Predictors of functional improvement in employed adults with major depressive disorder treated with desvenlafaxine

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We carried out a secondary analysis of a double-blind, placebo-controlled trial of desvenlafaxine for major depressive disorder (MDD) to explore the associations between depressive symptoms and subtypes, and functional outcomes, including work functioning. Employed outpatients with MDD were assigned randomly in a 2:1 ratio to receive desvenlafaxine 50 mg/day or placebo for 12 weeks. Analyses were carried out post-hoc with the intent-to-treat (ITT) sample ($N=427$) and a prospectively defined modified ITT sample ($N=310$), composed of patients with baseline 17-item Hamilton Rating Scale for Depression score of at least 20. Functional outcomes at week 12 included items and factors from the Montgomery–Åsberg Depression Rating Scale, Sheehan Disability Scale, and the Work Productivity and Activity Impairment questionnaire. In the modified ITT sample, but not in the ITT sample, desvenlafaxine-treated patients showed significantly greater improvement in several functional outcomes in the responder, nonanxious, and normal-energy patient subgroups. Improvement in the 17-item Hamilton Rating Scale for Depression total score at week 2 predicted change at week 12 in several functional outcomes. Functional improvement at 12 weeks was greater in subgroups of patients and was also significantly predicted by early improvement in depressive symptoms in employed patients with MDD treated with desvenlafaxine. ***Int Clin Psychopharmacol*** **29:239–251**

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Introduction

In addition to the emotional symptoms of depression, individuals with major depressive disorder (MDD) experience substantial functional impairment, including disruption in physical, social, and occupational functioning (Hirschfeld *et al.*, 2000; McKnight and Kashdan, 2009; Papakostas, 2009). Depression ultimately impacts an individual's ability to function normally in social settings, maintain personal and professional relationships, and achieve productivity in the workplace. Functional impairment is not always limited to the current depressive episode, and the degree and type of impairment can vary with the duration and severity of the depressive illness (McKnight and Kashdan, 2009; Papakostas, 2009). Given that depression is estimated to be the third leading cause of disease burden in 2030, (Mathers and Loncar, 2006) it is not surprising that the economic costs associated with depression are considerably higher than that of numerous other prevalent, chronic illnesses (Druss *et al.*, 2000).

Symptomatic improvement during the first few weeks of treatment has been shown to predict later response or remission with some antidepressants (Szegedi *et al.*, 2003, 2009; Kok *et al.*, 2009; Soares *et al.*, 2014) and may also be predictive of improvements in functioning. However, few randomized controlled trials have evaluated the effects of antidepressant treatment on functional outcomes in patients with MDD (Kocsis *et al.*, 2002; Szegedi *et al.*, 2003; Trivedi *et al.*, 2010; Dunlop *et al.*, 2011; Oakes *et al.*, 2012). Normalization of functioning is often reported by patients as more important than symptom-related outcomes and is considered by physicians as an important component of treatment response (Zimmerman *et al.*, 2006). Measures of functioning are not included in standard definitions of response or remission used in antidepressant clinical trials (Hirschfeld *et al.*, 2002; Zimmerman *et al.*, 2006); however, because they do not always correlate with symptom-based outcomes, functional outcomes should likely be assessed independently (Hirschfeld *et al.*, 2002; Zimmerman *et al.*, 2006; McKnight and Kashdan, 2009).

Desvenlafaxine (administered as desvenlafaxine succinate) is a serotonin-norepinephrine reuptake inhibitor (SNRI) approved for the treatment of adults with MDD (Pfizer Canada Inc., 2013; Wyeth Pharmaceuticals Inc.,

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2013). A 12-week, phase 3, randomized, double-blind, controlled trial assessed the efficacy of desvenlafaxine 50 mg/day for improving depressive symptoms and functional impairment in gainfully employed patients with MDD (Dunlop *et al.*, 2011). Patients in the intent-to-treat (ITT) population who received treatment with desvenlafaxine 50 mg/day showed a significant improvement in symptoms of depression [17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) (Hamilton, 1960) and Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total scores] compared with placebo. However, in the ITT population, improvement in functional outcomes [Sheehan Disability Scale (SDS) (Sheehan, 2000) score] only approached statistical significance ($P = 0.067$) for desvenlafaxine 50 mg/day compared with placebo. Patients with moderate to severe depressive symptoms at baseline showed a significant improvement in all three measures.

