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Timing of clinical improvement and symptom resolution in the treatment of major depressive disorder

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Abstract

The goal of the present work is to assess for the relationship between the timing of clinical improvement and the resolution of depressive symptoms in Major Depressive Disorder (MDD). 182 MDD outpatients (40.5±9.7 years; 53.8% female) who responded following an 8-week, 20 mg, open trial of fluoxetine were included in the analysis. The symptoms questionnaire (SQ) and Beck hopelessness scale (BHS) were also administered to 83 and 153 of these patients, respectively. Onset of clinical improvement was defined as a 30% decrease in 17-item Hamilton depression scale (HDRS-17) scores. Controlling for baseline symptom severity, we then assessed for the relationship between the timing of clinical improvement and depressive symptom at endpoint. Earlier clinical improvement in responders predicted lower HDRS-17, BHS, SQ-depression, SQ-anxiety, but not SQ-somatic symptom or SQ-anger/hostility scores at week 8. This was true regardless of whether improvement was defined as a continuous measure (30% decrease in symptom severity), as a dichotomous measure (clinical response occurring in the first two weeks of treatment). In conclusion, earlier clinical improvement with fluoxetine treatment is predictive of greater symptom resolution at endpoint. Further studies exploring the impact of various treatment modalities and placebo on the timing of clinical improvement and symptom resolution in MDD are warranted.

Keywords: Fluoxetine; Symptom; Residual; Onset

1. Introduction

An ever-increasing number of reports examine the relationship between the timing of improvement and outcome in the pharmacotherapy of major depressive disorder (MDD). On one hand, there have been studies suggesting that patients who experience a clinical response during the first two weeks of treatment that is sustained throughout treatment may not be responding to the antidepressant per se, but instead they may be displaying a "placebo" pattern of response (Quitkin et al., 1984, 1987; Goodnick et al., 1987; Dunlop et al., 1990; Stewart et al., 1998; McGrath et al., 2000; Nierenberg et al., 2004). In support of this argument, exclusion of early responders in a pooled, post hoc analysis of 3 double-blind, placebo-controlled trials of imipramine resulted in the augmentation of the difference in outcome between imipramine and placebo (Khan et al., 1989). In

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parallel, there is some evidence that these patients may not be afforded the same long-term prophylaxis from continuing on antidepressant treatment than patients who experience a delayed (occurring after week 2) and sustained clinical response (Stewart et al., 1998; McGrath et al., 2000; Nierenberg et al., 2004).

On the other hand, regardless of whether the improvement is attributable to "true" drug or placebo effects, clinical response during the first two weeks of treatment is highly predictive of clinical response at endpoint (Coryell et al., 1982; Katz et al., 1987; Nagayama et al., 1991; Pollock et al., 1993; Stassen et al., 1998, 1999; Szegedi et al., 2003) and vice versa (Nierenberg et al., 1995). In addition, a recent meta-analysis of published, placebo-controlled trials of antidepressants for MDD reports a numerically greater difference in depressive symptom improvement during the first two weeks of treatment than at endpoint (Posternak and Zimmerman, 2005). To complicate matters further, certain symptoms may improve earlier than others (Katz et al., 1987, 2004; Tollefson and Holman, 1994; Casper et al., 1994; Worthington et al., 1995; Boyer et al., 2000; Sonawalla et al., 2001; Tomarken et al., 2004) which would suggest that measures of global severity may not be as sensitive at detecting early antidepressant effects as symptom-specific measures. However, one clear limitation of these studies has been the lack of a placebo comparator. Therefore, until recently, it was not possible to estimate whether there were any differences in early symptom resolution between drug and placebo. A recent study suggests that the onset of clinical response in depression occurs earlier-on for several symptoms including depressed mood, psychomotor retardation and hostility in antidepressant than placebo-responders, and as early as the first two weeks (Katz et al., 2004). In addition, there is emerging data to suggest that earlier response to antidepressant treatment that is sustained may also confer an advantage with respect to the restoration of psychosocial functioning in depression (Papakostas et al., 2004). However, whether an early or earlier response confers an increased likelihood of greater endpoint symptom resolution than a late or later response in depression is unclear since, to our knowledge, studies examining the relationship between timing of clinical improvement and residual symptomatology in depression have yet to be published. Establishing such a relationship would be important since it would add to our existing knowledge regarding the relationship between the timing of symptom improvement and the *probability of experiencing* a clinical response (Nierenberg et al., 1995) to include the relationship between the timing of symptom improvement and the *quality* of the clinical response (i.e. lower residual symptomatology) in MDD. Therefore, in the present study we assessed for the relationship between the timing of clinical improvement and the degree of symptom resolution during the treatment of MDD with fluoxetine.

2. Methods

Outpatients, ages 18–65 years, who met criteria for a current major depressive episode according to the Structured Clinical Interview for DSM-III-R (SCID-P; Spitzer et al., 1989), who were medication-free for at least two weeks, with a baseline 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960) score $\geq$ 16 were eligible to enroll in an 8-week, fixed-dose, open-label trial of 20 mg fluoxetine conducted at the Massachusetts General Hospital (MGH) Depression Clinical and Research Program (DCRP). Patients were recruited through radio advertisements, newspaper advertisements or colleague referrals. Patients who were non- or partial-responders to this open trial were enrolled in a four-week, double-blind, triple-dummy, randomized study comparing high dose fluoxetine with augmentation of fluoxetine with either desipramine or lithium. The present study focuses on the first phase of the trial.

The following subjects were excluded:

a) Pregnant women and women of child bearing potential who were not using a medically accepted means of contraception.
b) Patients with serious suicidal risk or serious, unstable medical illness.
c) Patients with a history of seizure disorder.
d) Patients with the DSM-III-R diagnoses of organic mental disorders, substance use disorders, including alcohol, active within the last year, schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, or antisocial personality disorder.
e) Patients with a history of multiple adverse drug reactions or an allergy to the study drugs.
f) Patients with mood congruent or mood incongruent psychotic features, or with current use of other psychotropic drugs.
g) Patients with clinical or laboratory evidence of hypothyroidism.
h) Patients whose depression had failed to respond in the past to a trial of either higher doses of fluoxetine (60–80 mg/day), or to the combination of fluoxetine and desipramine, or the combination of fluoxetine and lithium.