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ORIGINAL PAPER

Divalproex Sodium for the Treatment of PTSD and Conduct Disordered Youth: A Pilot Randomized Controlled Clinical Trial

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Abstract We examined the efficacy of divalproex sodium (DVP) for the treatment of PTSD in conduct disorder, utilizing a previous study in which 71 youth were enrolled in a randomized controlled clinical trial. Twelve had PTSD. Subjects (all males, mean age 16, SD 1.0) were randomized into high and low dose conditions. Clinical Global Impression (CGI) ratings for core PTSD symptoms (Intrusion, avoidance and hyper arousal) were primary outcome measures, weekly slopes of impulsivity secondary ones. Intent-to-treat analyses showed significant positive associations between receiving high dose of DVP CGI's. Parallel analyses comparing outcome by drug level achieved strengthened the results.

Keywords PTSD · Conduct disorder · Divalproex sodium · Clinical trial

> ''My homey comes and visits me every night. I still hear the shots, then he falls down. And I am so scared I can't even scream''

Fifteen-year-old delinquent boy describing the killing of his friend in a drive by shooting which traumatized him, leading to PTSD.

Introduction

Posttraumatic stress disorder (PTSD) is a complex disorder that can significantly impair adults and children. PTSD is a common condition; in fact, it is the fifth most common

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psychiatric illness among individuals between the ages of 15 and 54, after major depression, simple phobia, social phobia, and alcohol dependence [1]. Prevalence rates reported in the literature reviewing pediatric PTSD vary greatly, from 6% in a community sample [2] to 34.5% [3] in youth exposed to community violence and 32 and 60% in incarcerated youths [4, 5]. It is estimated that at least 50% of children who experience interpersonal violence will develop PTSD symptoms [6, 7].

There is a dearth of empirical data documenting the efficacy of current psychopharamcological treatment modalities for pediatric PTSD [8, 9]. There are very few studies on the treatment of anxiety disorders in children-The recent RUPP (Research Unit on Pediatric Psychopharmacology Anxiety Study Group) study concluded that fluvoxamine is an effective treatment for children and adolescents with social phobia, separation anxiety disorder or generalized anxiety disorder [10].

Although there are too few controlled studies to confirm pharmacological treatment recommendations [9], some open label studies have demonstrated symptomatic response. Famularo et al. [11] found improved intrusion and arousal symptoms in 8 of 11 abused children with the use of propranolol (PROP). Clonidine (CLON) administered for a duration of 4 weeks, yielded an effective reduction in severe symptoms of trauma in 7 children ages 3–6 [12]. In cohort of children with PTSD aged 10–18 years, CLON was found to reduce the amount of arousal and startle response [13]. Together, these studies included about 20 subjects; each yielded positive results, however, none were properly controlled. Each study did not include standardized outcome measures and long term follow up.

Post has described a model which suggests that the learning and memory related processes in PTSD may be analogous to amygdala kindled seizures and sensitization [14] (See Fig. 1). An anti-kindling agent could potentially reduce reactive aggression in incarcerated delinquents with PTSD by interfering via two specific pathways with the link between negative affective arousal and reduced restraint [15, 16]. An anti-kindling agent may inhibit aggression either by decreasing affective arousal in response to frustration (reducing distress), or by inhibiting contagion between affective arousal and overtly aggressive behavior (inducing restraint).