Associations between functional impairment and depressive symptoms were evaluated in a post-hoc analysis using data from patients included in the primary study described above. The objectives of this secondary analysis were to assess the effects of desvenlafaxine treatment on functional impairment in employed patients with MDD; to assess functioning in subgroups of patients with anxious depression, lower energy, and clinical response; and to identify predictors of improvement in functional impairment for these patients.

Methods

Study design

The analysis was based on data from a phase 3b, parallel-group, randomized, placebo-controlled, double-blind study that evaluated the safety and efficacy of desvenlafaxine 50 mg/day in employed, adult outpatients with MDD who were experiencing impairments in functioning (Dunlop *et al.*, 2011). Details of the study design and methods for the primary efficacy analysis have been reported previously by Dunlop *et al.* (2011). The study was carried out at 55 research centers in the USA and Canada between February and November 2009. All patients were required to provide written informed consent before participating in the study, and the study was carried out in accordance with the Declaration of Helsinki and its amendments.

The study enrolled adult outpatients between 18 and 75 years of age with a primary diagnosis of MDD without psychotic features, consistent with the criteria described in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (American Psychiatric Association, 2000). Eligible patients were required to have been experiencing depressive symptoms for 30 or more days before the baseline visit and to have a MADRS total score of 25 or greater at both screening and baseline visits. All eligible patients were required to be gainfully employed (working $\geq$ 20 paid hours per week) and had a diagnosis of pretreatment functional impairment, defined as an SDS score of at least 10 (Sheehan and Sheehan, 2008) at screening and baseline. Inclusion criteria were designed to select a sample of medically stable patients with a principal diagnosis of MDD, and excluded bipolar, psychotic, and treatment-resistant depression. In addition, patients who had received venlafaxine in any formulation in the past 12 months or who had received any previous treatment with desvenlafaxine were excluded.

Eligible patients were randomly assigned to receive desvenlafaxine 50 mg/day or placebo at a ratio of 2 : 1 for a duration of 12 weeks. Concomitant treatment with hypnotic medications was allowed for the first 14 days of treatment after randomization, with a maximum of six doses allowed. The use of any over-the-counter or prescription medications with psychotropic effects was prohibited. No titration or tapering of desvenlafaxine treatment was included in the study.

Study assessments

The primary efficacy outcome, change in the $HAM\text{-}D_{17}$ total score from baseline to week 12, using the last observation carried forward (LOCF) method, has been described previously, as was the predefined, key secondary functional outcome, change in the SDS score from baseline to week 12 (Dunlop *et al.*, 2011). The adjusted mean changes from baseline for desvenlafaxine 50 mg/day versus placebo in the SDS individual items 1 (work/studies), 2 (social life), and 3 (family life/home responsibilities) were also assessed previously (Dunlop *et al.*, 2011). Additional efficacy outcomes reported by Dunlop *et al.* (2011) included change from baseline in the Clinical Global Impression – Improvement (Guy, 1976) (CGI-I) total scores, Clinical Global Impression – Severity (Guy, 1976) (CGI-S) total scores, and CGI-I response, which was defined as a final CGI-I score of 1 (very much improved) or 2 (much improved).

Additional measures of functional impairment were evaluated using adjusted mean change from baseline in the following assessments at week 12: $HAM\text{-}D_{17}$ work/activities item; $HAM\text{-}D_{17}$ psychomotor retardation factor [items 1 (depressed mood), 7 (work and activities), 8 (retardation), and 14 (genital symptoms) of $HAM\text{-}D_{17}$] (Tollefson and Holman, 1993; Judge *et al.*, 2000); MADRS item 7 (lassitude); and the Work Productivity and Activity Impairment (WPAI) (Reilly *et al.*, 1993) questionnaire. The self-administered WPAI questionnaire assesses work and activity impairment over the past 7 days across four domains: absenteeism (percentage of time at work missed because of health); presenteeism (percentage of impairment at work because of health); overall work impairment (absenteeism and presenteeism); and activity impairment because of the respondent's health (percentage of daily activity impairment outside of work

because of health). Within each domain, higher scores indicate greater impairment.

