[13–16] haloperidol,[14] risperidone,[17] and methylphenidate.[18,19] For the most part, these studies relied on small to moderate sample sizes evaluated over relatively short study periods; moreover, treatment effects were generally modest to moderate.

The antiepilepsy drug divalproex has shown efficacy in treating adolescents with disruptive behavior[20,21] as well as agitation associated with bipolar disorder.[22] In a recent 7-week double-blind trial in adolescents with severe conduct disorder,[23] attainment of plasma valproate levels consistent with antiseizure effect was associated with significant improvements in self-reported impulse control and self-restraint. However, over half the children responded, and the degree of improvement observed in this study suggests that the ability to predict treatment response on the basis of the specific symptomatology and severity of conduct disorder would be useful prior to initiating divalproex therapy.

Another problem that complicates the study of successful treatment of disruptive behavior disorders is their intrinsic heterogeneity. Conduct disorders are usually highly comorbid.[1] These comorbid conditions can range from neuropsychiatric syndromes, such as mental retardation, to internalizing syndromes, such as posttraumatic stress disorder (PTSD). Thus, it is reasonable to assume that conduct problems can be generated in conjunction with comorbid conditions, and, in this study, we will test the predictive power of these comorbidities regarding treatment response (hypothesis 1).

Given, however, that our sample size was relatively small, we anticipated that we might not generate sufficient power to test categorical variables as to their predictive potential. We thus decided to also look at sets of continuous variables that we had reasons to think would be of interest, building on the reduced power requisites for this type of assessment. One set of variables that we have shown[24] to be predictive of criminal outcomes in this population was personality traits, as assessed by the Weinberger Adjustment Inventory (WAI). In a larger sample of these youths, we showed that the levels of habitual distress and self-restraint predicted 4.5-year prospective naturalistic outcomes[24] better than age and previous convictions—2 robust measures of delinquent recidivism. The slopes of these 2 variables and their constituent subscales were significantly affected by the medication, as described in our previous publication.[23]

In addition, we selected a set of immature defenses, which we had shown to differentiate those subjects with PTSD from those with conduct disorder in a previous study of this population.[25] Because our study was theoretically informed by Post's kindling model of PTSD,[26] we thought that a compound such as divalproex, which has been described as possessing antikindling properties, might well influence these important traits.

Finally, because we knew from several studies in school-aged and high school populations at risk for and with manifest severely aggressive behavior[1,8,9] that severe difficulties with all forms of aggression predicted negative outcomes even in the long term, the 2 dimensions of the Achenbach Youth Self-Report (YSR) labeled "aggression" and "delinquent behavior" could have negative predictive power in a short-term and monomodal intervention study such as this one.

Therefore, we conducted an analysis of the impact of personality features and psychopathology (including distress, restraint, defenses, and psychopathologic severity and range) as well as specific comorbidities on treatment outcomes. We attempted to validate 3 separate hypotheses:

Hypothesis 1 (trait model): that distress and immature, trauma-related defenses would demonstrate a positive association and restraint, a negative association in response to treatment with divalproex at antiseizure doses.

Hypothesis 2 (diagnosis model): that when comorbid to conduct disorder, depression and PTSD, but not attention-deficit/hyperactivity disorder, would be positively associated with treatment response to divalproex.

Hypothesis 3: that a high level and/or wide range of psychopathology would be negatively associated with treatment response to divalproex (largely because of the short-term nature of the study).

The assessment tools used to evaluate these disease features are described in the Method section.

METHOD

Subjects

The study protocol was approved by the California Youth Authority (CYA), Sacramento, and the Stanford University Panel on Medical Human Subjects. The study protocol required both the subjects' informed consent and parental notification, allowing parents to withdraw permission to participate. The protocol included a provision for a neutral independent ombudsman, who was available throughout the study to discuss any subjects' concerns as well as to expedite any requests for withdrawal. All research files were inaccessible to CYA staff.

One hundred seventy-five adolescent boys were initially screened for participation. The primary inclusion criterion was a DSM-IV diagnosis of conduct disorder; additional inclusion criteria were: (1) ability to provide active consent to participation; (2) lack of parental objection to participation; (3) absence of acute psychoses, homicidality, suicidality, mental retardation, and/or active medical illness; (4) no additional medication currently needed; (5) history of at least 1 offense against persons; and (6) ability to complete the screening instrument (WAI) with a

validity score considered adequate (at least 3.667) for this study.

