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Journal

Psychiatry Research, 229(3)

ISSN

0165-1781

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Publication Date

2015-10-01

DOI

10.1016/j.psychres.2015.07.078

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Psychiatry Res. Author manuscript; available in PMC 2016 October 30.

Published in final edited form as:

Psychiatry Res. 2015 October 30; 229(3): 844–849. doi:10.1016/j.psychres.2015.07.078.

Inflammatory Markers and Chronic Exposure to Fluoxetine, Divalproex, and Placebo In Intermittent Explosive Disorder

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Abstract

Intermittent Explosive Disorder (IED) is a disorder of impulsive aggression affecting 4-7% of the U.S. population during some period of life. In addition to other biological correlates, elevations of plasma inflammatory markers have been reported in IED, compared with control, subjects. In this study we sought to explore if treatment exposure to anti-aggressive agents, compared with placebo, would be associated with a reduction in circulating levels of inflammatory markers. Thirty IED subjects, from a twelve-week, double-blind, randomized, placebo-controlled trial of fluoxetine and divalproex, in which both pre- and post-treatment levels of C-Reactive Protein (CRP), interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10 and tumor necrosis factor (TNF)-α were obtained. Efficacy measures included the Overt Aggression Scale-Modified (OAS-M) score for Aggression and for Irritability, rate of Clinical Global Impression of Improvement (CGI-I), and rate of IED Remitters at study completion. As compared to placebo, neither fluoxetine nor divalproex reduced any of the measures of aggression. In addition, levels of CRP and pro- and anti-inflammatory cytokines showed no changes from pre- to post-treatment for any treatment condition. Correlations between pre- and post- treatment plasma CRP/cytokines were substantial (mean $r = 0.71$, $r^2 = 0.50$, $p < 0.001$). Overall, circulating markers of inflammation markers were unaffected by treatment with fluoxetine or divalproex, consistent with the absence of change in measures of impulsive aggression.

Keywords

Aggression; Inflammation; Fluoxetine; Divalproex

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1.0 Introduction

A positive relationship between circulating inflammatory markers, such as the acute phase reactant, C-Reactive Protein (CRP), and the inflammatory cytokine interleukin-6 (IL-6), and measures of anger, hostility, and aggression has been reported in community samples (Suarez, 2004; Marsland et al., 2008) and in psychiatric subjects with personality disorder (Coccaro 2005) and/or Intermittent Explosive Disorder (Coccaro et al., 2014). A potential causative role for cytokines is suggested by animal studies which show that application of IL-1β and IL-2 to cells in the medial hypothalamus (MH) and in periaqueductal grey (PAG) increase defensive aggressive behavior in the cat (Zalcman and Siegel, 2006; Bhatt et al., 2008; Pesce et al., 2011) and by clinical studies which report emerging anger in patients treated with pro-inflammatory agents (McHuthison et al., 1998; Kraus et al., 2003).

If human aggressive behavior is causally related to elevations in circulating (and/or central) levels of inflammatory mediators, successful treatment of aggressive behavior should be associated with a reduction in circulating inflammatory mediators. While this work has not been performed in aggressive subjects, recent studies in depressed patients suggest that successful treatment of depression by antidepressants, or by cognitive behavioral therapy, in controlled double blind studies, is associated with a reduction in circulating levels of IL-6 (Doering et al., 2007; Pizzi et al., 2009). Demonstrating the same in aggressive subjects would suggest a causative role of inflammatory mediators in human aggression.

The present study reports on the results of thirty subjects with DSM-5 IED who completed a twelve week, double-blind, placebo-controlled trial of fluoxetine and divalproex and who participated in a sub-study examining the role of plasma inflammatory markers in the potential anti-aggressive response to psychopharmacologic intervention. We hypothesized that a placebo-controlled anti-aggressive response to fluoxetine, and/or divalproex, would be associated with a reduction in circulating levels of CRP and IL-6 and that the degree of these reductions would correlate with the degree of improvement in overt aggression scores. In addition to circulating levels of CRP and IL-6, we also assessed circulating levels of other inflammatory cytokines such as IL-1β, IL-2, IL-8, and TNF-α, as well as the anti-inflammatory cytokine IL-10, before and after 12 weeks of treatment with fluoxetine, divalproex, or placebo.