Statistical analysis

All secondary analyses were based on the ITT population, defined as all randomly assigned patients who received at least 1 dose of study medication and had at least 1 postbaseline evaluation on the primary efficacy end point, the HAM-D_{17} total score. Analyses were also carried out on the basis of a modified ITT (mITT) population, prospectively defined for the main study, which included all randomly assigned patients who received at least 1 dose of study medication, had at least 1 postbaseline evaluation on the primary efficacy end point, and had a baseline HAM-D_{17} total score of at least 20, which has been used previously to identify moderately to severely depressed patients (DeRubeis *et al.*, 2005; Dunlop and Aaron, 2010). All analyses were carried out at week 12 using the LOCF approach to account for missing data. Demographics and baseline characteristics were summarized by treatment, and changes from baseline in functional outcomes were analyzed using analysis of covariance with treatment, region, and baseline in the model.

A subgroup analysis compared change from baseline in functional outcomes in the following patients at week 12 using LOCF: responders ($\geq$ 50% reduction in HAM-D_{17} total score from baseline) and nonresponders; anxious depressed (baseline score $\geq$ 7 on HAM-D_{17} anxiety-somatization item) (Fava *et al.*, 2000) and nonanxious depressed patients; and lower energy (baseline HAM-D_{17} psychomotor retardation factor score > 8) (Judge *et al.*, 2000) and normal-energy patients. Although not necessarily the clinical consensus, for the purposes of this report, definitions of lower and normal energy were based on HAM-D_{17} psychomotor retardation factor (HAM-D_{17} items 1, 7, 8, and 14) scores, with lower energy defined as HAM-D_{17} psychomotor retardation factor score above the median baseline.

The predictive value of early change in depressive symptoms on each of the functional outcomes at week 12, LOCF, was assessed using a regression analysis with HAM-D_{17} psychomotor retardation, MADRS lassitude, SDS total, and the four WPAI domains as the dependent variables, and percent change from baseline in the HAM-D_{17} total score, CGI-I total score, and CGI-S total score at week 2 as the independent variable in separate models. In addition, the following baseline predictors of improvement in functioning were assessed using a regression model: age, sex, duration of depression, baseline HAM-D_{17} total score, and baseline MADRS total score. Correlations between change from baseline in HAM-D_{17}, CGI-I and CGI-S total scores, and HAM-D_{17} psychomotor retardation factor, MADRS lassitude, SDS total and item scores, and WPAI domains at week 12, LOCF, were computed overall and by treatment. All statistical tests used a two sided $P = 0.05$ as the criterion for statistical significance. Given that these were exploratory analyses, statistical analyses for the secondary efficacy outcomes were not adjusted for multiple comparisons.

Results

Patient demographics

A total of 427 patients were included in the ITT population (desvenlafaxine 50 mg/day, $n = 285$; placebo, $n = 142$); 310 patients were included in the mITT population (desvenlafaxine 50 mg/day, $n = 208$; placebo, $n = 102$). Demographics and baseline characteristics were similar between the treatment groups of both patient populations (Table 1). A majority of patients were women (66 and 68% in the ITT and mITT populations, respectively) and White (81 and 78%, respectively).

Functional outcomes

ITT population

Improvements from baseline for HAM-D_{17} work/activities, HAM-D_{17} psychomotor retardation, and WPAI presenteesim scores at week 12, LOCF, were significantly greater for patients in the ITT population who received desvenlafaxine 50 mg/day versus those who received placebo (Fig. 1). The adjusted mean difference in change from baseline at week 12, LOCF, for these measures was −0.23 [95% confidence interval (CI), −0.44, −0.01; $P = 0.04$]; −0.72 (95% CI, −1.26, −0.17; $P = 0.01$); and −5.11 (95% CI, −10.10, −0.13; $P = 0.04$), respectively.

mITT population

Improvements from baseline in HAM-D_{17} psychomotor retardation, WPAI presenteesim, and WPAI activity impairment scores at week 12, LOCF, were significantly greater for patients in the mITT population who received desvenlafaxine 50 mg/day versus those who received placebo (Fig. 1). The adjusted mean difference in change from baseline at week 12, LOCF, for these measures was −0.83 (–1.50, −0.16; $P = 0.02$); −7.40 (–13.34, −1.45; $P = 0.02$); and −6.47 (–12.32, −0.63; $P = 0.03$), respectively. The mean change from baseline in the HAM-D_{17} work/activities score narrowly missed significance for desvenlafaxine 50 mg/day versus placebo ($P = 0.067$).