The patient population for this study has been previously described.[23] All study participants were boys from a single CYA campus that tends to treat the youngest offender group in the CYA population. In general, the subjects for this study were comparable to the overall campus population, which has been characterized in previous studies,[24,25] with regard to age and anticipated length of commitment.

Self-Report Assessment Instruments

Achenbach Youth Self-Report (YSR). The Achenbach YSR[27] assesses 10 dimensions of psychopathology, in addition to internalizing, externalizing, and total problems, with good psychometric properties. Our previous experience with the YSR in the CYA has indicated that youths are able to both understand the survey content and complete the survey satisfactorily. The YSR was used to assess general severity and symptomatic extent of psychopathology and was administered at study entry and exit; a higher YSR score indicates more severe psychopathology.

62-Item Weinberger Adjustment Inventory (WAI-62). The WAI-62[28] measures subjective distress (including anxiety, depression, sense of well-being, low self-esteem) and self-restraint (including impulse control, suppression of aggression, sense of responsibility, consideration for others). The WAI-62 has demonstrated good psychometric properties as well as convergence with the Minnesota Multiphasic Personality Inventory,[29] discrimination between pathologic and normal states,[30] and predictive validity.[31] The WAI-62 was administered weekly: at screening and baseline, self-report was requested with regard to the preceding year; during the remainder of the study, subjects were asked to report on the preceding week.

Observer-Rated Assessments

Best estimate diagnoses. At study entry, a "best estimate" current psychiatric diagnosis was provided by the study managing clinician, who was a board-eligible child psychiatrist with 4 years of experience in this population. The managing clinician was provided full access to all clinical information about each subject, including medical, criminal, and social histories; CYA case reports; and previous psychiatric evaluations. The primary requirement was for a diagnosis of conduct disorder as defined in DSM-IV. The rationale for using the "best estimate" approach instead of structured interviews has been described previously.[23]

Clinical Global Impressions (CGI) assessments. The managing clinician also provided 2 CGI assessments, using scales described by Guy[32]: the CGI-Severity of Illness scale (CGI-S) at study entry and exit and the CGI-Improvement scale (CGI-I) at study exit. The scale for the CGI-S ranges from 0 (not at all ill) to 6 (among the most extremely ill patients), while the scale for the CGI-I ranges from 1 (very much improved) to 7 (very much worse).

In addition, a blinded clinician (H.S.: a board-certified child psychiatrist with 15 years of experience in this population) provided CGI ratings based on a single 1-hour interview at study exit. The blinded clinician elicited descriptions of both current and original symptomatology, enabling a judgment to be made with regard to disease severity (CGI-S) at baseline and exit and the degree of improvement experienced during the study (CGI-I). This clinician interacted with the subjects only during the 1-hour interview and was blinded to other assessments, criminal and clinical history, and subjects' self-reports.

These clinical ratings were the principal outcomes for the original and the current study. We recognize that this is a limitation, but as there currently is no uniformly accepted measure of aggression in youth that has been shown to be valid in treatment studies,[10] we thought that the blinded assessment by an experienced clinician was a solid way to proceed. We have described in detail how these ratings correlated with other concurrent measures of psychopathology in our original article.[23]

Response Evaluation Measure (REM-71). The REM-71[33] was used as a measure of the subjects' defenses and was administered at study entry and exit. Two subscores were of particular interest and were used as independent variables in logistic regression analysis: factor 1 measures immature defenses, while factor 2 measures mature defenses.[33] The immature defenses are acting out, conversion, displacement, dissociation, fantasy, omnipotence, passive-aggression, projection, repression, somatization, splitting, sublimation, undoing, and withdrawal. The mature defenses are altruism, denial, humor, idealization, intellectualization, reaction formation, and suppression.

Study Protocol

A 1-week washout period followed acceptance into the study, during which clinical evaluations were conducted and best estimate diagnoses were provided by the managing clinician.

Subjects were then randomly assigned to either a high-dose group (oral dose of 500–1500 mg/day or to achieve plasma levels sufficient for seizure control, i.e., 50–120 μg/mL) or a low-dose group (up to 250 mg/day) for 7 weeks. Subjects in both groups were started at an oral dose of 125 mg/day; side effects (including sleepiness and transient gastrointestinal upset) were mild. The high-dose subjects were gradually titrated over a 2-week period, intended to minimize side effects, up to plasma levels of 50 to 120 μg/mL. For both groups, open clinical management sought to minimize risk or side effects. The high-dose group was characterized by a modal oral dose

