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Psychosocial outcomes in patients with recurrent major depressive disorder during 2 years of maintenance treatment with venlafaxine extended release

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Abstract

Background—Psychosocial outcomes from the *Prevention of Recurrent Episodes of Depression with Venlafaxine ER for Two Years (PREVENT)* study were evaluated.

Methods—Adult outpatients with recurrent major depressive disorder (MDD) and response or remission following 6-month continuation treatment with venlafaxine extended release (ER) were randomized to receive venlafaxine ER or placebo for 1 year. Patients without recurrence on venlafaxine ER during year 1 were randomized to venlafaxine ER or placebo for year 2. Psychosocial functioning was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q), Life Enjoyment Scale—Short Version (LES-S), Social Adjustment Scale—Self-Report (SAS-SR) total and individual factors, Short Form Health Survey (SF-36) (vitality, social functioning, and role function-emotional items), and Longitudinal Interval Follow-up Evaluation (LIFE).

Results—At year 1 end, better overall psychosocial functioning was seen among patients randomly assigned to venlafaxine ER ($n=129$) vs placebo ($n=129$), with significant differences at end point on SF-36 role function-emotional, Q-LES-Q, and SAS-SR total, and work, house work,

social/leisure, and extended-family factor scores ($p = 0.05$). At year 2 end, significant differences favored venlafaxine ER ($n=43$) vs placebo ($n=40$) on SF-36 vitality and rolefunction-emotional, Q-LES-Q, LES-S, LIFE, and SAS-SR total, social/leisure, and extended-family factor scores ($p = 0.05$).

Limitations—Patients with chronic MDD or treatment resistance were excluded and long-term specialist care was a financial incentive for treatment compliance. Discontinuation-related adverse events may have compromised the integrity of the treatment blind.

Conclusions—For patients with recurrent MDD, 2 years' maintenance therapy with venlafaxine ER may improve psychosocial functioning vs placebo.

Keywords

Venlafaxine extended release; Psychosocial outcomes; Major depressive disorder; Maintenance treatment

1. Introduction

Major depressive disorder (MDD) is a chronic and recurrent psychiatric condition, with an estimated lifetime prevalence of 16.2% among United States adults (Judd et al., 2008; Kessler et al., 2003). Among participants in the Collaborative Depression Study (CDS), 71.8% of patients with MDD had experienced at least 1 other depressive episode prior to study enrollment (Judd et al., 2008). Episodes of MDD, marked by core depressive emotional and physical symptoms, are also accompanied by significant impairments in a broad range of psychosocial functions, including marital, parental, professional, and social dimensions (Kessler et al., 2003; Miller et al., 1998). MDD-related symptoms and impairments, in turn, are linked to disability and decreased quality of life (Kessler et al., 2003; Ormel et al., 1994). Those closest to the patient, including family members, display impaired psychosocial functioning as well (Keitner et al., 1995), likely reflecting to some degree the demands related to coping with an illness in a loved one. Moreover, the immediate community and broader society bear enormous economic burdens related to impaired psychosocial functioning with MDD, arising from missed work days, increased health care resource use, mortality costs, and academic and professional underperformance (Greenberg et al., 2003).

The long-term impairments in social functioning experienced by patients with MDD are becoming better characterized (Judd et al., 2000, 2008; Kennedy et al., 2007). When clinically significant depressive symptoms resolve, impairments in psychosocial functioning typically become less severe, but nevertheless persist over time, often alongside residual subthreshold depressive symptoms. In the longitudinal CDS study, "Fair function—mild impairment" was seen in 27% to 29% of assessed follow-up months and "Poor function—moderate impairment" was seen in 19% to 23% of assessed follow-up months (Judd et al., 2008). The most severe functional impairments were found in the area of work and employment, where individuals with MDD were "Virtually unable to carry out work role function" for 21.0% of the follow-up months. Similarly, in a comprehensive literature review from Kennedy et al. (2007), longitudinal follow-up of patients with MDD has repeatedly revealed broad psychosocial impairments that persist after improvement in clinical MDD symptoms. Importantly, worsening of residual psychosocial impairments appears to predict the relapse or recurrence of MDD (Solomon et al., 2004; Vittengl et al., 2009), contributing to a poor long-term prognosis.

The goals of therapy in MDD should therefore include not only remission of core depressive symptoms but also a return to premorbid levels of social functioning (Trivedi, 2001). Some

evidence from controlled trials suggests that psychosocial functioning can improve with acute antidepressant treatment (Miller et al., 1998; Papakostas et al., 2004). In the report from Papakostas et al. (2004), patients with MDD given a fixed dose of open-label fluoxetine for 8 weeks displayed significant improvements in overall psychosocial functioning. Those whose depressive symptoms responded or remitted had significantly better psychosocial functioning at end point than those who did not respond to therapy; a greater number of residual depressive symptoms at end point predicted worse psychosocial functioning. One report further indicates modest improvement in psychosocial functioning with antidepressant maintenance therapy using sertraline (Kocsis et al., 2002). Some researchers (Kennedy et al., 2007) have suggested that better longer-term psychosocial outcomes are related to more vigorous continuation therapy, marked by receiving care from a specialist, and combination treatment with antidepressant medication and psychotherapy, compared to outcomes for patients who receive typical, less aggressive continuation treatment.