2.0 Methods

2.1 Subjects

Thirty male and female subjects who completed a twelve-week, placebo-controlled, double-blind trial of fluoxetine and divalproex and who volunteered to provide a blood sample prior to, and at completion of, the full trial were included for analysis. Sixty other subjects took part in this clinical trial, but were not included in this analysis because either these subjects did not complete the full trial (n = 42) or did not have both pre- and post-treatment (i.e., subjects with one but not both blood: n = 18) samples for assay of inflammatory markers (figure 1). Subjects examined in this analysis did not differ from the remaining subjects in the randomized clinical trial with regard to any demographic [e.g., Age (+ sd) for Study Subjects: 34.3 + 8.9 years vs. Non-Study Subjects: 35.8 + 9.1 years] or psychometric

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parameter [e.g., mean (+ sd) LHA Aggression scores for Study Subjects: 19.7 + 3.5 vs. Non-Study Subjects: 19.4 + 3.7]. Overall, subjects were recruited by outpatient referral or by self-referral in response to public service announcements for a clinical trial of impulsive aggression. Subjects with a life history of mania or hypomania, schizophrenia or delusional disorder, subjects with current major depression or subjects currently dependent on alcohol or other drugs of abuse, were excluded from study. Written informed consent, using an IRB-approved consent document, was obtained from all subjects after all procedures were fully explained.

2.2 Diagnostic and Medical Evaluation

Syndromal, and personality disorder diagnoses were made according to DSM-5 criteria (American Psychiatric Association, 2013). Diagnoses were made using information from: (a) the Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1997) for syndromal disorders and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP; Pfohl et al., 1997) for personality disorders by masters or doctorate level clinical psychologists; (b) clinical interview by a research psychiatrist; and, (c) review of all other available clinical data. Final diagnoses (Table I) were assigned by team best-estimate consensus procedures (Leckman et al., 1982; Kosten and Rounsaville, 1992) involving research psychiatrists and clinical psychologists as previously described (Coccaro et al., 2012). Nearly all of the IED subjects (92.9%) reported history of formal psychiatric evaluation and/or treatment (56.7%) or history of behavioral disturbance during which the subject, or others, thought they should have sought mental health services but did not (36.2%). Medical evaluation, including medical history, physical examination, and blood hematology/metabolic panels, urinalysis, and urine toxicology, ruled out significant medical conditions that would preclude entry into the trial or preclude the validity of plasma inflammatory markers (e.g., evidence of an active inflammatory condition).

2.3 Assessment of Current and Lifetime History of Impulsive Aggressive Behavior and Clinical Response to Treatment

Current history of impulsive aggression was assessed by weekly interview (OAS-M) assessments for overt aggressive behavior and irritability (Coccaro et al., 1991; Endicott et al., 2002). OAS-M Aggression scores represent a frequency/severity weighted assessment of overt aggressive behavior for the past week (on a scale of 0 to > 999). OAS-M Irritability scores represent the sum of subjective and overt irritability assessments (both on a scale of 0-5) and, as such, reflect a global, clinical, assessment of impulsive aggression over the past week. Lifetime history of impulsive aggressive behaviors was assessed using the Aggression Score from the Lifetime History of Aggression (Coccaro et al., 1997) interview assessment (scale 0 – 25). Other assessments of aggression and impulsivity included the Verbal and Physical Assault scales from the Buss-Perry Aggression Questionnaire, Life History of Impulsive Behavior (LHIB; (Coccaro and Schmidt-Kaplan, 2012), and the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). State depression was assessed with the Beck Depression Inventory-2 (BDI-2; Beck and Brown 1996).