Table 1. Baseline Demographic and Clinical Characteristics of 61 Adolescent Males Treated With Divalproex for Conduct Disorder

Characteristic	Mean (SD)
Age, y	15.9 (0.8)
Race/ethnicity	N (%)
White	23 (37.7)
Latino	23 (37.7)
African American	10 (16.4)
Asian	2 (3.3)
Other/unspecified	3 (4.9)
Baseline diagnoses	
Conduct disorder	61 (100.0)
Substance abuse disorder	54 (88.5)
Learning disability	37 (60.7)
Dysthymia/depression	33 (54.1)
ADHD	31 (50.8)
PTSD	13 (21.3)
APD traits	4 (6.6)
Major depressive disorder	2 (3.3)
Pedophilia	2 (3.3)
Pyromania	1 (1.6)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, APD = antisocial personality disorder, PTSD = posttraumatic stress disorder.

of 1000 mg/day, while the low dose group was characterized by a modal oral dose of 125 mg/day. All dosages, response, side effects, and plasma levels were monitored by the clinical team.

Statistical Analyses

Logistic regression analyses were used to evaluate the impact of baseline traits (hypothesis 1) and baseline diagnoses (hypothesis 2) on 2 dimensions of treatment response: illness severity at endpoint and improvement in illness from baseline to endpoint. These analyses used plasma divalproex levels and results from the assessment instruments of interest as the independent variables and binary definitions of illness severity and improvement as dependent variables, based on blind CGI-S and CGI-I scoring at study exit. For the purposes of these analyses, the CGI-S was dichotomized to 2 levels: "recovered," comprising scores 0 to 1 (not ill and borderline ill) and "ill," comprising scores 2 to 6 (ranging from mildly ill to extremely ill). The CGI-I was dichotomized into a "responder" cluster (scores 1–2: very much improved and much improved) and a "nonresponder" cluster (scores 3–7: slightly improved to very much worse). All statistical analyses were performed using SAS (version 9.1, SAS Institute, Cary, N.C.). Data were collected from June 1997 to April 1998.

RESULTS

Of 175 possible subjects who were screened, 71 met all criteria for inclusion and consented to participation in the study; 61 completed the full course of treatment, receiving exit evaluations from at least 1 evaluator. Of these, 58 completed all measures and received exit evaluations from 2 raters; these constitute the sample for this study.

Table 2. Baseline Traits of 58 Adolescent Males Treated With Divalproex for Conduct Disorder as Predictors of Endpoint Severity: Recovered Versus Ill[a]

Variable (postulated effect direction)	Wald χ^2	p[b]	OR Point Estimate (95% CI)
Plasma divalproex level (+)	7.04	.008	1.03 (1.00 to 1.06)
Age	0.89	.34	0.66 (0.28 to 1.55)
REM-71 factor 1 (+)	1.23	.26	2.17 (0.55 to 8.60)
REM-71 factor 2 (–)	0.03	.85	0.90 (0.30 to 2.69)
WAI-62 distress (+)	3.97	.04	3.96 (1.02 to 15.38)
WAI-62 restraint (–)	2.10	.14	0.28 (0.05 to 1.56)
YSR delinquency (–)	0.02	.87	0.97 (0.75 to 1.26)
YSR aggression	8.84	.002	0.72 (0.58 to 0.89)

[a]Recovered: CGI-S score < 2; ill: CGI-S score ≥ 2.
[b]Significant at $p < .05$.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, REM-71 = Response Evaluation Measure, WAI-62 = 62-item Weinberger Adjustment Inventory, YSR = Youth Self-Report.

The demographic and clinical attributes of the 58 subjects are summarized in Table 1. The subject population differed somewhat from the general CYA population with regard to ethnicity, with whites overrepresented (study population, 38% [N = 23]); CYA population, 15% [N = 381]), and Latinos (study population, 38% [N = 23]; CYA population, 47% [N = 1170]) and African Americans (study population, 16% [N = 10]; CYA population, 30% [N = 738]) underrepresented.

To test hypothesis 1, we entered all personality attributes at baseline and the divalproex level achieved during the trial into logistic regression analyses with respect to illness severity and improvement. Using the dichotomized CGI-S, 22 subjects were classified as recovered, while the remaining 36 were classified as ill (CGI-S score of 2 or greater). When the dichotomized CGI-I was applied to the study population, 22 were classified as responders (CGI-I of "very much improved" or "much improved"), while 36 were classified as nonresponders.