Patient subgroup analyses

ITT population

In patients in the ITT population who achieved a HAM-D_{17} response, improvements from baseline in WPAI presenteeism (percent work impairment), and overall work impairment scores were numerically greater with desvenlafaxine 50 mg/day versus placebo, but not statistically significant (Fig. 2). The adjusted mean differences in change from baseline at week 12, LOCF for these measures were −5.41 (95% CI, −11.13, 0.32; $P = 0.06$) and −6.04 (95% CI, −12.17, 0.09; $P = 0.05$), respectively. No significant differences were observed for any other

Table 1 Demographics and baseline characteristics, ITT and mITT populations

	ITT population		mITT population	
Characteristics	Placebo ($n=142$)	Desvenlafaxine ($n=285$)	Placebo ($n=102$)	Desvenlafaxine ($n=208$)
Age (years)				
Mean±SD	41.6±12.6	43.2±11.7	40.1±12.1	43.3±12.2
Range	19–71	20–72	19–67	20–72
Sex [*n* (%)]				
Female	93 (65.5)	188 (66.0)	69 (67.7)	142 (68.3)
Male	49 (34.5)	97 (34.0)	33 (32.4)	66 (31.7)
Race [*n* (%)]				
Asian	3 (2.1)	0 (0)	1 (1)	0 (0)
Black or African American	17 (12.0)	46 (16.1)	16 (15.7)	38 (18.3)
White	117 (82.4)	229 (80.4)	80 (78.4)	162 (77.9)
Other	4 (2.8)	9 (3.2)	4 (3.9)	7 (3.4)
Duration of current episode (months)[a]				
Mean±SD	13.9±24.4	13.5±24.2	13.2±22.9	13.6±26.0
Range	0.5–173	0.4–220	0.5–160	0.4–220
Baseline total score (mean±SD)				
HAM-D_{17}	21.8±4.5	22.0±4.2	23.9±3.0	23.8±3.2
HAM-D_{17} item 1 (depressed mood)	2.9±0.6	2.9±0.5	3.0±0.5	3.0±0.4
HAM-D_{17} item 7 (work/activities)	2.8±0.5	2.7±0.5	2.8±0.4	2.8±0.4
HAM-D_{17} item 8 (psychomotor retardation)	1.0±0.8	1.0±0.7	1.1±0.8	1.1±0.7
HAM-D_{17} item 14 (genital symptoms)	1.3±0.8	1.3±0.8	1.5±0.7	1.4±0.7
HAM-D_{17} items 1, 7, 8, 14 (psychomotor retardation factor)	7.9±1.7	7.9±1.5	8.5±1.1	8.3±1.3
MADRS total	31.0±3.8	30.7±3.5	31.7±3.9	31.5±3.4
MADRS lassitude	3.7±0.9	3.7±0.8	3.7±0.9	3.8±0.7
CGI-S	4.4±0.6	4.4±0.7	4.5±0.6	4.5±0.6
SDS	20.4±4.7	19.8±4.3	20.8±4.6	20.1±4.3
SDS work/studies	6.2±2.2	6.2±1.9	6.4±2.1	6.3±1.9
SDS social life	7.2±1.8	6.9±1.7	7.4±1.8	7.0±1.7
SDS family	7.0±1.9	6.7±1.8	7.1±1.9	6.8±1.8
WPAI percent work missed[b]	8.2±14.6	9.4±15.1	8.5±14.2	9.8±15.2
WPAI percent work impairment[b]	55.7±24.4	55.6±21.4	58.4±21.6	56.0±20.6
WPAI percent overall work impairment[c]	58.0±24.6	58.6±22.2	61.0±21.5	59.1±21.5
WPAI percent activity impairment[d]	66.5±21.2	65.2±18.8	67.7±19.2	66.4±17.7