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2.4 Treatment Study Design

After a screening OAS-M Aggression score > 15, eligible subjects, entered a two-week placebo “lead-in phase” after which subjects were either randomized to fluoxetine, divalproex, or placebo, at a 1:1:1 ratio, for an additional 12 weeks. OAS-M scores during this period served as a two-week “placebo-control” baseline for these assessments. During the trial, weekly behavioral assessments included OAS-M Aggression and OAS-M Irritability at end of trial. All assessments were made blind to study assignment. OAS-M scores were determined by a trained behavioral assessor; other assessments were performed by the research psychiatrist. For the first four weeks of the double-blind treatment phase, the fluoxetine dose was set at 20 mg po qd. At the end of Week 4 (or later) fluoxetine (or placebo) could be raised to 40 mg (two placebo capsules) if the average OAS-M Aggression score for the previous two weeks had not decreased to < 25% of the average OAS-M Aggression score during the placebo lead-in phase. Fluoxetine could be increased to a maximum of 60 mg qd (three placebo capsules) again after Week 8 if the average OAS-M Aggression score for the previous two weeks still had not dropped to 25% of the mean two-week OAS-M Aggression score at randomization. Divalproex-Controlled Release was begun at 250 mg bid (500 mg qd) for the first three days increasing the dose on day 4 to 500 mg po bid (1,000 mg qd) of blinded study drug. The dose was increased to 750 mg po bid at Week 2 (1,500 mg qd) and then to 1,000 mg po bid (2,000 mg qd) at Week 3. Further dosage adjustments (in increments of 250 qd) were made on, or after Day 29, depending on tolerability and response in OAS-M Aggression scores as with fluoxetine. The maximum daily dose of divalproex was 2,500 mg qd.

2.5 Inflammatory Markers

Subjects were not on psychotropic medications at time of recruitment and were free of all medications for at least four weeks at time of study. Sample collection took place at the start of the placebo-lead in phase (pre-treatment) and once more at the closeout visit 14 weeks later. At time of sample collection, subjects were afebrile, without recent history of physical injury, and without report of any significant stressor on the study day. Whole blood, anticoagulated with EDTA, was obtained between 9-11 AM through venipuncture of a forearm vein. Plasma was processed after centrifugation and stored at −80°C until assay. A commercially available high sensitivity enzyme-linked immunosorbent assay (ELISA; ALPCO Assays) was used to quantify plasma CRP. The lower limit of sensitivity for the plasma CRP assay was 0.035 mg/L with a coefficient of variation < 6%. A commercially available multiplex assay system (Luminex, R&D Systems) was used to quantify plasma IL-1β, IL-2, IL-6, IL-8, IL-10 and TNF-α. Plasma samples were diluted 1:2 for multiplex and 1:200 or 1:500 for ELISA according to manufacturer's instructions, and assayed in duplicate. Pilot studies of these six cytokine markers resulted in strong overall correlations in direct comparison to high sensitivity ELISAs from R&D Systems ($r > 0.90$, $p < 0.001$) with a sensitivity for each cytokine at 0.10 pg/ml (Breen et al., 2014).

2.6 Statistical Analysis

The primary outcome variables were mean OAS-M Aggression score and mean OAS-M Irritability score at end of trial controlled by baseline values of these scores at

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randomization. OAS-M Aggression and OAS-M Irritability scores were not normally distributed and, thus, all OAS-M scores were log-transformed. OAS-M "response" to treatment required significant reductions in both OAS-M Aggression and in OAS-M Irritability scores. The primary statistical procedure used was factorial ANCOVA using the baseline score of the specific variable in question as covariate at study completion. Other statistical procedures included t-test (with correction for unequal variances where appropriate (Minium, 1982), Pearson correlation, and Chi-Square and Fisher's Exact Test, where appropriate. Probability values were set at a two-tail alpha level of 0.05. All plasma inflammatory variables were log-transformed.

3.0 Results

3.1 Demographic, psychometric, and inflammatory marker values of the thirty subjects randomized to fluoxetine (n = 10), divalproex (n = 11), and placebo (n = 9) are displayed in Table II

There were no significant differences in any of these characteristics among fluoxetine, divalproex or placebo subjects. In addition, there were no differences in demographic features or in LHA Aggression, OAS-M Aggression, or OAS-M Irritability scores, among subjects with both pre- and post- inflammatory markers compared with subjects who did not have any assessment for inflammatory markers.

3.2 Anti-Aggression Outcome as a Function of Fluoxetine, Divalproex, and Placebo

ANCOVA, with baseline OAS-M scores as covariate, revealed no significant differences for OAS-M Aggression ($F[2,26] = 0.17$, $p = 0.850$) or OAS-M Irritability ($F[2,26] = 0.25$, $p = 0.780$) scores as a function of treatment condition. In a secondary analysis, we looked at the aggression outcome measures over time, regardless of drug condition in all subjects. This analysis revealed a significant reduction in pre- vs. post- treatment score for mean log OAS-M Aggression (Pre-Treatment: 1.52 + 0.35 vs. Post-Treatment: 0.87 + 0.59, $p < 0.001$) but not for mean log OAS-M Irritability (Pre-Treatment: 0.60 + 0.21 vs. Post-Treatment: 0.64 + 0.32, $p = 0.429$). Since parallel responses to these outcome measures are required to document a clinical response, it is clear that no anti-aggressive response was observed in this study.