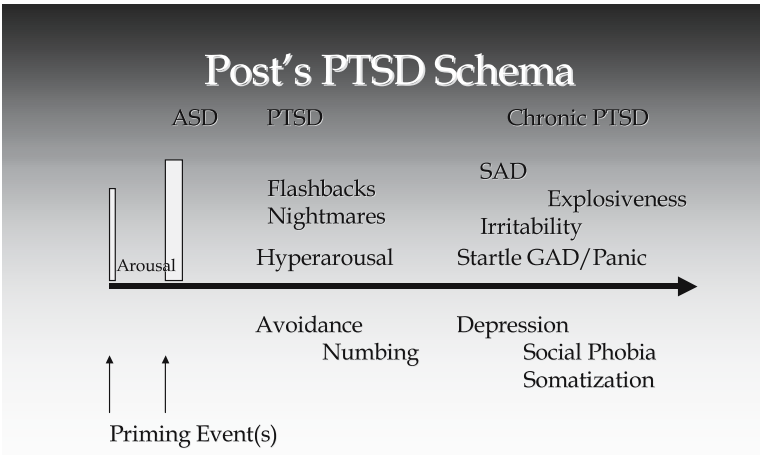

Fig. 1 Post's PTSD Schema

There is some evidence that two mood stabilizers, carbamazepine [17] and divalproex sodium (DVP), an enteric form (for less G.I. side effects) of sodium valproate and valproic acid [18], are effective in the treatment of PTSD in adults. However, for psychiatric applications in underage populations, the majority of studies using DVP addressing any diagnosis have been neither blinded nor controlled; nevertheless, the medication is extensively prescribed ''off-label'' in youths of all ages for psychiatric targets such as aggression and mania [19].

We have published previously a randomized controlled 7-weeks clinical trial in severe conduct disorders with DVP [20], examining the comorbidity profile of these youths, we noted that several subjects fulfilled diagnostic criteria for PTSD by Psychiatric diagnostic interview- revised (PDI-R) DSM-III-R criteria, a measure of PTSD which we have tested in previous studies and which produced reliable and valid results [4, 5]. This presented the unique opportunity to reanalyze the portion of the sample who fulfilled PTSD criteria and examine their outcomes in this randomized controlled clinical trial, which to date would be the first of its kind in the juvenile population.

We postulated that treatment with DVP at doses effective for seizures would result in fewer core symptoms of PTSD (arousal, intrusion, avoidance), and higher restraint (or less impulsivity). We thought that administration of divalproex sodium in doses considered therapeutic for seizures would (1) result in global clinical improvement at the end of a seven week trial, with minor side effects; (2) reduce subjectively experienced distress leading to increased levels of restraint; and (3) reduce verbal and behavioral manifestations of anger and aggression.

To test these hypotheses, we reexamined a seven-week, double-blinded, randomized, controlled trial of severe CD youth, all of whom met DSM-III-R criteria for PTSD. The following paper describes the results of the reanalysis of this sub sample of youths.

Methods

Subjects

This protocol was approved by the California Youth Authority (CYA) 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.

The initial study ''Divalproex sodium for the treatment of severe conduct disorder: randomized controlled clinical trial'' reports the subject characteristics and the crime profile of the subjects; please refer to the original study [20]. Study participants were all males from one particular campus, which tends to treat the youngest offender group in the California Youth Authority. The average length of stay at time of participation in the study was 3 months (range 1–20). From this sample of 71 youth, 12 subjects (Mean age = 15.9 years, SD = 1.1, ethnicity = more whites, few minorities) had active ongoing PTSD as established by the open managing clinician according to the PDI-R [21] and had completed all study variables. The blinded clinician used the Othmer PTSD module to score CGI-S & I ratings at completion of the study as they applied to core symptoms of intrusion, hyper arousal and avoidance. These 12 boys constitute the sample for this report.

The original randomization resulted in a perfect split: 6 subjects were in the high dose, 6 in the low dose condition (See Table 1).

Instruments-self report

All these instruments are described in some detail in our previous study; we will only state briefly their properties.

Achenbach Youth Self Report (YSR)

The YSR is a well-known standardized clinical screening survey assessing ten dimensions of psychopathology, as well as internalizing, externalizing, and total problems. Clinical and borderline ranges are available. The instrument has good psychometric properties [22].

Weinberger Adjustment Inventory (WAI-62)

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) [23].

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

Observer ratings

Best estimate diagnoses

At entry all participants were examined by the managing clinician, a board-eligible child psychiatrist with 4 years of experience in this 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 it was required that a subject fulfill Conduct Disorder criteria by DSM-IV. As the best estimate diagnoses are in many ways comparable to structured interviews, we felt there was no need to add structured interviews and increase the burden on the participants to make the diagnosis of CD in the original study [20].

Table 1 Subject characteristics

	Low Condition ($N = 6$)	High Condition ($N = 6$)	Total ($N = 12$)
Age	16.2 SD = .75	15.7 SD = 1.11	15.9 SD = .95
African American	0.0% ($N = 0$)	14.3% ($N = 1$)	7.7% ($N = 1$)
Hispanic	50.0% ($N = 3$)	14.3% ($N = 1$)	30.8% ($N = 4$)
Caucasian	33.3% ($N = 2$)	57.1% ($N = 3$)	46.2% ($N = 5$)
Asian	16.7% ($N = 1$)	14.3% ($N = 1$)	15.4% ($N = 2$)

The managing clinician also provided two NIMH Clinical Global Ratings at Entry into and at Exit from the study: Severity of illness at entry and exit and Improvement at exit. The Scales described by Guy [24] were used. For Severity, the anchors Not at all ill (0) and among the most extremely ill patients (6) were used. For Improvement, the range was Very much improved (1) to Very much worse (7).