Although it is known that antidepressant maintenance therapy is crucial for preventing MDD relapse and recurrence, research is still required for a full understanding of the impact of such treatment on long-term psychosocial functioning. The *Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT)* study was a prospective, 3-year, longitudinal, randomized, placebo-controlled trial designed to assess the long-term efficacy and safety of the serotonin–norepinephrine reuptake inhibitor venlafaxine extended release (ER) for the prevention of MDD recurrence in adult outpatients with recurrent unipolar MDD. This multiphase trial included 2 consecutive, year-long, placebo-controlled maintenance phases (A and B). Previous published reports have described efficacy and safety outcomes observed in the trial, including outcomes on psychosocial measures during acute and continuation phase treatment (Keller et al., 2007a, b; Kocsis et al., 2007). In the current report, we describe the psychosocial outcomes observed in patients with recurrent MDD who received up to 2 years of maintenance therapy with venlafaxine ER or placebo.

2. Methods

2.1. Study design

The aim of the present analysis was to examine psychosocial outcomes in patients with recurrent depression given maintenance therapy with venlafaxine ER or placebo as part of the PREVENT trial. Fig. 1 illustrates the flow and timing of the various study phases. The trial was conducted in accordance with the Declaration of Helsinki and its amendments. The internal review boards of each study site approved the protocol and all patients provided written informed consent prior to study enrollment. Only psychosocial outcomes in the placebo and venlafaxine ER treatment groups from maintenance phases A and B are presented in this paper.

For the acute phase, patients were randomly assigned to receive 10 weeks of double-blind treatment with either venlafaxine ER (75 to 300 mg/day) or fluoxetine (20 to 60 mg/day). For the 6-month continuation phase, patients achieving a satisfactory therapeutic response (17-item Hamilton Rating Scale for Depression [HAM-D₁₇] (Hamilton, 1960) total score 12 and 50% decrease from acute-phase baseline) or remission (HAM-D₁₇ 7) during the acute phase could continue treatment with the highest tolerated dose of venlafaxine ER or fluoxetine achieved during the acute phase. Patients who continued to demonstrate a satisfactory therapeutic response or remission at the end of the continuation phase could enter the first of two 12-month maintenance phases.

For maintenance phase A, patients on venlafaxine ER underwent double-blind randomization to receive either venlafaxine ER or placebo (placebo A) for 12 months; patients continuing to respond to fluoxetine at the end of the continuation phase remained on fluoxetine in maintenance phase A for 12 months. For maintenance phase B, patients continuing to respond to venlafaxine ER at the end of maintenance phase A were rerandomized to either venlafaxine ER or placebo (placebo B) for an additional 12 months. Patients continuing to respond to placebo or fluoxetine at the end of maintenance phase A were continued on placebo (placebo A) or fluoxetine, respectively, for an additional 12 months.

2.2. Patients

2.2.1. Inclusion criteria—Detailed inclusion/exclusion criteria for this trial have previously been described (Keller et al., 2007a, b; Kocsis et al., 2007). Briefly, eligible patients were men and women 18 years of age who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 2000) criteria for MDD based on a structured diagnostic interview and had recurrent depression, defined as 3 episodes of major depression, with 2 episodes in the past 5 years, including the current episode, with an interval 2 months between the end of the previous episode and the beginning of the present episode; a HAM-D₁₇ total score 20 at screening and 18 at randomization; depressive symptoms for 1 month prior to study entry; in otherwise good medical and psychiatric health, based on medical/psychiatric history, structured diagnostic interview, physical examination, and screening laboratory results; and able to provide written informed consent prior to study entry.

2.2.2. Exclusion criteria—Patients were excluded if they had a history of failure to respond to an adequate trial of fluoxetine, venlafaxine, or venlafaxine ER during the current episode of MDD; treatment resistance, defined as having failed in the past 3 years: (a) 3 previous adequate trials of 2 classes of antidepressant medications, or (b) electroconvulsive therapy (ECT), or (c) 2 adequate trials of psychotherapy empirically demonstrated to be effective (eg, behavior therapy, behavior-marital therapy); and known hypersensitivity to venlafaxine or fluoxetine. Patients with a known hypersensitivity to venlafaxine or fluoxetine were not eligible to participate, as were those the investigator judged to be at risk for suicide; and women of childbearing age who were breastfeeding, pregnant, or not using a medically acceptable method of birth control. Patients using any of the following were not permitted to participate: any investigational drug, antipsychotic drug, fluoxetine, or a monoamine oxidase inhibitor (MAOI) within 30 days, or ECT within 3 months of randomization; any antidepressant, other than fluoxetine or an MAOI, within 14 days of randomization; any anxiolytic or sedative-hypnotic drug (except chloral hydrate or zaleplon), sumatriptan (and similar agents) or any other psychotropic drug or substance within 7 days of randomization; any nonpsychopharmacologic drug with psychotropic effects within 7 days of randomization unless a stable dose of the drug had been maintained for 1 month prior to randomization; and chronic use of benzodiazepines whereby withdrawal could not be completed >2 weeks prior to randomization.