3.3 Plasma Inflammatory Markers (Figure 3)

Neither CRP, nor other pro- and anti-inflammatory cytokine concentration differed as a function of treatment group at study completion, or for all subjects over time. In addition, no significant correlations were observed between the plasma inflammatory markers and change scores for log OAS-M Aggression (mean + sd: $r = -0.04 + 0.14$, range: −0.18 to 0.21) or for log OAS-M Irritability (mean + sd: $r = 0.03 + 0.14$, range: −0.24 to 0.17). Finally, no differences were observed in OAS-M scores among the 21 of 30 subjects with elevated levels of inflammatory markers (e.g., CRP: 6.6 + 7.2 mg/L) compared with the nine subjects with normal levels of inflammatory markers (e.g., CRP: 0.5 + 0.3 mg/L).

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3.4 Intra-Class Correlations Among Plasma Inflammatory Markers Over Time

Intra-Class correlations among each of the inflammatory markers were high over a 14 week period (mean + sd: r = 0.71 + 0.11, r^2 = 0.50; range: r = 0.58 to 0.87, r^2 = 0.34 to 0.76).

4.0 Discussion

The primary finding of this study is that inflammatory markers (CRP, five inflammatory cytokines, and one anti-inflammatory cytokine) were unaffected by treatment with fluoxetine or divalproex (compared with placebo) and, in all subjects, were unchanged over a 14 week period of time. The robust intra-class correlations for each inflammatory marker, over fourteen weeks, suggest substantial temporal stability of these inflammatory markers in IED subjects.

Compared with placebo, neither fluoxetine nor divalproex demonstrated anti-aggressive efficacy. Given evidence of anti-aggressive efficacy from larger, previous, double-blind, placebo controlled trials of fluoxetine (Coccaro and Kavoussi, 1997; Coccaro et al., 2009; Silva et al., 2010; George et al., 2011) and divalproex (Hollander et al., 2003), this result was unexpected. This could be explained by the fact that the size of each cell was small. However, review of the larger data set from which these subjects (30 of 90) were drawn also revealed no significant differences in OAS-M Aggression, or OAS-M Irritability, scores for fluoxetine or divalproex, compared with placebo. Despite the observation that OAS-M Aggression scores dropped between pre-treatment baseline and post-treatment endpoint, OAS-M Irritability scores displayed no change at all. Because the latter variable is a global measure, assessed by external raters, the absence of any pre/post- change in OAS-M Irritability scores indicates that no actual clinical change in impulsive aggressive behavior had occurred in these subjects by the end of the trial.

The reason for this negative result is most likely due to differences in the entry criteria for this study compared with our previous positive study (Coccaro and Kavoussi, 1997; Coccaro et al., 2009). Careful analysis of our previous data reveals that an OAS-M Aggression score of > 15 and an OAS-M Irritability score > 6, at the randomization point, represent the optimal, if not the necessary, entry criteria needed to identify potential responders to anti-aggressive intervention. Subjects meeting this, more stringent, entry criteria in our earlier study displayed a significant effect favoring fluoxetine over placebo (p = 0.008, n = 67, d = 0.60); subjects who had an OAS-M Aggression score > 15 at screening, only, showed no separation of fluoxetine from placebo (p = 0.735, n = 28, d = 0.14). Since only a third (10 of 30) of subjects (21 of 90 in the full sample) met the more stringent entry criteria, it is not surprising that no drug-placebo effect was observed in these subjects. Accordingly, these data suggest that plasma inflammatory markers in IED subjects do not change over time and may not do so in the absence of a clinically meaningful change in impulsive aggressive behavior. This interpretation is further supported by the observation of no significant correlations between change scores in OAS-M Aggression or OAS-M Irritability and levels of inflammatory markers at study completion.