Blind clinician exit interview for target symptom ratings and clinical global ratings

At exit from the study a second blinded clinician, a board-certified child psychiatrist with 15 years of experience in this population, examined subjects and rated them according to the NIMH Clinical Global Impression Ratings (CGI) [24], rating subjects on severity. Additionally, the blinded clinician also estimated how improved the subjects were compared to entry into the study. In the course of the 1 h exam, 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 and PTSD occurred in this subject compared to them starting out in the study. This was expressed along the usual CGI-I dimension of Very much improved (1) to very much worse (7). This clinician was blind 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 core symptoms of PTSD (hyper arousal, avoidance and reliving). Final CGI-S and CGI-I were based on this discussion.

Protocol

Following enrollment in the study, subjects spent one week in washout of the medications they were taking prior to the enrollment into the study. During this week, the managing clinician conducted clinical evaluations of all participants, assessed their self-reports (YSR and WAI) and completed the ''best estimate'' diagnoses. Participants were randomized into either a high (between 500–1500 mg per day or therapeutic plasma levels for seizure control between 50–120 ng/ml) or low dose (up to 250 mg per day) condition, as described in the original study [20]

According to the Federal Legislation the studies of the incarcerated population have to offer two active treatments varying in strengths, hence a placebo group could not be used to compare with DVP in this study.

The clinical team monitored dosages, response, side effects, and blood levels. The blood levels of DVP were monitored at two points in the study (between weeks (2–4) and weeks (6–8) and this also helped in documenting and ensuring the compliance with the medication by these subjects. The subjects were not allowed to be on any other medication while in the study, in order to avoid any drug interactions with DVP. As they completed the protocol, CGI ratings were reapplied and rating scales were completed.

Statistics

All statistical analysis was performed using SAS. All variables were found to be non-normally distributed, as expected. Therefore we employed non-parametric statistics throughout. Cronbach's alpha, Spearman correlation, Wilcoxon and Fisher's Exact tests

were thus used as appropriate. Linear regression of WAI scores collected throughout the study were used to estimate each subject's responses in all dimensions of the WAI. Regression equations employed as many data points as were available for each subject (mean = 6.2, SD = 1.7, range = 2–8).

Results

Descriptive characteristics of the sample

To check the representative ness of this sub sample, we performed a series of case control analyses. There was no significant difference between the original study sample [20] and the current sample on demographics, crime history, co morbidity and YSR scores, with of course the exception of the diagnosis of PTSD for which the current sample was selected. We also examined the sub samples for this study and did not find them to be significantly different at baseline when dose assignment or achievement of blood levels was used as the grouping variable. There were no differences in the baseline CGI (means 4.6 versus 4.6, *P* not significant).

Correlation of diagnoses, dimensional psychopathology and observer CGI ratings in the original study [20]

In the original sample several analysis showed significant convergence of different methods of assessing psychopathology. We did not repeat these analyses here because of the small sample size involved. There was no significant difference in the magnitude of the CGI-I ratings between managing clinician (mean = 2.03 + /−0.82) and blind outcome rater (mean = 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 (rho = 0.55, $P = 0.0001$). The blind clinician's CGI-S and CGI-I ratings at exit correlated significantly (rho = .76, $P = 0.0001$). Both results support the two raters' consistency.

CGI-I ratings by the blinded clinician were distributed as follows: 5(42%) were rated as very much improved, 4(34%) as much improved and 3(25%) as minimally improved. CGI-I ratings by the blinded clinician and managing clinicians agreed significantly (Spearman's rho = 0.44; weighted kappa = 0.37; 95% CI: 0.18–0.57; Fisher's Exact $P < 0.01$).

Efficacy by Intent to Treat

Efficacy by Intent to Treat was the same, as by blood level achieved therefore we will only report results by blood level achieved.