Baseline Traits as Predictors of Divalproex Response (Illness Severity)

The results of logistic regression analyses using severity of illness at study exit (dichotomized CGI-S) as the dependent variable are summarized in Table 2. The results with the trait model were significant (model fit statistics AIC [Akaike Information Criterion] intercept with covariates = 73.53; likelihood ratio $\chi^2 = 25.23$, $df = 8$, $p < .001$), with plasma divalproex level achieved, baseline WAI-62 distress score, and baseline YSR aggression score all achieving significance. None of the other variables contributed a uniquely significant variance. Higher plasma levels of divalproex and higher levels of baseline distress were both associated with reduced illness severity at endpoint; higher levels of overt

Table 3. Baseline Comorbid Diagnoses in 58 Adolescent Males Treated With Divalproex for Conduct Disorder as Predictors of Endpoint Severity: Recovered Versus Ill[a]

Variable (postulated effect direction)	Wald χ^2	p[b]	OR Point Estimate (95% CI)
Plasma divalproex level (+)	13.01	.00	1.04 (1.02 to 1.06)
Age	0.09	.75	1.14 (0.48 to 2.67)
PTSD (+)	1.11	.29	2.38 (0.47 to 11.89)
ADHD	0.03	.85	0.87 (0.20 to 3.67)
Major depressive disorder	0.04	.82	1.16 (0.30 to 4.43)

[a]Recovered: CGI-S score < 2; ill: CGI-S score ≥ 2.
[b]Significant at p < .05.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions-Severity of Illness scale, PTSD = posttraumatic stress disorder.

Table 4. Baseline Traits in 58 Adolescent Males With Conduct Disorder as Predictors of Divalproex Response: Responder Versus Nonresponder[a]

Variable (postulated effect direction)	Wald χ^2	p[b]	OR Point Estimate (95% CI)
Plasma divalproex level (+)	8.34	.003	1.12 (1.03 to 1.22)
Age	0.30	.58	0.68 (0.17 to 2.64)
REM-71 factor 1 (+)	8.15	.004	77.92 (3.91 to > 999.99)
REM-71 factor 2 (–)	0.71	.39	0.62 (0.21 to 1.85)
WAI-62 distress (+)	3.46	.06	0.10 (0.009 to 1.13)
WAI-62 restraint (–)	5.63	.01	0.002 (< 0.001 to 0.32)
YSR delinquency (–)	4.16	.04	0.62 (0.39 to 0.98)
YSR aggression	6.01	.14	0.69 (0.51 to 0.92)

[a]Responder: CGI-I rating of "very much" or "much" improved; nonresponder: CGI-I rating of "slightly improved" to "very much worse."
[b]Significant at p < .05.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, REM-71 = Response Evaluation Measure, WAI-62 = 62-item Weinberger Adjustment Inventory, YSR = Youth Self-Report.

aggression at baseline were associated with higher levels of illness severity at endpoint.

Baseline DSM-IV Comorbid Diagnoses as Predictors of Divalproex Response (Illness Severity)

The results of logistic regression analyses evaluating the association of baseline comorbid diagnosis with illness severity at endpoint (CGI-S) are summarized in Table 3. The results with the diagnosis model were not significant (model fit statistics AIC intercept with covariates = 82.95; likelihood ratio $\chi^2 = 9.80$, df = 5, p = .08). As expected, plasma divalproex level achieved was significantly associated with reduced severity; however, none of the individual diagnoses reached statistical significance as a predictor of endpoint severity.

Baseline Traits as Predictors of Divalproex Response (Improvement)

The results of logistic regression analyses evaluating the association of baseline traits with symptomatic improvement (CGI-I) are summarized in Table 4. The results with the trait model were significant (model fit statistics AIC intercept with covariates = 62.12; likelihood ratio $\chi^2 = 34.73$, df = 8, p < .00). As anticipated from the previous study,[23] plasma divalproex level was a significant predictor of response (Wald $\chi^2 = 8.34$, p = .003). The only other significant positive predictor of response was REM-71 factor 1 (immature defenses) (Wald $\chi^2 = 8.15$, p = .004), while the WAI-62 restraint score and YSR delinquency score were negatively associated with response.