Little is known regarding “state” and “trait” aspects of elevated inflammatory markers/ mediators in psychiatric patients. While animal studies provide some evidence that

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antidepressants (e.g., SSRIs) possess anti-inflammatory properties in vitro (Horikawa et al., 2010) and in vivo (Ohgi et al., 2013), human studies are equivocal (Hannestad et al., 2011). The majority of human studies in this area have been conducted in depressed patients during the acute phase of illness. While studies following depressed patients up to 12 weeks suggest a reduction in inflammatory markers with state change, few studies were placebo controlled. A recent meta-analysis of twenty-two such studies (Hannestad et al., 2011) concluded that while antidepressant treatment appears to reduce circulating levels of IL-1β, but not of IL-6 and TNF-α, in depressed patients. Of greater relevance to the present investigation, two studies report a reduction in circulating IL-6 levels with sertraline treatment (Pizzi et al., 2009) and with cognitive-behavioral therapy (Doering et al., 2007), and a third reports a reduction in circulating CRP, monocyte production of proinflammatory cytokines and gene expression associated with the improvement of insomnia after cognitive behavioral therapy or Tai Chi compared with a control condition (Irwin et al., 2015). Since each study had a treatment control, “state changes” in depression or in insomnia, rather than medication, itself, appear to account for the reduction in CRP or cytokine levels in these subjects.

As with many psychopharmacological trials in these types of subjects, these results should be interpreted with some caution. First, only one-third of subjects entered into the parent study were included in this analysis. This is because only individuals who completed the trial had both pre- and post-treatment samples for assay of inflammatory markers; other completers did not have available samples for assay because the sample was unobtainable from, or declined by, the subject. Regardless, the subjects in this analysis did not differ from the remaining subjects in the trial in demographic or psychometric parameters. Second, the recruitment of subjects from the community, as described, may limit the generalizability of these findings to those in community treatment settings. However, nearly all subjects had reported evaluation and/or treatment for a behavioral problem and, so, these subjects may not be very different from those found in community treatment settings. Third, the study sample was modest in size and a larger sample might have detected significant differences. However, the time-related change values for circulating inflammatory markers in this study were small in size [mean (+ sd): d = 0.09 + 0.03, range: d = 0.07 to 0.14] and a sample of nearly 500 subjects would have been necessary to detect effects of this size at an alpha < 0.05 with 80% power.

In conclusion, these data show that inflammatory markers in IED subjects do not change over time in the absence of a clinically meaningful change in impulsive aggressive behavior. A definitive test of this hypothesis will require examining inflammatory measures in medication-free IED subjects during a period of exacerbation and examining the same subjects, again, after a sustained period of medication-free remission of impulsive aggressive behavior.

ACKNOWLEDGEMENTS

This project was supported in part by NIMH Grants RO1MHXXXXX (Dr. Coccaro) and R01-AG034588, R01 AG026364, CA160245, R01DA032922, R01 HL095799-01, P30 AG028748, R01-CA119159; UL RR 033176; the Cousins Center for Psychoneuroimmunology, and UCLA Claude D. Pepper Older Americans Independence Center (Dr. Irwin).

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HIGHLIGHTS

- We examined the role of circulating inflammatory markers as a function of treatment with fluoxetine, divalproex, or placebo.
- In concert with no clinical change in impulsive aggression, the circulating markers of inflammation were unchanged over a 14 week interval despite exposure to fluoxetine, divalproex, or placebo.
- It is possible that circulating inflammatory markers remain stable in the absence of a clinically meaningful change in impulsive aggressive behavior.