Efficacy by blood level achieved

The mean blood level was 71.5 μg/ml (+/−12.4) in the high dose condition, and 15.6 μg/ml (+/−3.55) in the low dose condition. Of the 12 subjects, six were assigned to high dose group, and all of them achieved therapeutic levels.

Table 2 CGI-S ratings

Condition	CGI- S Rating		
	None 0–1	Moderate 2–3	Marked 4–5
High Dose (1000 mg) ($N = 6$) (% in row)	67% ($N = 4$)	17.0% ($N = 1$)	17.0% ($N = 1$)
High Level (>45 μg/ml) ($N = 6$)	17% ($N = 4$)	50.0% ($N = 1$)	33% ($N = 1$)
Low Dose (125 mg) ($N = 6$)	17% ($N = 1$)	50% ($N = 3$)	33% ($N = 2$)
Low Blood Level (<45 μm/ml) ($N = 6$)	17% ($N = 1$)	50% ($N = 3$)	33% ($N = 2$)

[1] Intent to Treat: Wilcoxon Test- $P < 0.08$; Drug Level Achieved: Wilcoxon Test $P < 0.08$ Gray-Analysis based on Intent to Treat White-Analysis based on Drug Level Achieved.

Wilcoxon test revealed non-significant association between blind CGI-S and therapeutic drug level (mean = 1.94, z = 1.22, and $P = 0.1235$) (Table 2). Furthermore, an additional Wilcoxon test revealed a highly significant association between CGI-I and therapeutic drug level (mean = 1.83, z = 2.14 and $P = 0.03$) (See Table 3).

Analysis of secondary efficacy measures also supported results from the intent-to-treat analysis. There was a significant improvement in Restraint compared to distress on the WAI in the subjects with high blood levels of DVP (mean = 0.05, z = 2.09, $P = 0.03$) (See Table 4).

Significant differences were found between conditions in PTSD core symptoms of intrusion, avoidance and hyper arousal, supporting results from intent-to-treat analysis. According to the CGI, that was clinician rated-subjects, who achieved therapeutic drug level, self-reported significantly less intrusion, (mean rank = 1.33, z = 1.6, $P = 0.06$) than other subjects (low level), and also reported significantly less avoidance (mean = 1.16, z = 1.79, $P = 0.05$) than others (low level). Marginally significant results were found by condition in regards to symptoms of hyper arousal, (mean = 1.91, z = 1.48 and $P = 0.08$) (See Table 5).

Tolerability

Similar to the larger study, DVP was well tolerated by all subjects in this subset. Generally, the adverse effect profile was mild and in accordance with previous studies [16], consisting

Table 3 Blind CGI-I ratings

Condition	CGI- I Rating		
	None 0–1	Moderate 2–3	Marked 4–5
High Dose (1000 mg) ($N = 6$) (% in row)	17% ($N = 1$)	0.0% ($N = 0$)	88% ($N = 5$)
High Level (>45 μg/ml) ($N = 6$)	17% ($N = 1$)	0.0% ($N = 0$)	83% ($N = 5$)
Low Dose (125 mg) ($N = 6$)	33% ($N = 2$)	67% ($N = 4$)	0% ($N = 0$)
Low Blood Level (<45 μm/ml) ($N = 6$)	33% ($N = 2$)	67% ($N = 4$)	0% ($N = 0$)

Intent to Treat: Wilcoxon Test- $P < 0.016$; Drug Level Achieved: Wilcoxon Test $P < 0.016$ Gray-Analysis based on Intent to Treat White-Analysis based on drug level achieved.

Table 4 Change in WAI scores

Change (Slope)	High Dose/ High Blood Level	Low Dose/ Low Blood Level
Distress	−.05 (SD = .07)	.005 (SD = .06)
	−.05 (SD = .07)	−.005 (SD = .06)
Low Self-Esteem	−.04 (SD = .10)	−.02 (SD = .10)
	−.04 (SD = .10)	−.02 (SD = .10)
Low Well Being	−.03 (SD = .08)	.005 (SD = .10)
	−.03 (SD = .07)	.004 (SD = .09)
Anxiety	−.06 (SD = .06)	−.01 (SD = .04)
	−.05 (SD = .06)	−.01 (SD = .03)
Depression	−.07 (SD = .12)	.05 (SD = .03)
$P < 0.04$	−.07 (SD = .11)	0.05 (SD = .03)
Restraint	−.03 (SD = .06)	−.08 (SD = .04)
$P < 0.025$	0.05 (SD = .06)	−.03 (SD = .03)
Consideration	−.12 (SD = .12)	−.017 (SD = .13)
	0.02 (SD = .11)	−0.02 (SD = .13)
Responsibility	.05 (SD = .08)	−.10 (SD = .05)
$P < 0.03$	.06 (SD = .08)	−.04 (SD = .05)
Impulse Control	.05 (SD = .07)	−0.1 (SD = .07)
	0.04 (SD = .07)	−0.04 (SD = .07)
Supp. Of Aggression	.004 (SD = .05)	−0.1 (SD = .05)
$P < 0.02$	0.06 (SD = .05)	−0.04 (SD = .05)

