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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 12-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.

1. 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 gray (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 30 subjects with DSM-5 IED who completed a 12 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

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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. Methods

2.1. Subjects

Thirty male and female subjects who completed a 12-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 (Fig. 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 ($\pm$ sd) for Study Subjects: 34.3 $\pm$ 8.9 years vs. Non-Study Subjects: 35.8 $\pm$ 9.1 years] or psychometric parameter [e.g., mean ($\pm$ sd) LHA Aggression scores for Study Subjects: 19.7 $\pm$ 3.5 vs. Non-Study Subjects: 19.4 $\pm$ 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 1) 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

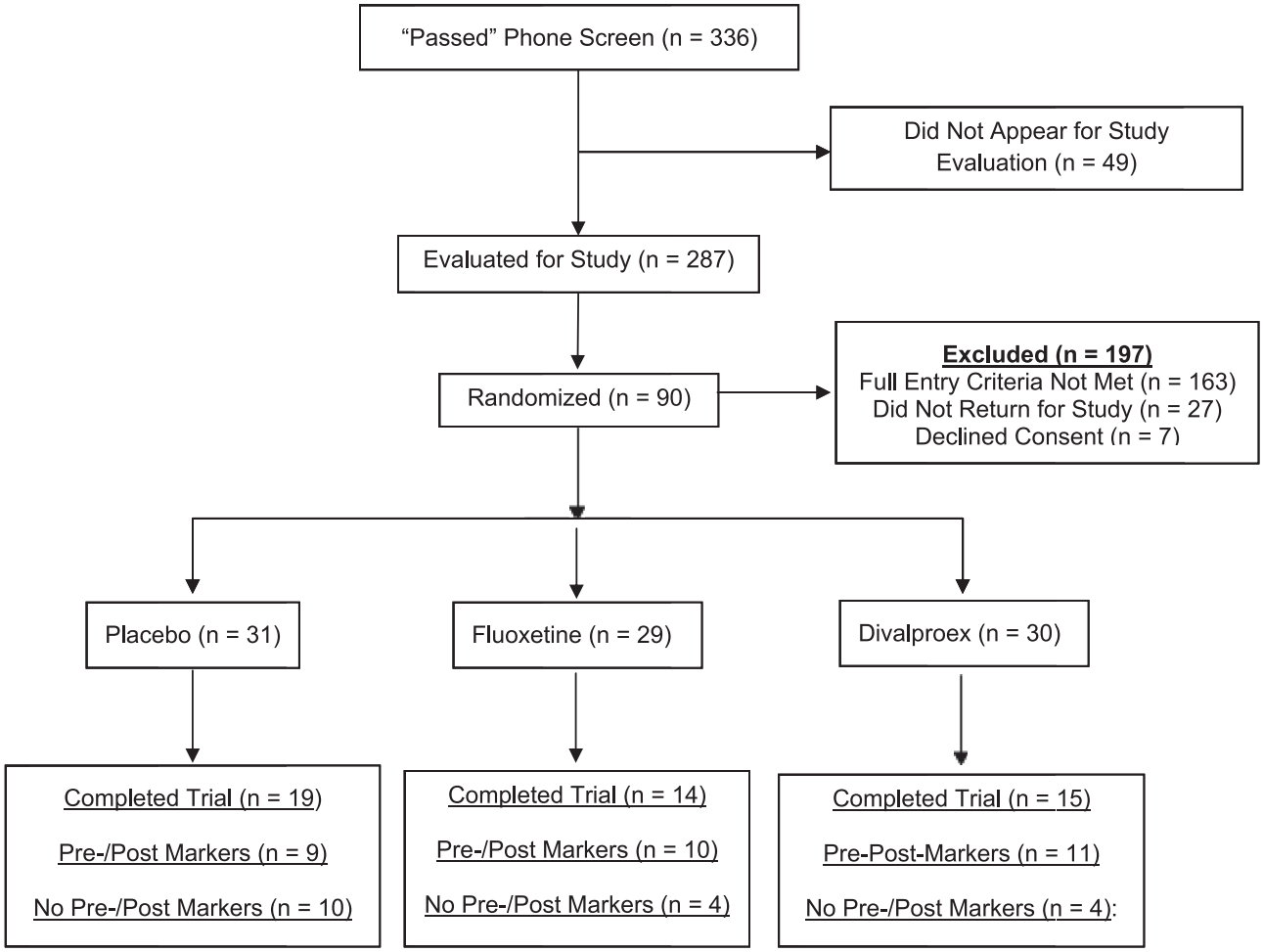

Fig. 1. CONSORT diagram.