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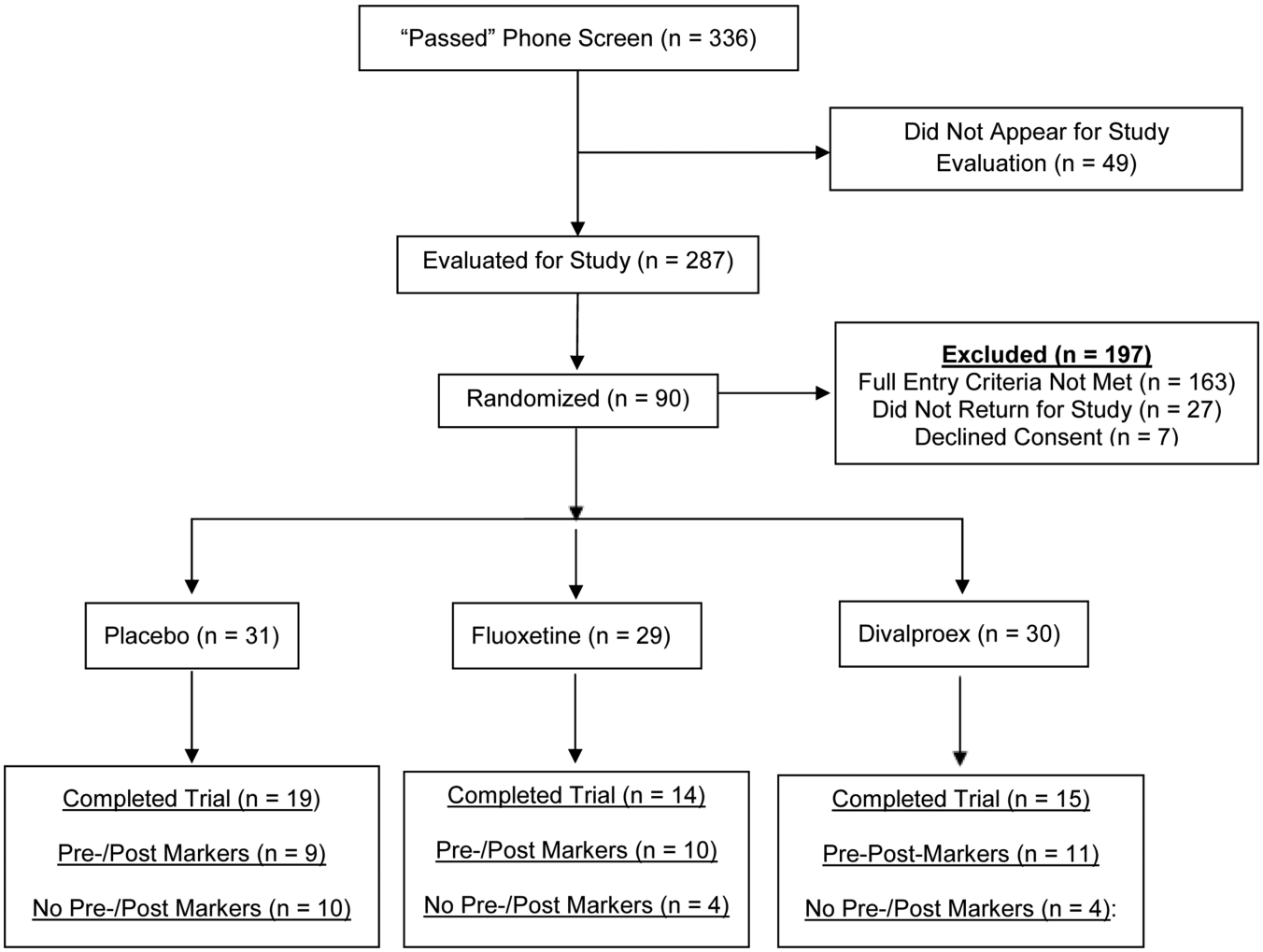

Figure 1.
CONSORT Diagram.

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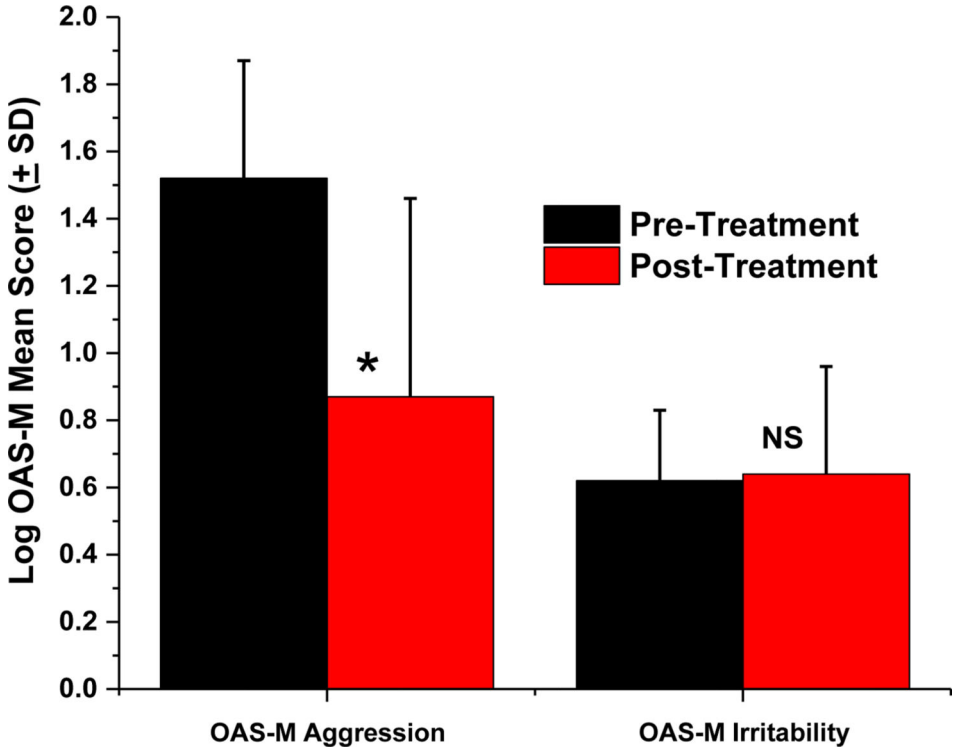

