

Improvement of anger at one week predicts the effects of sertraline and placebo in PTSD

Jonathan Davidson^{a,*}, Lawrence R. Landerman^a, Cathryn M. Clary^b

^a Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Trent Drive, Yellow Zone, Box 3812, 4th Floor, Room 4082B, Durham, NC 27710, USA

^b Pfizer Inc., NY 10017 USA

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Abstract

In previous work we demonstrated an early, robust and sustained effect for sertraline vs placebo on irritability and anger in subjects with PTSD. In this report, we explore the same dataset to assess whether a clinician might usefully predict ultimate response to sertraline, on the basis of its effect upon anger after one week.

Three hundred and eighteen subjects were assessed. Outcome was measured by whether or not the score was reduced by at least 50% from baseline. Ordinary least squares regression was used to estimate the effects of change in anger at one week. Logistic regression was applied to estimate the effects on odds of a 50% drop in score. Cut points were developed for one-week change scores on anger for sertraline and placebo. The best cut point was selected as predictive of non-response, i.e. a cue suggesting that treatment switch would be in order. An increase in anger of 30% at one-week best predicted the likelihood of not responding to treatment in both the drug and placebo groups. Twenty-five percent of all non-responders were incorrectly identified, while only 7% of all improvers were incorrectly categorized as non-responders using this cutoff. Our findings imply that, for patients similar to those in this study, an increase in anger after one week of treatment might be one factor to consider when making a decision about continuation of the medication.

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1. Introduction

In a study which looked at the effects of sertraline and placebo on individual symptoms of PTSD, we noted a broad-spectrum effect on practically all symptoms, with notable improvement of irritability/anger after one week, which was sustained throughout the remaining period of treatment. The magnitude of this change was significantly greater for sertraline than placebo at every visit, starting at week one. In further exploring the early improvement on anger, we found it explained some of the subsequent improvements in other symptoms (Davidson et al., 2002). The robust nature of this finding led us to ask whether the early changes in anxiety/irritability

could perhaps serve as a predictor of likely response or non-response over the ensuing weeks.

We therefore present a report which assesses the importance of early change in anger after one week of treatment. In particular, we wish to know whether, on the basis of change in anger at one week, the clinician could determine whether or not the likelihood of an unsuccessful outcome was strong enough that a change in treatment might be considered. In other words, we are concerned mostly with early detection of non-response at 12 weeks, defined as a reduction of 50% or more in PTSD symptoms.

2. Materials and methods

2.1. Study design and procedures

The samples were obtained from two almost identical clinical studies of sertraline vs placebo in posttraumatic

* Corresponding author. Tel.: +1-919-684-2880; fax: +1-919-684-8866.

E-mail address: jonathan.davidson@duke.edu (J. Davidson).

stress disorder (Brady et al., 2000; Davidson et al., 2001), differing in the length of placebo lead-in (one or two weeks respectively). Subjects were male and female outpatients aged at least 18 years, and met criteria for PTSD, based upon the Diagnostic and Statistical Manual of Mental Disorders Revised, 3rd Edition (DSM-III-R) (American Psychiatric Association, 1987). At least six months illness was required, along with a minimum score of 50 on the Clinician Administered PTSD Scale version that assesses symptoms over the past week (CAPS-II) (Blake et al., 1995). Other inclusion criteria, which are listed in full detail elsewhere (Brady et al., 2000; Davidson et al., 2001) included absence of psychotropic drugs for 2 weeks, non-pregnant status, absence of lifetime bipolar, schizophrenia or other psychotic disorder, or alcohol or substance use disorders within six months, clinically unstable disorder and use of cognitive behavioral therapy during the trial. With respect to comorbid depression, investigators used clinical judgment to determine which was primary (i.e. at the time of study, was the most clinically salient). Such judgment was based on information obtained via clinical history and the numerous structured rating scales. It was necessary for PTSD to be the primary disorder. Each study had received institutional review board approval, and written informed consent was obtained from all subjects.

Treatment was preceded by a one to two week single-blind placebo lead-in, following which subjects were randomized to receive sertraline or placebo for 12 weeks, on a double-blind basis. Among the various assessments, the Davidson Trauma Scale (DTS) (Davidson et al., 1997) was one of the main self-rating scales for assessing PTSD symptom severity.

2.1.1. Statistical methods

In the initial analyses we examine (1) whether decline in anger/irritability between baseline and week one predicts a favorable outcome after 12 weeks; (2) whether the impact of decline in anger is the same in the sertraline and placebo groups. Based upon findings in (1) and (2), we estimate the sensitivity and specificity Insel and Goodwin (1983) of various cut points for early change in anger, and then present an empirically-based threshold for initial (i.e. one week) change in anger, which can be used as an indication that the likelihood of a successful outcome is sufficiently small that a change in treatment could be considered.

2.1.2. Sample

Forty-three subjects were excluded due to insufficient baseline anger and 24 were dropped for additional reasons, as follows. From an original sample of 385, whose demographic and clinical characteristics were described elsewhere (Brady et al., 2000; Davidson et al., 2001), we selected 342 respondents with a score of 2 or more on

the DTS anger item at baseline. These included 173 in the treatment group, and 169 controls. 23.9% were male and 76.1% female; 84.9% were white, 11.0% black, 2.6% Asian and 2.5% other. 10.6% were between ages 18–24, 27% between 25–34, 31.8% between 35–44, 29.9% between 45–64, 0.7% 65 or greater. Fifty-one (of 342) sample members dropped out of the study prior to week 12. Eight of these provided no follow-up data on PTSD symptoms, and were dropped from the analyses. For the remaining 43, we imputed the week 12 summary symptom measure by carrying the last observation forward. In preliminary analyses, we regressed imputed and unimputed versions of the summary symptom measure on (baseline to wave 1) change in anger. Results were the same across versions. An additional 8 respondents were dropped because they were missing on summary symptom data at baseline, and 8 more respondents were dropped because they were missing on (baseline or week 1) measures of anger needed to construct change in anger. We were left with an analysis sample of 318. Of the 24 subjects dropped for missing data 19 (11%) belonged to the treatment group, while 5 (3.1%) belonged to the placebo group.

2.1.3. Measures

2.1.3.1. Change in anger. In initial analyses, we measured change in anger as (baseline to week 1) raw change in PTSD score on anger, and percent change on the same measure. For the analyses described below, results using the measure of raw change were virtually identical to those using percent change. We report results for the percent change measure below. While models using both measures had adequate fit (Hosmer and Lemeshow, 1989), those based on the percent change measure had slightly better scores on this and other (Somers's D, Gamma) standard measures of model fit (Cox and Snell, 1989; SAS Institute, 1990). Anger was assessed by summing the total frequency (0–4) and severity (0–4) scores for item 14 on the DTS. The scale asks subjects to assess whether they have experienced outbursts of anger or been irritable in the past week. The specific wording for this question is as follows: “have you been irritable or had outbursts of anger?” The frequency ranges from not at all (0), once only (1), 2–3 times (2), 4–6 times (3), and every day (4). The severity choices are: not at all distressing (0), minimally distressing (1), moderately distressing (2), markedly distressing (3), and extremely distressing (4). The total score thus ranges from 0–8.

2.1.3.2. PTSD score at week 12. For the analyses below, the summary PTSD score was first recalculated with the anger item excluded. Two dependent variables were then created. The first is percent change in total PTSD (minus the anger item, i.e. the 16 remaining items) between baseline and week 12. Assuming the relationship between

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