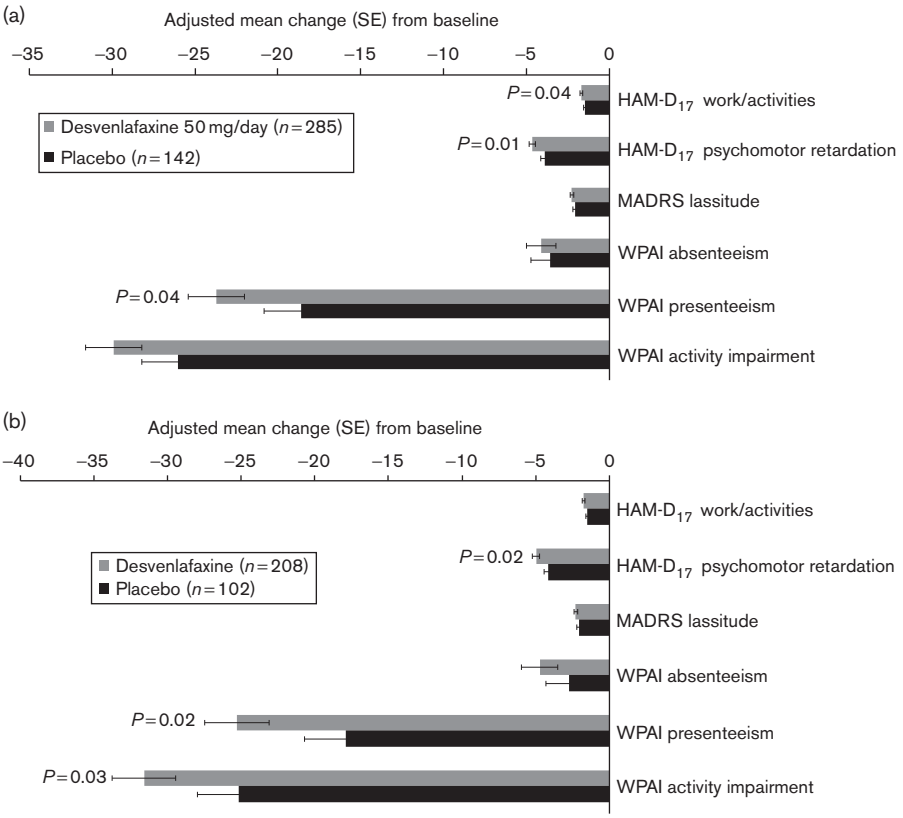
CGI-S, Clinical Global Impression Scale – Severity of Illness; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.
[a]Duration data missing for one patient in the desvenlafaxine group.
[b]WPAI percent work missed and work impairment data missing for two patients in the desvenlafaxine group and two patients in the placebo group.
[c]WPAI percent overall work impairment data missing for three patients in the desvenlafaxine group and three patients in the placebo group.
[d]WPAI percent activity impairment data missing for two patients in the desvenlafaxine group and one patient in the placebo group.

functional outcomes assessed in the subgroup of HAM-D_{17} responders ($P=0.11$–0.97) or for any functional outcomes in the patient subgroup of nonresponders ($P=0.22$–0.87).

In the subgroup analysis of patients with lower energy at baseline (HAM-D_{17} psychomotor retardation factor score > 8), desvenlafaxine 50 mg/day significantly improved HAM-D_{17} total, HAM-D_{17} psychomotor retardation factor, and SDS work/studies scores from baseline at week 12, LOCF (Fig. 3). The corresponding adjusted mean differences in change from baseline were −2.16 (95% CI, −3.87, −0.45; $P=0.01$); −0.85 (95% CI, −1.57, −0.14; $P=0.02$); and −0.69 (95% CI, −1.32, −0.06; $P=0.03$), respectively. Improvements from baseline in HAM-D_{17} work/activities, SDS total, and SDS family scores narrowly missed statistical significance ($P=0.05$–0.066, respectively). No significant differences were observed in WPAI absenteeism, presenteeism, overall work impairment, or percent activity impairment for desvenlafaxine versus placebo in low-energy patients ($P=0.08$–0.85). In addition, compared with patients who received placebo, lower energy patients treated with desvenlafaxine showed significant improvements in CGI-I and CGI-S total scores ($P=0.001$ for both comparisons), and a greater percentage of CGI-I or CGI-S scores equal to 1 or 2 (CGI-I: 70 vs. 51%; $P=0.003$; CGI-S: 48 vs. 32%; $P=0.01$). No significant differences were observed in functional outcomes in normal-energy patients (i.e. patients without psychomotor retardation) ($P=0.08$–0.92).