Table 5. Baseline Comorbid Diagnoses in 58 Adolescent Males With Conduct Disorder as Predictors of Divalproex Response: Responder Versus Nonresponder[a]

Variable (postulated effect direction)	Wald χ^2	p[b]	OR Point Estimate (95% CI)
Plasma divalproex level (+)	13.01	.000	1.04 (1.02 to 1.06)
Age	0.09	.75	1.14 (0.48 to 2.67)
PTSD (+)	1.11	.29	2.38 (0.47 to 11.89)
ADHD	0.03	.85	0.87 (0.20 to 3.67)
Major depressive disorder	0.04	.82	1.16 (0.30 to 4.43)

[a]Responder: CGI-I rating of "very much" or "much" improved; nonresponder: CGI-I rating of "slightly improved" to "very much worse."
[b]Significant at p < .05.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-I = Clinical Global Impressions-Improvement scale, PTSD = posttraumatic stress disorder.

Table 6. Logistic Regression Analysis of REM-71 Factor 1 (immature defenses) as Contributors to Divalproex Response in 58 Adolescent Males With Conduct Disorder

Variable (postulated effect direction)	Wald χ^2	p[a]	OR Point Estimate (95% CI)
Plasma divalproex level (+)	9.79	.0001	1.1 (1.03 to 1.11)
Acting out (+)	3.57	.0587	1.79 (0.97 to 3.3)
Repression (+)	2.75	.097	1.7 (0.91 to 3.2)
Withdrawal (+)	0.96	.91	1.03 (0.50 to 2.46)
Dissociation (+)	1.12	.64	1.01 (0.51 to 1.99)
Projection (+)	1.04	.87	1.12 (0.68 to 2.31)

[a]Significant at p < .05.
Abbreviation: REM-71 = Response Evaluation Measure.

Baseline DSM-IV Comorbid Diagnoses as Predictors of Divalproex Response (Improvement)

The results of logistic regression analyses evaluating the association of baseline comorbid diagnoses with symptomatic improvement (CGI-I) are summarized in Table 5. The results with the diagnosis model were significant (model fit statistics AIC intercept with covariates = 72.56; likelihood ratio $\chi^2 = 18.29$, df = 5, p = .00). The only variable reaching significance was plasma divalproex level achieved.

Immature Defenses (REM-71 Factor 1) as Contributors to Divalproex Response

Because of the strong positive association between REM-71 factor 1 (immature defenses) and divalproex response, we conducted a secondary analysis of the predictive power of specific immature defenses. Based on previously established relationships with PTSD status

in boys with conduct disorder,[25] we selected acting out, repression, withdrawal, dissociation, and projection for these analyses; the results are summarized in Table 6. Although none of the specific defenses reached statistical significance as predictors of response, positive trends were associated with acting out and repression (acting out, Wald $\chi^2 = 3.57$, $p = .0587$; repression, Wald $\chi^2 = 2.75$, $p = .097$).

DISCUSSION

The goal of this study was to determine the extent to which features of conduct disorder, personality attributes, comorbidities, and defense/coping styles, measured at baseline, could predict treatment response to divalproex. Understanding the relationships between these features and the probability of response would be helpful in determining the most beneficial therapeutic approach to treatment of this often frustrating disorder.

With regard to baseline traits, a significant positive association with treatment response assessed using illness severity at endpoint (Table 2) was observed for the WAI-62 distress score. Significant associations with treatment response assessed using improvement (Table 4) were observed for REM-71 factor 1 (immature defenses) (positive association) and for WAI-62 restraint (negative association). Taken in total, these results validate part of hypothesis 1. An exploratory analysis of specific immature defenses showed acting out and repression as the most important contributors to the REM-71 factor 1 association, but, considered individually, neither achieved statistical significance.

These results, as summarized in Tables 3 and 4, suggest that boys with severe conduct disorders who ultimately have a good chance of responding to this medication exhibit the following characteristics when untreated: habitually low levels of self-restraint (i.e., impulsivity) in combination with habitually high levels of distress (i.e., negative emotions, such as depression). At the same time, they show immature ways of handling stress (such as by acting out). This responsiveness to treatment seems to be tempered by the presence of high levels of delinquent behavior, which predicts negative outcomes even in the presence of these other positive predictors.

The dosing strategy in this study was very conservative in order to work effectively with this extremely difficult population. Subjects were randomly assigned to either a high-dose group (oral dose of 500–1500 mg/day) or a low-dose group (up to 250 mg/day). Subjects in both groups were started at an oral dose of 125 mg/day. The high-dose group was characterized by a modal oral dose of 1000 mg/day, while the low-dose group was characterized by a modal oral dose of 125 mg/day. We titrated the dose of divalproex to reach therapeutic plasma levels of 50 to 120 μg/mL. Subjects reported minimal side effects, and very few dropped out.