2.3. Psychosocial function assessments

Psychosocial functioning was assessed using 5 scales: Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993), Life Enjoyment Scale, Short Version (LES-S) (Fawcett et al., 1983), Social Adjustment Scale—Self-Report (SAS-SR) (Weissman and Bothwell, 1976) total and individual factors, Short Form Health Survey (SF-36) (Ware and Snow, 1993) total and individual factors, and the Longitudinal Interval Follow-Up Evaluation (LIFE) (Keller et al., 1987). During the maintenance phases, all 5

scales were administered every 3 months (ie, study days 250 [maintenance phase A baseline], 340, 430, 520, 610, 700, 790, 880, and 970).

2.3.1. Q-LES-Q—The 16-item Q-LES-Q-short version used in the present investigation is a self-rated questionnaire consisting of the 14 items that comprise the general activities subscale of the full-length, 93-item Q-LES-Q scale (Endicott et al., 1993), as well as 2 items assessing satisfaction with medication and overall life satisfaction. Each item is scored on a 5-point scale (very poor to very good); higher scores indicate greater satisfaction and enjoyment (range: 14 [worst] to 70 [best]) and here are presented as percent of total possible score. In a community sample of individuals with no history of mental illness, mean (SD) percent total Q-LES-Q general activities score was 81.8 (11.3) (Schechter et al., 2007).

2.3.2. LES-S—The LES-S consists of items 1 through 25 of the LES, a self-rated scale that measures life enjoyment (type and degree of enjoyment) based on ratings of imagined pleasure in response to described fictional situations encompassing various areas of daily functioning, including parenting, work, sexuality, personal activity, and social activity (Fawcett et al., 1983). Items are rated on a 5-point scale (1 — “no pleasure at all” to 5 — “extreme and lasting pleasure”). In samples of normal subjects from the community, average item scores have been 3.6 to 3.8 (Fawcett et al., 1983). In this investigation, LES-S item scores were summed to determine a total score.

2.3.3. SAS-SR—The SAS-SR is a self-rated scale that assesses functioning across 9 domains, including work, housework, student/ academic, social/leisure, extended family, marital, sexual dysfunction, parental, and family unit, as well as generating a total adjustment score (Weissman and Bothwell, 1976). In one study, mean SAS-SR total score (SD) in a community sample was 1.60 (0.33) (Weissman et al., 1978). The version of the SAS-SR used in this study included 54 items.

2.3.4. SF-36—The SF-36 is a self-rated scale that measures general health status and functioning using the following 8 subscales: physical functioning, role limitations due to physical health problems (role physical), bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems (role emotional), and mental health (Ware and Snow, 1993). Higher SF-36 scores indicate better functioning; in community surveys (McHorney et al., 1994), SF-36 mean (SD) subscale scores ranged from 58.2 (21.3) on the Vitality subscale to 87.0 (21.7) on the Social Functioning subscale.

2.3.5. LIFE—The LIFE is a clinician-rated scale used to assess various aspects of psychosocial functioning over time, and in the present investigation included scoring on the following factors: work, interpersonal relations, sexual functioning, satisfaction, recreation, and global assessment (Keller et al., 1987). Ratings for individual items were summed to arrive at a total LIFE score, with higher scores indicating worse functioning.

Because the assessment scales used in this study contain a number of subscales that overlap, the variables are grouped into 5 categories (Miller et al., 1998): (1) overall psychosocial adjustment, (2) quality of life, (3) work functioning, (4) interpersonal functioning, and (5) physical health. For the Q-LES-Q, LES-S, and SF-36 scale scores, higher values indicate better outcomes.

2.4. Statistical analysis

For maintenance phase A, analyzed psychosocial data were from the efficacy evaluable population, which included all patients in the intent-to-treat (ITT) population (ie, all patients who took at least one dose of study medication and had at least one postbaseline HAM-D₁₇

assessment during maintenance phase A), except 33 patients who were excluded from all safety and efficacy analyses due to a drug-dispensing error during maintenance phase A. For maintenance phase B, psychosocial data were from the ITT population, which included all patients who took at least one dose of study medication and had at least one postbaseline HAM-D₁₇ assessment during maintenance phase B.