Figure 2.

Aggression outcome measures assessed pre-treatment and 12 weeks post-treatment in Current IED subjects. Only mean log OAS-M Aggression score is significantly lower post-treatment compared with its pre-treatment score; mean log OAS-M Irritability score post-treatment did not differ from the pre-treatment score. Changes in both OAS-M scores are required to document a clinical change in impulsive aggression (see text).

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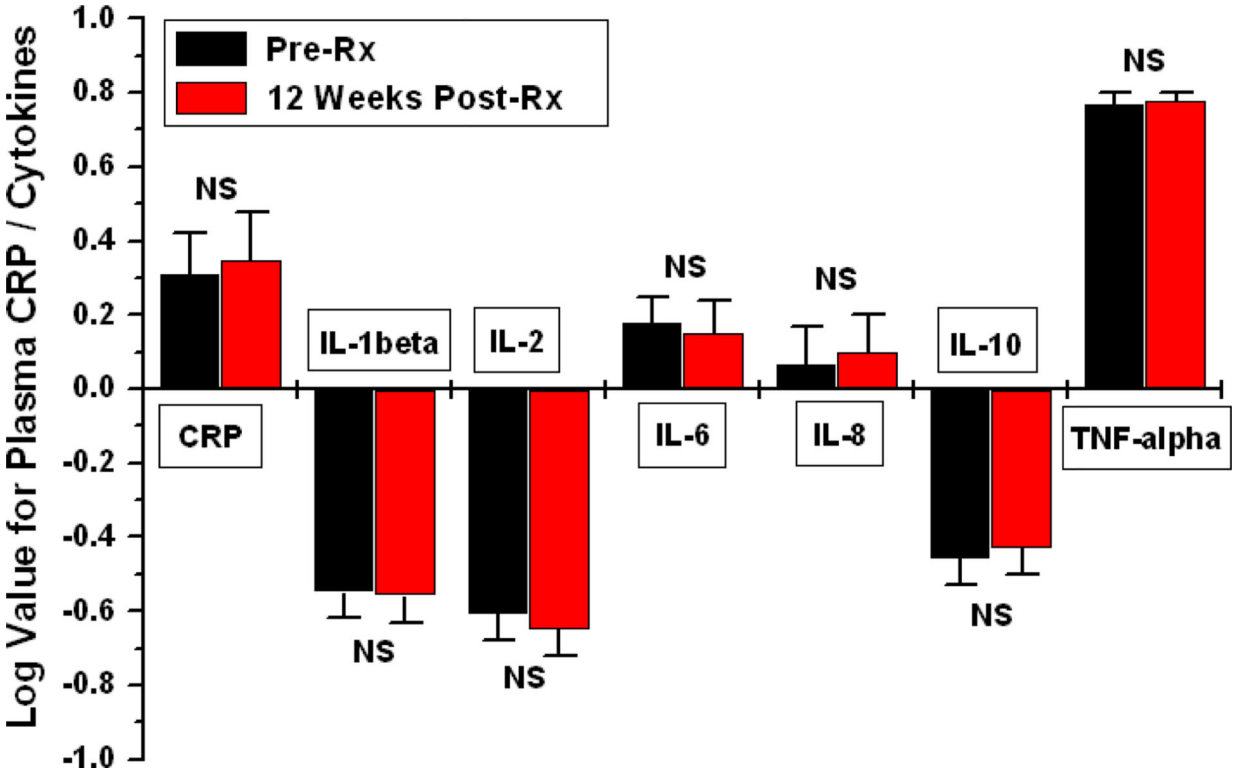

Figure 3.
Plasma CRP and Six Cytokines do not differ before treatment (Pre-Rx) and 12 weeks after treatment (Post-Rx).

