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Recovery and subsequent recurrence in patients with recurrent major depressive disorder

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ABSTRACT

In contrast to "remission" from an episode of major depressive disorder (MDD), for which there is general agreement in the literature, the optimal definition of "recovery" from MDD is uncertain. Previous definitions of recovery have used inconsistent thresholds for symptom severity and duration of wellness. To address the effects of duration and degree of recovery from an episode of MDD on recurrence risk, and the impact of maintenance antidepressant treatment on recurrence, we analyzed 258 patients from a randomized, double-blind study of outpatients with recurrent MDD. All patients had responded to 8½ months of venlafaxine extended release and were subsequently randomized to receive venlafaxine ER or placebo during 2 consecutive 12-month maintenance phases. Four definitions of recovery were used to evaluate recovery rates and time to recurrence: (1) 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) total score $\leq$3 with duration $\geq$120 days; (2) $HAM\text{-}D_{17}$ $\leq$3 with duration $\geq$56 days; (3) $HAM\text{-}D_{17}$ $\leq$7 with duration $\geq$120 days; and (4) $HAM\text{-}D_{17}$ $\leq$7 with duration $\geq$56 days. Recovery definitions using lower symptom severity and longer duration thresholds produced lower rates of recurrence. Patients on placebo were more likely to have a recurrence than patients on venlafaxine ER, with hazard ratio (HR) ranging from 2.5 among patients who recovered by the most relaxed criteria (definition 4), to 5.3 among patients who recovered by the most stringent criteria (definition 1). We conclude that protection against recurrence derives from the degree and duration of recovery, particularly for patients maintained on antidepressant medication.

1. Introduction

The goal of antidepressant treatment of major depressive disorder (MDD) is recovery from the episode. Recovery is thought to provide the best protection against the return of a new depressive episode (ie, recurrence), and is generally regarded as maintaining remission (usually defined as a rating scale score below a specific threshold) for a given period of time. However, specific time- and symptom level criteria used to define recovery vary considerably between studies. Enhancing the definition of recovery would directly impact clinical care, as it would inform decisions about whether to augment a patient's current treatment, and when discontinuation of antidepressant medication is appropriate.

The MacArthur Foundation task force proposed 3 different sets of operational criteria for recovery, based on different assessment scales and using different durations [i.e., Schedule for Affective Disorders and Schizophrenia (Spitzer et al., 1978) $\leq$2 symptoms for at least 8 weeks, 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$; Hamilton, 1960) $\leq$7 for at least 6 months, and Beck Depression Inventory (Beck et al., 1961) $\leq$8 for at least 4 months] (Frank et al., 1991). The definition used in the National Institute of Mental Health Collaborative Depression Study specified the presence of no symptoms or 1–2 symptoms to a mild degree for a minimum of 8 consecutive weeks (Keller et al., 1983; Solomon et al., 1997). The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (DSM-IV-TR) defines the end of a depressive episode as a period of at least 2 months during which full criteria for a major depressive episode are not met, although this relatively weak definition allows for significant ongoing symptomatology (American Psychiatric Association, 1994). Other studies of long-term outcomes defined recovery

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using a minimum duration of 3 months (Spijker et al., 2002; Yiend et al., 2009).

Recurrence of a depressive episode after recovery is thought to be related to both to the level of symptoms present during recovery, and the duration of the recovery period. The presence of residual symptoms is associated with an increased risk of recurrence and a shorter time to recurrence (Judd et al., 1998, 2000), whereas a longer duration of recovery is associated with a lower risk of recurrence (Solomon et al., 2000). Thus, the criteria used to define recovery may have implications when considering the impact of recovery on long-term outcomes. For example, in a recent analysis of outcomes during 10 years of follow-up of patients with MDD, recovery defined using a duration of 4–6 months was associated with a median time to subthreshold recurrence (no longer meeting criteria for recovery, but not meeting full MDD criteria) of 3 years, whereas a duration of 2 months was associated with subthreshold recurrence within 1.5 years for more than half of patients (Furukawa et al., 2008).

Maintenance treatment with antidepressants is effective in reducing rates of recurrence as well as increasing time to recurrence in patients with a history of recurrent depression (Lepine et al., 2004; Hochstrasser et al., 2001; Kocsis et al., 2007; Keller et al., 2007a,b; Hansen et al., 2008). However, very little placebo-controlled research has examined whether gradations of residual symptoms in patients meeting remission criteria (i.e., HAM-$D_{17} \leq 7$) or whether variability in the duration of sustained remission differentially impact rates of recurrence. It is also unknown whether antidepressant treatment provides differing levels of protection against recurrence among patients achieving different levels of recovery. Exploring these questions are important for understanding differential recurrence risks among "recovered" patients, and to determine the degree to which maintenance antidepressant treatment provides added benefit in preventing recurrences.