For maintenance phase A, 12-month outcomes (maintenance A baseline to month 12) for patients randomly assigned to venlafaxine ER vs placebo (placebo A) were compared for continuous variables with a baseline value using a 2-way analysis of covariance (ANCOVA) model with treatment group and center as factors and baseline values as a covariate; for continuous variables without a baseline value, comparisons were conducted using a 2-way analysis of variance (ANOVA) model. For maintenance phase B, 12-month outcomes (month 12 to month 24) for patients randomly assigned to venlafaxine ER vs placebo (placebo B) were compared using a 1-way ANOVA model and a 1-way ANCOVA model. For all comparisons, missing data were imputed using the last-observation-carried-forward (LOCF) method; all tests were 2-sided with alpha level set at 0.05.

3. Results

3.1. Patient characteristics and disposition

The study patient population for the acute, continuation, and maintenance phases has been previously described (Keller et al., 2007a, b; Kocsis et al., 2007). Briefly, patients in each treatment group at acute-phase trial baseline were of similar age (mean (SD) range: 42.0 (10.4) to 44.8 (11.3)), mostly female (range: 60% to 70%), and white (range: 80% to 88%). At baseline of the acute-phase trial, mean (SD) HAM-D₁₇ total scores for the treatment groups were similar and ranged from 21.5 (2.7) to 22.5 (3.0). At the beginning of maintenance phase A, a total of 258 patients in the efficacy evaluable population were randomly assigned to receive venlafaxine ER (*n*=129) or placebo (*n*=129). Patients continuing to respond to venlafaxine ER at the end of maintenance phase A were rerandomized at the beginning of maintenance phase B; 43 patients randomly assigned to receive venlafaxine ER and 40 randomly assigned to receive placebo comprised the ITT population for maintenance phase B. For both maintenance phases A and B, the most common reasons cited for study discontinuation in either treatment group included unsatisfactory efficacy response, failed to return for assessments, patient request unrelated to study, and other nonmedical events.

3.2. Dosage summary

As previously reported (Keller et al., 2007a; Kocsis et al., 2007), the mean (SD) venlafaxine ER daily dose during maintenance phase A was 220.8 ± 71.8 mg (median: 225.0 mg) and during maintenance phase B mean venlafaxine ER daily dose was 213.5±75.2 mg (median: 221.8 mg).

3.3. Overall psychosocial adjustment

As summarized in Table 1, SAS-SR total scores in the venlafaxine ER treatment group were significantly lower vs the placebo group at the end points of both maintenance phases A (1.9 vs 2.0, *p*=0.006) and B (1.8 vs 2.0, *p*=0.036), indicating better overall psychosocial adjustment in the venlafaxine ER group. Similarly, a significant difference favoring the venlafaxine ER group was detected in the LIFE scale at end point for maintenance phase B (7.7 vs 9.8, *p*=0.001).

3.4. Quality of life

Table 2 summarizes quality of life outcomes for patients given placebo or venlafaxine ER during maintenance phases A and B. Q-LES-Q scores were significantly higher in the venlafaxine ER group than in the placebo group at the end points of both maintenance phases A (72.3 vs 67.3, $p=0.004$) and B (74.7 vs 66.9, $p=0.013$), reflecting higher quality of life in the venlafaxine ER group. With the LES-S scale, no difference between the venlafaxine ER and placebo groups was detected during maintenance phase A, but LES-S scores were significantly higher in the venlafaxine ER group at the end of maintenance phase B (66.1 vs 55.2, $p=0.018$).

3.5. Work functioning

Work functioning outcomes are summarized in Table 3. There were significant differences favoring venlafaxine ER vs placebo in several of the work functioning assessments. In maintenance phase A, the end point SAS-SR house work subscale score was significantly lower (indicating superior outcome) in the venlafaxine ER group than in the placebo group (1.8 vs 2.0, $p=0.025$), and the SF-36 role function-emotional score was significantly higher. Moreover, for both maintenance phases A and B, the SF-36 role function-emotional score was significantly higher in the venlafaxine ER group than in the placebo group (73.2 vs 58.5, $p=0.010$, and 80.2 vs 55.8, $p=0.007$, respectively).

3.6. Interpersonal functioning

At the end point of maintenance phase A, SAS-SR scores for social/leisure (2.1 vs 2.3, $p=0.004$) and extended family (1.6 vs 1.7, $p=0.005$) were significantly lower in the venlafaxine ER treatment group than in the placebo group (Table 4). Significant differences favoring the venlafaxine ER treatment group vs placebo were also found for the SAS-SR social/leisure (2.0 vs 2.2, $p=0.048$) and SAS-SR extended family (1.4 vs 1.6, $p=0.035$) scores at the end point of maintenance phase B.

3.7. Physical health

Physical health outcomes observed in maintenance phases A and B are summarized in Table 5. Only 1 of 4 SF-36 measures of physical health was found to be significantly different between the venlafaxine ER and placebo groups (Table 5): at the end of maintenance phase B, the SF-36 general health outcome measure was significantly higher in the venlafaxine ER group vs placebo (73.0 vs 65.9, $p=0.042$). All other measures of physical health were statistically comparable between the 2 treatment groups.