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TABLE I

Syndromal and Personality Disorder Diagnoses in the IED Sample

	IED (N = 30)
Current Syndromal Disorders:	
Any Depressive Disorder	5 (16.7%)
Any Anxiety Disorder	6 (20.0%)
Any Substance Use Disorder	0 (0.0%)
Stress and Trauma Disorders	4 (13.3%)
Obsessive Compulsive Disorders	1 (3.3%)
Eating Disorders	1 (3.3%)
Non-IED Impulse Control Disorders	0 (0.0%)
Lifetime Syndromal Disorders:	
Any Depressive Disorder	18 (60.0%)
Any Anxiety Disorder	8 (26.7%)
Any Substance Use Disorder	16 (53.3%)
Stress and Trauma Disorders	7 (23.2%)
Obsessive Compulsive Disorders	1 (3.3%)
Eating Disorders	2 (6.7%)
Non-IED Impulse Control Disorders	2 (6.7%)
Personality Disorder:	
Cluster A	5 (16.7%)
Cluster B	17 (56.7%)
Cluster C	5 (16.7%)
Personality Disorder-NOS	10 (33.3%)

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TABLE II

Demographic, Clinical, Psychometric, and Marker Data Among Groups

	Placebo Group (N = 9)	Fluoxetine Group (N = 10)	Divalproex Group (N = 11)
Demographic / Clinical Variables[1]			
Age[2] (Years + SD)	29.9 + 5.2	38.1 + 7.1	34.1 + 8.8
Gender[3] (Male / Female)	3 / 6	4 / 6	8 / 3
Race[3] (White / AA / Non-White)	5 / 2 / 2	4 / 5 / 1	6 / 3 / 2
SES Score[2]	44.6 + 12.6	38.9 + 11.1	36.6 + 9.4
GAF Score[2]	54.5 + 7.9	51.4 + 7.4	54.3 + 6.5
Psychometric Variables[1]			
LHA Aggression Score[2]	19.1 + 3.2	20.1 + 4.3	19.3 + 4.4
BPA Aggression Score[2]	49.4 + 10.8	54.8 + 5.4	48.2 + 11.3
LHIB Impulsivity Score[2]	45.8 + 20.3	54.3 + 18.1	50.2 + 7.6
BIS Impulsivity Score[2]	66.8 + 6.0	68.3 + 11.5	76.1 + 6.4
OAS-M Aggression[4]	69.8 + 31.1	101.0 + 125.2	50.9 + 41.2
OAS-M Irritability[4]	6.1 + 2.2	6.1 + 1.8	5.7 + 1.7
Raw Marker Variables[1]			
CRP[4] (mg/L)	4.1 + 6.3	3.6 + 3.2	6.5 + 9.1
IL-1β[4] (pg/ml)	0.5 + 0.4	0.4 + 0.4	0.5 + 0.8
IL-2[4] (pg/ml)	0.5 + 0.5	0.5 + 0.5	0.2 + 0.1
IL-6[4] (pg/ml)	1.7 + 1.2	3.2 + 2.2	1.5 + 1.1
IL-8[4] (pg/ml)	1.2 + 0.9	1.7 + 1.1	7.1 + 18.4
IL-10[4] (pg/ml)	0.6 + 0.5	0.8 + 0.8	0.3 + 0.2
TNF-α[4] (pg/ml)	5.5 + 1.6	6.3 + 2.2	6.8 + 2.1
Marker Relevant Variables[1]			
Body Mass Index[2] (BMI)	26.7 + 6.1	36.0 + 12.6	33.1 + 5.9
State Depression[2] (BDI-II)	10.2 + 8.9	12.9 + 11.3	16.0 + 13.3

[1] All comparisons non-significant

[2] ANOVA on raw values

[3] Chi-square test

[4] ANOVA on log-transformed values.