In anxious depressed patients (baseline score ≥ 7 on HAM-D_{17} anxiety-somatization item), desvenlafaxine 50 mg/day significantly improved HAM-D_{17} total and HAM-D_{17} retardation factor scores from baseline at week 12, LOCF (Fig. 4), with adjusted mean differences in change from baseline of −2.50 (95% CI, −4.59, −0.41; $P=0.02$) and −0.85 (95% CI, −1.68, −0.01; $P=0.046$), respectively. Improvement from baseline in the HAM-D_{17} work/activities score narrowly missed significance ($P=0.05$). Similar to lower energy patients, anxious depressed patients who received desvenlafaxine showed significant improvements in CGI-I and CGI-S total scores versus placebo ($P=0.01$ and 0.006, respectively) and a greater percentage of CGI-I or CGI-S scores equal to 1 or 2 versus patients who received placebo (CGI-I: 63 vs. 45%;

Fig. 1



Adjusted mean change from baseline in functional outcomes, week 12, LOCF, ITT, and mITT populations. (a) ITT population. (b) mITT population. *P* values were obtained from the ANCOVA model including therapy, region, and baseline value as covariates. HAM-D_{17} total scores, SDS items of work/studies, social life, and family, and WPAI overall work impairment are not included, as these findings were reported previously by Dunlop *et al.* (2011) ANCOVA, analysis of covariance; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.

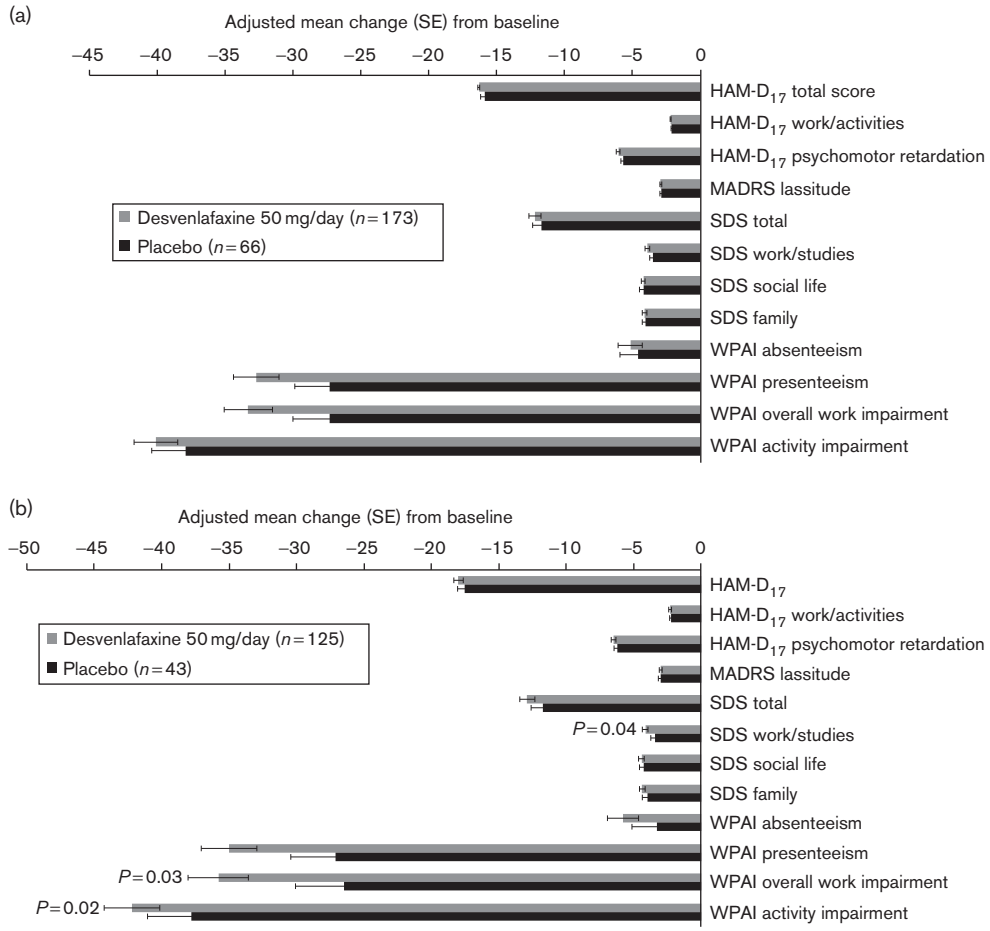
$P = 0.01$; CGI-S: 45 vs. 30%; $P = 0.03$). No significant differences were observed in other functional outcomes in the subgroup of anxious depressed patients ($P = 0.13$–0.62). In addition, no significant differences were observed in functional outcomes for nonanxious depressed patients ($P = 0.08$–0.97).