1.1. Objectives of the study

This analysis was conducted to assess rates of recovery during up to 2 years of maintenance treatment with venlafaxine extended release (ER) or placebo in patients with recurrent MDD, and to evaluate the effects of different definitions of recovery on time to and probability of recurrence. We hypothesized that a definition of recovery incorporating lower thresholds for symptom severity and a longer duration at that threshold would predict lower recurrence rates than the current standard definition of recovery. We also expected that the risk of depression recurrence between venlafaxine ER and placebo would be more evident in patients with more fragile recoveries (ie, short duration; higher symptom scores), as these patients may be most vulnerable to recurrence and therefore most in need of continued antidepressant treatment.

2. Methods

We conducted a post hoc analysis on the randomized sample of 258 patients from the Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) trial (Kocsis et al., 2007; Keller et al., 2007a, b), a multiphase, double-blind trial of adult outpatients with recurrent MDD. The study was conducted in accord with the Declaration of Helsinki and its amendments. The study was reviewed and approved by the ethics review body responsible for each site, and all participants provided written informed consent prior to any study procedures being performed.

A schematic diagram of the PREVENT trial was previously published (Thase et al., 2011). In the PREVENT trial, patients were randomly assigned to 10-week double-blind acute treatment with either flexible-dose venlafaxine ER (75–300 mg/d) or fluoxetine (20–60 mg/d). Patients who met criteria for response (HAM-D_{17} total score $\leq$12 and $\geq$50% reduction from acute phase baseline) at the end of acute treatment entered a 6-month continuation phase on the same double-blind medication. Responders at the end of the continuation phase were enrolled in the first of 2 consecutive double-blind 12-month maintenance phases (A and B). There were 258 patients in the venlafaxine ER group who were randomly assigned to venlafaxine ER or placebo and were evaluable for efficacy during maintenance phase A. Patients responding to venlafaxine ER at the end of maintenance phase A were again randomized to receive either venlafaxine ER or placebo during maintenance phase B. Non-relapsing placebo-treated patients from phase A continued on placebo in phase B. Data from both maintenance phases A and B will be used in the current analysis. Each participating clinical site for the PREVENT trial received approval to conduct the study from their respective institutional review board.

2.1. Patients

Eligible participants were outpatients $\geq$18 years of age with recurrent MDD (defined as $\geq$3 lifetime major depressive episodes, with $\geq$2 episodes including the current episode occurring in the past 5 years, and with an interval $\geq$2 months between the end of the previous episode and the beginning of the present episode). Episode onset and resolution were defined per Structured Clinical Interview for DSM-IV-TR criteria (First et al., 2007). Patients were required to have a HAM-D_{17} total score $\geq$20 at screening and $\geq$18 at randomization and meet DSM-IV-TR criteria for major depressive episode for $\geq$1 month prior to study entry.

Major exclusion criteria included failure to respond to an adequate trial of fluoxetine, venlafaxine, or venlafaxine ER during the current episode of MDD; known hypersensitivity, previous intolerance, or unsuccessful treatment with venlafaxine or fluoxetine; previous treatment resistance, defined as having failed in the past 3 years: (a) $\geq$3 previous adequate trials of $\geq$2 classes of antidepressants; (b) electroconvulsive therapy; or (c) 2 adequate trials of psychotherapy; history/presence of bipolar disorder or eating disorder (if not remitted for 5 years), or significant axis II disorders; or a primary diagnosis of panic disorder, obsessive compulsive disorder, generalized anxiety disorder, social phobia, or posttraumatic stress disorder within 6 months prior to screening.

At acute phase baseline, 821 patients were randomized to receive venlafaxine ER, 530 of whom entered into the continuation phase. Patients included in the current analyses had all responded to the acute 10-week treatment course of flexibly dosed venlafaxine ER, and had maintained their response during the 6-month continuation phase.

2.2. Study assessments

Patients visited the study sites weekly or biweekly during the acute treatment phase, and monthly throughout the 6-month continuation phase and both 1-year maintenance phases. The HAM-D_{17} was performed at each visit throughout the study. Vital signs and adverse events (AEs) were collected at each visit, and laboratory evaluations were performed at screening, at the end of the continuation phase, and at the last visit of each maintenance phase. Detailed information on study protocol and assessments has been previously published (Keller et al., 2007b).