4. Discussion

In this study of patients with recurrent MDD who were responders to venlafaxine ER therapy during acute and continuation phases, 1 and 2 years of maintenance treatment with venlafaxine ER were associated with higher levels of psychosocial functioning compared with responders who were switched to placebo. Significant differences favoring venlafaxine ER compared with placebo were found in multiple psychosocial domains, including quality of life, work functioning, and interpersonal functioning. For both maintenance phase A and B, overall psychosocial adjustment at end point, based on the SAS-SR, was significantly better among responders who continued treatment with venlafaxine ER than among responders who were switched to placebo. A similar advantage was seen at the end point of maintenance phase B based on the LIFE scale.

The advantages in quality of life and psychosocial functioning are consistent with the significant differences between venlafaxine ER and placebo on depression-related outcomes (eg, recurrence, HAM-D₁₇ total score) (Keller et al., 2007a, b; Kocsis et al., 2007). Although

most items on the quality of life and psychosocial functioning scales used here do not specifically assess symptoms of depression per se, there is some degree of overlap with depression-related scales (eg, life satisfaction is related to depressed mood, and patients with greater depression symptom severity have significantly worse quality of life across multiple domains (Daly et al., 2010; Trivedi et al., 2006)); thus, improvement in depressive symptoms would be reflected in assessments of functioning as well as depression-specific assessments. In addition, data from the Sequenced Treatment Alternatives to Relieve Depression study demonstrate statistically significant independent associations of quality of life measures (12-item Short Form Health Survey [SF-12 Mental Health, SF-12 Physical Health]), (Ware et al., 1996) and Q-LES-Q with depression severity (16-item Quick Inventory of Depressive Symptomatology–Interactive Voice Recognition) (Trivedi et al., 2004) (Wisniewski et al., 2007).

Prospective, naturalistic, longitudinal studies of patients with MDD have allowed us to better understand the course, nature, and magnitude of psychosocial impairments seen in patients with MDD (Judd et al., 2000, 2008; Kennedy et al., 2007; Solomon et al., 2004; Vittengl et al., 2009). In the CDS, psychosocial functioning of patients with MDD was assessed monthly over a 10-year period. During the acute illness stage, this study showed that psychosocial functioning tends most often to be “poor” or “very poor” and to extend across family, interpersonal, and work domains (Judd et al., 2000; Miller et al., 1998). Functional impairments decrease in severity in concert with recovery from MDD. Nevertheless, many patients continue to experience residual, subthreshold MDD symptoms and functional impairments over long periods of time; even patients who become asymptomatic continue to report mild psychosocial impairments compared with well controls.

Solomon et al. (2004) and others (Pettit et al., 2009; Vittengl et al., 2009) have found that persistent impaired psychosocial functioning following an MDD episode predicts later recurrence or a chronic course of MDD. In one 15-year, longitudinal analysis of individuals with MDD, even patients who met stringent criteria for recovery (asymptomatic 8 weeks) but who had functional impairment exhibited an elevated risk of MDD recurrence (Odds ratio: 1.16, $p < 0.001$). More recently Vittengl et al. (2009) described psychosocial functioning in patients with MDD who responded to acute cognitive therapy and were followed for up to 24 months. In this patient group, monthly assessments showed that a worsening of psychosocial functioning in a given month predicted worsening of MDD symptoms and a relapse or recurrence in the following month. These findings clearly establish ongoing persistent psychosocial impairment as a predictive factor related to MDD recurrence. They also raise the challenge of addressing psychosocial impairments as a means of improving long-term prognosis and outcomes.

The current investigation, as well as other controlled clinical trials, are beginning to shed light on the long-term impact of antidepressant treatment (Kocsis et al., 2002) and cognitive therapy (Jarrett et al., 2001; Lenze et al., 2002; Vittengl et al., 2009) on psychosocial functioning in patients with MDD. Currently it was demonstrated that up to 2 years of maintenance treatment with venlafaxine ER had a significant positive effect on a broad range of psychosocial function domains, compared with the level of functioning among patients who were switched to placebo during maintenance therapy. Importantly, the advantage of continued venlafaxine ER therapy persisted through the second year (ie, maintenance phase B). When patients were switched to placebo during either of the maintenance phases, psychosocial functioning deteriorated. At end points for both maintenance phases A and B, the most statistically robust advantages of continued therapy with venlafaxine ER were seen in the domains of global psychosocial adjustment, emotional functioning, social/leisure, and extended family. More modest advantages were seen in a

number of other functional areas. Such findings indicate that up to 2 years of maintenance treatment with an antidepressant in patients with a history of a recurrent MDD course continues to yield a benefit in terms of psychosocial functioning.

The present findings are similar to those of a placebo-controlled trial of maintenance therapy with sertraline in patients with chronic MDD or double depression, described by Kocsis et al. (2002). Using a design closely comparable to that of the current investigation, Kocsis et al. randomized patients who were responders to continuation treatment with sertraline to continue active treatment with sertraline or to be switched to placebo for a maintenance period of 18 months. Compared with patients switched to placebo, those given maintenance sertraline treatment showed significant advantages on global psychosocial measures at end point, such as the SAS-SR total score and LIFE interviewer assessment scores. In line with the current data, Kocsis et al. showed that long-term antidepressant treatment with sertraline in patients with chronic depression was associated with psychosocial benefits, compared with treatment discontinuation (eg, placebo).