mITT population

For patients in the mITT population who achieved a HAM-D_{17} response, improvements from baseline in SDS work/studies, WPAI presenteeism, and WPAI overall work impairment were statistically significant for desvenlafaxine 50 mg/day versus placebo (Fig. 2). The adjusted mean differences in change from baseline at week 12, LOCF, for these measures were −0.69 (95% CI, −1.33, −0.05; $P = 0.04$; −7.85 (95% CI, −14.92, −0.77; $P = 0.03$); and −9.32 (95% CI, −16.88, −1.75; $P = 0.02$), respectively. No significant differences were observed for any other functional outcomes assessed in the subgroup of HAM-D_{17} responders ($P = 0.21$–1.0) or for any functional outcomes in the patient subgroup of nonresponders ($P = 0.21$–0.99).

For patients in the mITT population with lower energy at baseline, no significant improvements from baseline were observed ($P = 0.11$–0.91) with desvenlafaxine 50 mg/day for any of the functional outcomes assessed at week 12, LOCF (Fig. 3). In the subgroup of normal-energy patients (i.e. patients without psychomotor retardation), desvenlafaxine 50 mg/day significantly improved HAM-D_{17} total, HAM-D_{17} work/activities, HAM-D_{17} psychomotor retardation factor, SDS total, SDS work/studies, WPAI presenteeism, and WPAI overall work impairment scores from baseline at week 12, LOCF. The adjusted mean differences in change from baseline for these outcomes were −2.47 (95% CI, −4.35, −0.59; $P = 0.01$); −0.31 (95% CI, −0.61, −0.01; $P = 0.04$); −0.96 (95% CI, −1.75, −0.18; $P = 0.02$); −2.11 (–4.09, −0.14; $P = 0.04$); −0.83 (–1.51, −0.14; $P = 0.02$); −7.15 (–13.98, −0.33; $P = 0.04$); and −7.12 (–14.18, −0.05; $P = 0.048$), respectively. In addition, compared with patients who received placebo,