Table 5 CGI-S and core symptoms of PTSD

	High dose/ High blood level ($N = 6$)	Low dose/Low blood level/ ($N = 6$)
CGI-S	1.02	0.15
Intrusion	3.17	1.33
Avoidance	2.83	1.17
Hyper arousal	1.91	1.92

of G.I. upset and sleepiness, and decreasing rapidly over time, with no instances of more serious adverse effects that have been reported elsewhere [25].

Discussion

This is the one of the very few controlled clinical trials of a psychopharmacological treatment for PTSD in children and adolescents, the first to compare an agent in two parallel arms. This trial provides preliminary evidence for the short-term efficacy of DVP for the treatments of PTSD in severely conduct disordered boys. At the end of treatment, patients in the high dose compared to low dose condition had significantly less symptom

severity, with greater improvement in and fewer core symptoms of PTSD as evidenced by significant CGI-S scores. Main effects in core PTSD symptoms were seen in Intrusion and Avoidance with Hyper arousal showing a trend toward improvement. Subjects also showed a significantly greater reduction in Distress and a greater increase in Restraint for high blood level group.

In accordance with our hypotheses, divalproex also had an effect beyond acute reduction in PTSD symptoms. Subjects in the high-dose divalproex group reported significantly greater increases in restraint and decreases in distress and depression than subjects in the low-dose group. Increases in restraint and decreases in distress are significant to this population because more restraint leads to better choices like- time to make decisions and thus delay the emotional acting out behavior. And less distress actually predicts the level of restraint [26], which in turn prevents acting out. Furthermore, aggression was decreased, and responsibility increased, in the high-dose group.

Increased impulsive Aggression is regarded as a property of PTSD, rather than a direct consequence of trauma [27, 28]. At the same time, aggression is a core symptom of Conduct disorder (DSM-IV CRITERIA), hence decreasing aggression in PTSD and CD population is very important. This finding also mirrors findings of decreased aggression in patients with mixed disorders of mood and conduct treated with DVP [29, 30]. Therefore, DVP may also have activity towards decreasing aggression in children and adolescents independent of psychiatric diagnosis [31].

Our findings also point to a dosage and serum level threshold for efficacy of DVP in treating PTSD. As our low dose and low serum level groups had significantly less response than the high dose counterparts, it would appear necessary to treat patients with PTSD at levels and doses in the range of guidelines for bipolar disorder [32] and epilepsy [33].

Numerous limitations are evident in this study. Foremost, this is a re-analysis of an existing data set, and thus we could not expand on our previous set of measures and use measures more specific for PTSD. We did not assess all disorders by structured interview. We did not have standardized staff ratings throughout the study's duration and the primary outcome measure, the CGI-S, was delivered by a single blinded rater. In the larger study, we reported good coherence between managing clinician and research psychiatrist [20]. In this cohort, such effects were very difficult to show, most likely due to the small sample size. The relatively small sample size also limited the amount of between-group comparisons that could be made. The diagnoses of PTSD was made using DSM-IIIR criteria. Subjects had significant comorbidity of conduct and other disorders, making it possible that improvement in PTSD symptoms were partially due to alleviation of symptoms common to co morbid disorders. Finally, this was an all-male sample of incarcerated youth as dictated by the nature of the cohort. Therefore the effects of DVP on PTSD symptoms cannot be generalized to females or non-incarcerated adolescents as well.