Despite the encouraging psychosocial improvements seen currently and previously (Hirschfeld et al., 2002; Jarrett et al., 2001; Kocsis et al., 2002; Lenze et al., 2002), patients with recurrent or chronic MDD appear not to reach normal levels of functioning, even with long-term treatment. In the Kocsis et al. trial, psychosocial functioning at maintenance phase baseline had not reached normative, community levels in 8% to 40% of patients (depending on the psychosocial measure), indicating persistent impairment in a substantial proportion of patients, despite ongoing long-term antidepressant treatment and MDD symptomatic improvement. The baseline maintenance period scores in the current analysis were closely similar to those reported by Kocsis et al. From this we may conclude that antidepressant therapy improves but does not eliminate functional impairments, and it highlights the potential need for a more aggressive treatment approach. Combining medication treatment with cognitive behavioral therapy may be one strategy for addressing specific areas of psychosocial dysfunction, while at the same time helping to maintain the gains made during the acute treatment phase. In one trial conducted in older adults with recurrent MDD (Lenze et al., 2002), patients who received combined nortriptyline maintenance therapy and interpersonal psychotherapy over a 1-year follow-up period showed maintained improvements on the SAS, whereas those given either nortriptyline or psychotherapy alone actually showed declines on the SAS. Moreover, patients who maintained the acute-phase psychosocial improvements throughout the maintenance period were less likely to experience MDD recurrence, compared with patients who showed psychosocial declines. Further research concerning the clinical benefits of combination therapy for psychosocial functioning and MDD recurrence is currently underway (Trivedi et al., 2008).

4.1. Limitations

The randomized and placebo-controlled nature of the maintenance phases of this trial lends particular strength to the interpretability of the present findings. It is important to note, however, that certain study design attributes may have contributed to the positive psychosocial outcomes observed in the current analysis. Patients eligible to enroll in the PREVENT trial at baseline exhibited a recurrent, episodic MDD course, rather than chronic MDD; moreover, the study excluded patients who had a history of treatment resistance. The long-term nature of the trial allowed enrolled patients who exhibited treatment success to receive specialist care for up to 30 months at no cost, a substantial financial incentive for treatment compliance. Patients who received long-term treatment with venlafaxine ER and were switched to placebo may have noticed a change in adverse events (AEs), or may have experienced some level of discontinuation-related AEs. Such AEs may have cued patients to a change in treatment regimen and may have compromised the integrity of the treatment blind. Finally, over the lengthy treatment period, patient discontinuation rates were high and

while this was not unexpected, such attrition may have introduced bias into the remaining sample. The psychosocial outcomes observed in this sample, therefore, may not be representative of outcomes that might be observed in the broader, nonselected clinical population with MDD.

5. Conclusion

Long-term maintenance treatment with venlafaxine ER can aid in reducing a broad range of psychosocial impairments associated with recurrent depression.

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Conflict of interest

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Dr. Zajecka has received grants/research from AstraZeneca, GlaxoSmithKline McNeil, the National Institute of Mental Health, Bristol-Myers Squibb, Cephalon, CNS Response, Cyberonics, Eli Lilly, Forest, Novartis, PamLab, Pfizer, and sanofi-aventis. He is a consultant for Abbott, Eli Lilly, Biovail, Bristol-Myers Squibb, Pfizer, Otsuka, Takeda, Wyeth-Ayerst, Novartis, and PamLab. He is part of the speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Covidien, Cyberonics, Eli Lilly, GlaxoSmithKline, PamLab, Pfizer, and Wyeth-Ayerst.

Dr. Rothschild has been a consultant for Eli Lilly, Forest, GlaxoSmithKline, and Takeda and has received research grants from the National Institute of Mental Health, Cyberonics, and Wyeth. He has received royalties from the Rothschild Scale for Antidepressant Tachyphylaxis and American Psychiatric Press.

Dr. Friedman has provided scientific consultation to Cephalon, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Wyeth, and Pfizer. He has been on the speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Pfizer, Pharmacia & Upjohn, Roerig Division of Pfizer, and Wyeth. Dr. Friedman has received grants from AstraZeneca, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Northstar, Novartis, Organon, Pharmacia & Upjohn, Pfizer, sanofi-aventis, and Wyeth. He owns stock in Cephalon and has received other financial or material support from Abbott (expert testimony, patents, royalties).