While this dosing strategy achieved significant results, we believe that higher doses, which have been described as being effective in those who do not respond, could be tried.[34] We would recommend starting individuals at the dosing described here; however, if after 6 to 8 weeks there has been insufficient response, we would recommend targeting the upper limits of the plasma drug level.

Hypothesis 2, that specific baseline comorbidities would predict treatment response, was largely invalidated. Although the overall logistic regression for predicting outcome from baseline comorbid diagnoses was significant, it was not possible to link any single specific comorbid diagnosis, such as PTSD or depression, with treatment response. We must be cautious in interpreting this result, as we are dealing with a small sample and relatively small subsamples of comorbidities, requiring considerably more power than the analyses conducted previously with continuous data.

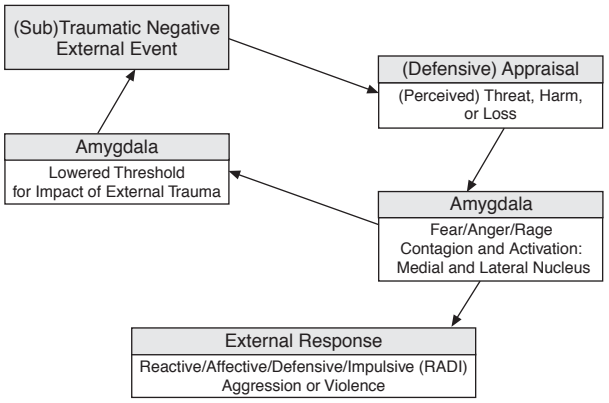
In general, however, the relationships illustrated using logistic regression analyses support the concept that traits (including personality attributes and defense styles), measured at baseline, are more useful than the diagnosis of disorders comorbid to conduct disorder in predicting treatment response to divalproex. Of particular interest is the association of trauma-related profiles with response.

As anticipated, the overall level and range of psychopathology, measured using the YSR, was negatively correlated with treatment response, confirming the relationship we had anticipated based primarily on study duration and the use of monotherapy (hypothesis 3). It is not possible from these analyses to predict whether a longer treatment period might have produced a higher response rate among subjects with high YSR scores.

As we had anticipated from the results of the earlier study,[23] high divalproex dose was strongly and positively associated with treatment response. Using our criteria for response, only 2 subjects in the low-dose group responded, making it impossible to identify response predictors for this group. A post hoc analysis, using only the high-dose group, confirmed the association of low restraint and high immature defenses (data not shown).

The observed response profiles to an established mood stabilizer and antikindling agent, divalproex, are generally consistent with a RADI model of conduct disorder–related aggression in juveniles. Kindling processes have been postulated to play a significant role in the gradual evolution of affective disorders from psychosocial stressors.[26] In our proposed model for the development of conduct disorder, kindling underlies the establishment of a RADI aggression pattern, as shown in Figure 1, and an antikindling agent may be able to disrupt the cyclic pattern of progression from (1) a negative external event to

Figure 1. Proposed Traumatic Kindling Model for RADI Aggression: A Homologous Paradigm After R.M. Post[a]



[a]Based on Post.[26]

(2) perception of threat or harm, to (3) fear/anger/rage, and finally to (4) aggression/violence.

This study has several limitations, some of which have been addressed previously.[23] The exclusive use of boys limits our interpretation to male juvenile aggression; it is unclear whether the roots of female aggression are similar to or diverge significantly from this model. The drawback of a relatively small sample size was exacerbated by poor response in the low-dose group, leaving our analysis underpowered to effectively examine the contribution of comorbidities and to some extent disease attributes. In addition, the short-term nature of the study prevents us from drawing meaningful conclusions with regard to long-term efficacy and tolerability of divalproex in this population.

To our knowledge, however, this study represents the first randomized, controlled double-blind clinical trial that examines the baseline disease and personality attributes that may be useful in predicting treatment response to divalproex in conduct disorder. The level of treatment response observed in the previous study,[23] combined with the ability (even with the small sample size) to identify baseline contributors to response, strongly suggests the need for further study. Future study should be targeted at delineating the appropriate role for divalproex therapy in conduct disorder and at assessing the validity of the RADI aggression model, which may in turn point the way to more effective intervention. Our findings also support the usefulness of assessing habitual traits relevant to specific domains of functioning. This assessment makes it possible to capture more fully the impact of syndromal psychopathology on variables that can be directly measured and that may permit more accurate prediction of outcomes and response.[24]

Drug names: divalproex (Depakote), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Methylin, Concerta, and others), risperidone (Risperdal).

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