However, our study design also shows some strength. First, raters were blinded to diagnoses and dose-condition and thus assessment of outcome was not biased. Second, the effects seen were hypothesized and derived from a model of PTSD, which attributes importance to emotional kindling and would predict the efficacy of DVP. Randomization was successful and delivered comparable subgroups who were exposed to high and low doses of DVP. Despite the fact that this study really compared two active agents (low dose versus high dose), i.e. two treatments, we could report significant results on several key outcomes, which was difficult to achieve because of power considerations. Finally, all limitations notwithstanding, this is the first report of a randomized psychopharmacological study of PTSD in youth.

Our findings are also interesting in that they support the often-reported association between disturbances of anxiety, mood and aggression [34]. In many cases, these disturbances were chronic, and overlapped with personality dimensions. As DVP appeared to have a positive impact on trait like variables, such as self-restraint, the possibility exists that longstanding nonadaptive temperament characteristics may be altered by DVP. Long-term effects, while not studied here, could therefore mean decreased recidivism. Long-term follow up would also reveal the utility of DVP as an antikindling agent in pediatric PTSD. Post's model of affective kindling (see Fig. 1) in PTSD would suggest that there may be continuing effects of treatment beyond acute improvement, perhaps in preventing further development of PTSD symptoms. Future controlled studies with greater numbers of subjects and longitudinal follow up are needed to fully investigate the utility of DVP in this population.

Summary

This study examined the efficacy of a specific compound, divalproex sodium, for the treatment of PTSD in youth, in the context of conduct disorder. Drawing on the data from a previously published study, we examined Clinical Global Impression (CGI) ratings for the core symptoms of PTSD (Intrusion, avoidance and hyper arousal) and weekly slopes of the WAI. Intent-to-treat analyses showed significant and positive associations between assignment to the high dose condition and Clinical Global Impression ratings both severity and improvement. Subjects on a high dose of DVP achieving therapeutic blood levels showed reduced severity of illness and greater improvement than subjects who received minimal doses. Subjects also showed a significantly greater reduction in Distress and a greater increase in Restraint along with decrease in Impulsivity for both the high dose and high blood level groups. This is the first reported RDBCT of a psychopharmacological agent comparing a high and low dose intervention in two parallel arms for the treatment of PTSD in youth, suggesting a role for DVP in treating PTSD in CD.

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References

1. Kessler RC, Sonnega A, Bromet, E (1999) Risk factors for posttraumatic stress disorder. In: Yehuda R (ed) American Psychiatric Association, Washington, DC, US, pp 23–59
2. Giaconia RM, Reinherz HZ, Silverman AB (1995) Traumas and posttraumatic stress disorder in a community population of older adolescents. J Am Acad Child Adolesc Psychiatry 34(10):1369–1380
3. Berman SL, Kurtines WM, Silverman WK (1996) The impact of exposure to crime and violence on urban youth. Am J Orthopsychiatry 3(66):329–336
4. Cauffman E, Feldman SS, Waterman J, Steiner H (1998) Posttraumatic stress disorder among incarcerated females. J Am Acad Child Adolesc Psychiatry 37(11):1209–1216
5. Steiner H, Garcia IG, Matthews Z (1997) Posttraumatic stress disorder in incarcerated juvenile delinquents. J Am Acad Child Adolesc Psychiatry 36(3):357–365
6. McLeer SV, Deblinger EB, Henry D (1992) Sexually abused children at high risk for post-traumatic stress disorder. J Am Acad Child Adolesc Psychiatry 31(5):875–879
7. Famularo R, Fenton Terence, Augustyn M (1996) Persistence of pediatric posttraumatic stress disorder after 2 years. Child Abuse & Neglect 20(12):1245–1248
8. Pfefferbaum B (1997) Posttraumatic stress disorder in children: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 36(11):1503–1511