Dr. Shelton has received grants from the National Institute of Mental Health, Bristol-Myers Squibb, Eli Lilly, Forest, Janssen, Novartis, Otsuka, PamLab, Pfizer, Repligen, AstraZeneca, Cyberonics, GlaxoSmithKline, and Wyeth. He has been a consultant or served on advisory boards for the National Institute of Mental Health, Best Practice Project Management Inc, Forest, Janssen, Novartis, Otsuka, PamLab, Repligen, EVOTEC AG, AstraZeneca, Cyberonics, GlaxoSmithKline, and Wyeth. Dr. Shelton has been on the speaker's bureau for AstraZeneca, Best Practice Project Management Inc, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Otsuka, PamLab, Repligen, and Wyeth.

Dr. Keller has been a consultant or received honoraria from Abbott, CENEREX, Cephalon, Cypress Bioscience, Cyberonics, Forest, Janssen, JDS, Medtronic, Organon, Novartis, Pfizer, Roche, Solvay, and Wyeth. He has received grants from Pfizer and Wyeth, and has served on advisory boards for Abbott, Bristol-Myers Squibb, CENEREX, Cyberonics, Cypress Bioscience, Forest, Janssen, Neuronetics, Novartis, Organon, and Pfizer.

Dr. Kocsis has received grants from the National Institute of Mental Health, the National Institute on Drug Abuse, the Burroughs Wellcome Trust, Pritzker Consortium, AstraZeneca, sanofi-aventis, Forest, Novartis, CNS Response, and Roche. He has served on the speaker's bureau for Pfizer, Wyeth, and AstraZeneca and on advisory boards for Pfizer and Wyeth.

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Fig. 1.
Study flow diagram.
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Table 1

Overall psychosocial adjustment.

Variable, LS mean (SE)	Placebo	Venlafaxine ER	<i>p</i> value
<i>Maintenance phase A</i>			
<i>n</i>	129	129	–
SAS-SR total			
Baseline	1.7 (0.04)	1.7 (0.04)	0.842
End point	2.0 (0.04)	1.9 (0.04)	0.006
LIFE			
Baseline	8.0 (0.2)	7.6 (0.2)	0.145
End point	9.7 (0.3)	9.0 (0.3)	0.057
<i>Maintenance phase B</i>			
<i>n</i>	40	43	–
SAS-SR total			
Baseline	1.7 (0.07)	1.8 (0.07)	0.235
End point	2.0 (0.07)	1.8 (0.06)	0.036
LIFE			
Baseline	7.6 (0.4)	8.2 (0.4)	0.267
End point	9.8 (0.5)	7.7 (0.4)	0.001

Abbreviations: ER, extended release; LIFE, Longitudinal Interval Follow-up Evaluation; LS mean, least-squares mean; SAS-SR, Social Adjustment Scale Self-Report; SE, standard error.

Baseline = last measurement prior to the first dose of study drug in the phase.

End point = last postbaseline observation for the phase.

Table 2

Quality of life.

Variable, LS mean (SE)	Placebo	Venlafaxine ER	<i>p</i> value
<i>Maintenance phase A</i>			
<i>n</i>	129	129	–
Q-LES-Q			
Baseline	75.5 (1.1)	76.8 (1.1)	0.414
End point	67.3 (1.3)	72.3 (1.3)	0.004
LES-S			
Baseline	68.1 (1.9)	70.3 (1.9)	0.383
End point	58.1 (2.2)	62.9 (2.1)	0.103
<i>Maintenance phase B</i>			
<i>n</i>	40	43	–
Q-LES-Q			
Baseline	76.1 (1.8)	76.7 (1.8)	0.818
End point	66.9 (2.2)	74.7 (2.1)	0.013
LES-S			
Baseline	66.7 (3.6)	67.6 (3.4)	0.868
End point	55.2 (3.4)	66.1 (2.9)	0.018

Abbreviations: ER, extended release; LES-S, Life Enjoyment Scale—Short Version; LS mean, least-squares mean; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form.

Baseline = last measurement prior to the first dose of study drug in the phase.

End point = last postbaseline observation for the phase.

Table 3

Work functioning.

Variable, LS mean (SE)	Placebo	Venlafaxine ER	<i>p</i> value
<i>Maintenance phase A</i>			
<i>n</i>	129	129	—
SAS-SR work			
Baseline	1.4 (0.05)	1.3 (0.05)	0.439
End point	1.6 (0.06)	1.5 (0.05)	0.022
SAS-SR house work			
Baseline	1.7 (0.06)	1.7 (0.06)	0.352
End point	2.0 (0.07)	1.8 (0.07)	0.025
SF-36 role function-emotional			
Baseline	82.2 (2.8)	84.2 (2.8)	0.592
End point	58.5 (4.4)	73.2 (4.1)	0.010
<i>Maintenance phase B</i>			
<i>n</i>	40	43	—
SAS-SR work			
Baseline	1.3 (0.06)	1.4 (0.06)	0.355
End point	1.6 (0.09)	1.4 (0.09)	0.051
SAS-SR house work			
Baseline	1.6 (0.09)	1.6 (0.09)	0.945
End point	2.0 (0.11)	1.8 (0.10)	0.082
SF-36 role function-emotional			
Baseline	83.3 (4.7)	81.8 (4.5)	0.811
End point	55.8 (6.4)	80.2 (6.0)	0.007

Abbreviations: ER, extended release; LS mean, least-squares mean; SAS-SR, Social Adjustment Scale—Self-Report; SE, standard error; SF-36, Short Form Health Survey.