9. Donnelly CL, Amaya JL, March JS (1999) Psychopharmacology of pediatric posttraumatic stress disorder. J Child Adolesc Psychopharmacol Ann 9(3):203–220
10. RUPP STUDY GROUP (2001) Fluvoxamine for the treatment of anxiety disorders in children and adolescents. New England Journal of Medicine 1279–1285
11. Famularo R, Kinscherff R, Fenton T (1988) Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study. Am J Dis Child 142(11):1244–1247
12. Harmon RJ, Riggs PD (1996) Clonidine for posttraumatic stress disorder in preschool children. J Am Acad Child Adolesc Psychiatry 35(9):1247–1249
13. Nader KO, Pynoos RS, Fairbanks LA, Al-Ajeel M, Al-Asfour A (1993) A preliminary study of PTSD and grief among the children of Kuwait following the Gulf crisis. Br J Clin Psychol 32(Pt 4):407–416
14. Post RM, Weiss SRB, Smith M, Li H, McCann U (1997) Kindling vs. quenching: implications for the evolution and treatment of PTSD. Ann NY Acad Sci 821:285–295
15. Wilcox J (1994) Divalproex sodium in the treatment of aggressive behavior. Ann Clin Psychiatry 6(1):17–20
16. Donovan SJ, Susser ES, Nunes EV, Stewart JW, Quitkin FM, Klein DF (1997) Divalproex treatment of disruptive adolescents: a report of 10 cases. J Clin Psychiatry 58:12–15
17. Loof D, Grimley P, Kuller F (1995) Carbamazepine found efficacious for some children, adolescents with PTSD. Special Report: Anxiety Disorders. Psychiatric Times 23
18. Fesler FA (1991) Valproate in combat related posttraumatic stress disorder. J Clin Psychiatry 52: 361–364
19. Rana M, Khanzode LA, Karnik N, Saxena K, Chang K, Steiner H (2005) Divalproex sodium in the treatment of pediatric psychiatric disorders. Expert Rev Neurother 5(2):165–176
20. Steiner H, Petersen M, Saxena K, Ford S, Matthews Z (2003) Divalproex Sodium for the treatment of Severe Conduct Disorder: a randomized controlled clinical trial. J of Clinical Psychiatry 64:1183–1191
21. Othmer E, Penick EC, Powell BJ, Read MR, Othmer SC (1981) Psychiatric Diagnostic Interview-Revised (PDI-R). Los Angeles, Western Psychological Services
22. Achenbach TM (1991) Manual for Youth Self-Report and 1991 Profile. Burlington, VT, University of Vermont Dept. of Psychiatry
23. Weinberger D (1997) Distress and self-restraint as measures of adjustment across the life Span: confirmatory factor analysis in clinical and nonclinical samples. Psychol Assess 9(2):132–135
24. Guy W (1976) ECDEU Assessment Manual for Psychopharmacology, 2nd ed. Washington DC, US Government Printing Office
25. Deltito JA, Levitan J, Damore J, Hajal F, Zambenedetti M (1998) Naturalistic experience with the use of divalproex sodium on an in-patient unit for adolescent psychiatric patients. Acta Pschiatr Scand 97: 236–240
26. Feldman SS, Weinberger DA (1995) Self-restraint as a mediator of family influences on boys' delinquent behavior: a longitudinal study. Child Dev 65: 195–121, 1994. Weinberger DA, Gomes ME: Changes in daily mood and self-restraint among under controlled preadolescents: a time series analysis of ''acting out''. J Am Acad Child Adolesc Psychiatry 34(11):1473–1482
27. Lasko NB, Gurvits TV, Kuhne AA, Orr SP, Pitman RK (1994) Aggression and its correlates in Vietnam veterans with and without chronic posttraumatic stress disorder. Compr Psychiatry 35(5):373–381
28. Begic D, Jokie BN (2001) Aggressive behavior in combat veterans with post-traumatic stress disorder. Mil Med 166(8):671–676
29. Donovan SJ, Stewart JW, Nunes EV, Quitkin FM, Parides M, Daniel W (2000) Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. Am J Psychiatry 157(5):818–820
30. Donovan SJ, Nunes EV, Stewart JW, Ross D, Quitkin FM, Jensen PS et al (2003) ''Outer-Directed Irritability'': a distinct mood syndrome in explosive youth with a disruptive behavior disorder? J Clin Psychiatry 64(6):698–701
31. Steiner H, Saxena K, Chang K (2003) Psychopharmacological Strategies for the treatment of Aggression in Juveniles. CNS Spectrum 8(4):298–308
32. Wagner K (2002) An Open–label trial of divalproex in children & adolescents with Bipolar disorder. J Am Acad Child Adolesc Psychiatry 41(10):1224–1230
33. Ohtsuka Y, Amano R, Mizukawa M, Oka E, Ohtahara S (1992) Treatment of intractable childhood epilepsy with high-dose valproate. Epilepsia 33(1):158–164
34. Steiner H, and AAACAP Work Group on Quality Issues (1997) Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. J Am Acad Child Adolesc Psychiatry 36(10):122S–19S