Baseline = last measurement prior to the first dose of study drug in the phase.

End point = last postbaseline observation for the phase.

Table 4

Interpersonal functioning.

Variable, LS mean (SE)	Placebo	Venlafaxine ER	p value
<i>Maintenance phase A</i>			
<i>n</i>	129	129	–
SAS-SR social/leisure			
Baseline	2.0 (0.05)	2.0 (0.05)	0.807
End point	2.3 (0.06)	2.1 (0.06)	0.004
SAS-SR extended family			
Baseline	1.5 (0.04)	1.5 (0.05)	0.854
End point	1.7 (0.04)	1.6 (0.04)	0.005
SAS-SR marital			
Baseline	2.0 (0.10)	2.1 (0.11)	0.535
End point	2.4 (0.11)	2.4 (0.11)	0.952
SAS-SR parental			
Baseline	1.4 (0.09)	1.4 (0.07)	0.841
End point	1.8 (0.12)	1.8 (0.10)	0.996
SAS-SR family unit			
Baseline	1.6 (0.07)	1.6 (0.07)	0.757
End point	1.8 (0.07)	1.8 (0.07)	0.917
SF-36 social functioning			
Baseline	77.4 (1.8)	79.9 (1.8)	0.274
End point	68.6 (2.1)	70.7 (2.0)	0.443
<i>Maintenance phase B</i>			
<i>n</i>	40	43	–
SAS-SR social/leisure			
Baseline	2.0 (0.09)	2.1 (0.09)	0.544
End point	2.2 (0.08)	2.0 (0.07)	0.048
SAS-SR extended family			
Baseline	1.4 (0.06)	1.5 (0.06)	0.038
End point	1.6 (0.06)	1.4 (0.06)	0.035
SAS-SR marital			
Baseline	2.0 (0.2)	2.4 (0.2)	0.205
End point	2.4 (0.2)	2.2 (0.1)	0.233
SAS-SR parental			
Baseline	1.4 (0.1)	1.6 (0.1)	0.140
End point	1.7 (0.1)	1.5 (0.1)	0.489
SAS-SR family unit			
Baseline	1.6 (0.1)	1.7 (0.1)	0.436
End point	1.9 (0.1)	1.7 (0.1)	0.338
SF-36 social functioning			
Baseline	78.1 (2.7)	75.0 (2.6)	0.411

Variable, LS mean (SE)	Placebo	Venlafaxine ER	<i>p</i> value
End point	63.1 (3.4)	71.5 (3.2)	0.073

Abbreviations: ER, extended release; LS mean, least-squares mean; SAS-SR, Social Adjustment Scale—Self-Report; SE, standard error; SF-36, Short Form Health Survey.

Baseline = last measurement prior to the first dose of study drug in the phase.

End point = last postbaseline observation for the phase.

Table 5

Physical health.

Variable, LS mean (SE)	Placebo	Venlafaxine ER	<i>p</i> value
<i>Maintenance phase A</i>			
<i>n</i>	129	129	—
SF-36 physical functioning			
Baseline	88.1 (1.7)	90.3 (1.7)	0.306
End point	83.2 (1.6)	85.8 (1.5)	0.200
SF-36 role function — physical			
Baseline	79.4 (2.9)	85.4 (2.9)	0.115
End point	69.0 (3.8)	76.2 (3.6)	0.142
SF-36 bodily pain			
Baseline	74.5 (1.9)	81.4 (1.9)	0.007
End point	74.6 (2.2)	75.1 (2.1)	0.866
SF-36 general health			
Baseline	70.9 (1.6)	75.9 (1.7)	0.023
End point	71.0 (1.6)	72.7 (1.5)	0.440
<i>Maintenance phase B</i>			
<i>n</i>	40	43	—
SF-36 physical functioning			
Baseline	85.1 (2.9)	90.5 (2.8)	0.195
End point	84.8 (2.8)	86.2 (2.7)	0.706
SF-36 role function — physical			
Baseline	83.8 (4.9)	84.3 (4.7)	0.936
End point	65.8 (5.2)	74.2 (4.9)	0.240
SF-36 bodily pain			
Baseline	78.1 (3.5)	77.9 (3.4)	0.961
End point	71.2 (3.4)	77.4 (3.2)	0.192
SF-36 general health			
Baseline	76.0 (2.9)	76.3 (2.8)	0.939
End point	65.9 (2.5)	73.0 (2.3)	0.042

Abbreviations: ER, extended release; LS mean, least-squares mean; SE, standard error; SF-36, Short Form Health Survey.

Baseline = last measurement prior to the first dose of study drug in the phase.

End point = last postbaseline observation for the phase.