Fig. 2

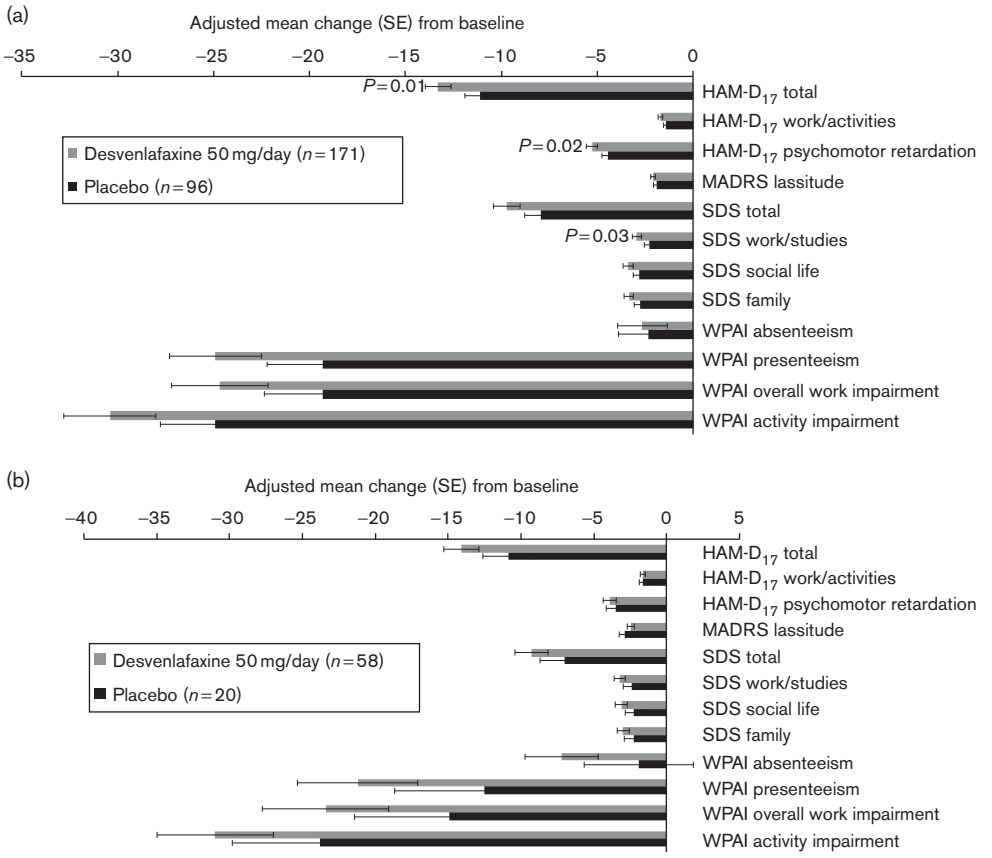


Adjusted mean change (SE) from baseline in functional outcomes at week 12, LOCF, in responders to treatment with desvenlafaxine 50 mg/day or placebo, ITT, and mITT populations. (a) ITT population. (b) mITT population. Responders were patients who showed at least 50% reduction in the HAM-D_{17} total score from baseline. *P* values were obtained from the ANCOVA model including therapy, region, and baseline value as covariates. ANCOVA, analysis of covariance; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.

normal-energy patients treated with desvenlafaxine showed significant improvements in CGI-I ($P = 0.002$) and CGI-S total scores ($P < 0.001$). Improvement from baseline in SDS social life, SDS family, and WPAI percent activity impairment scores narrowly missed statistical significance ($P = 0.05$–0.07). Change from baseline in MADRS lassitude and WPAI absenteeism scores were not significant in normal-energy patients ($P = 0.15$ and 0.53, respectively).

For anxious depressed patients in the mITT population, desvenlafaxine 50 mg/day significantly improved HAM-D_{17} total ($P = 0.03$) and HAM-D_{17} retardation factor scores ($P = 0.04$) from baseline at week 12, LOCF (Fig. 4). Improvement from baseline in the HAM-D_{17} work/activities score narrowly missed statistical significance ($P = 0.06$). No significant differences were observed in other functional outcomes in the subgroup of anxious depressed patients ($P = 0.23$–0.63). In the subgroup of nonanxious depressed patients at baseline (baseline score < 7 on HAM-D_{17} anxiety-somatization item), desvenlafaxine 50 mg/day significantly improved SDS total, SDS work/studies, SDS family, SDS social, WPAI presenteeism, and WPAI overall work impairment scores from baseline at week 12, LOCF. The adjusted mean differences in change from baseline for these outcomes were −3.47 (95% CI, −6.38, −0.57; $P = 0.02$); −1.27 (95% CI, −2.31, −0.23; $P = 0.02$); −1.11 (95% CI, −2.12, −0.10; $P = 0.03$); −1.10 (95% CI, −2.11, −0.09; $P = 0.03$); −12.13 (–22.32, −1.93; $P = 0.02$); and −12.58 (–23.12, −2.05; $P = 0.02$), respectively. Improvement from baseline in HAM-D_{17} total and WPAI percent activity impairment scores narrowly missed significance ($P = 0.05$–0.06). No significant differences were observed in other functional outcomes for nonanxious depressed patients ($P = 0.3$–1.0).

Fig. 3



Adjusted mean change (SE) from baseline in functional outcomes at week 12, LOCF, in patients with lower energy treated with desvenlafaxine 50 mg/day or placebo, ITT, and mITT populations. (a) ITT population. (b) mITT population. Lower energy patients had a HAM-D_{17} retardation factor score of at least the baseline median of 8. *P* values were obtained from the ANCOVA model including therapy, region, and baseline value as covariates. ANCOVA, analysis of covariance; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.

Predictive value of baseline severity and early improvement

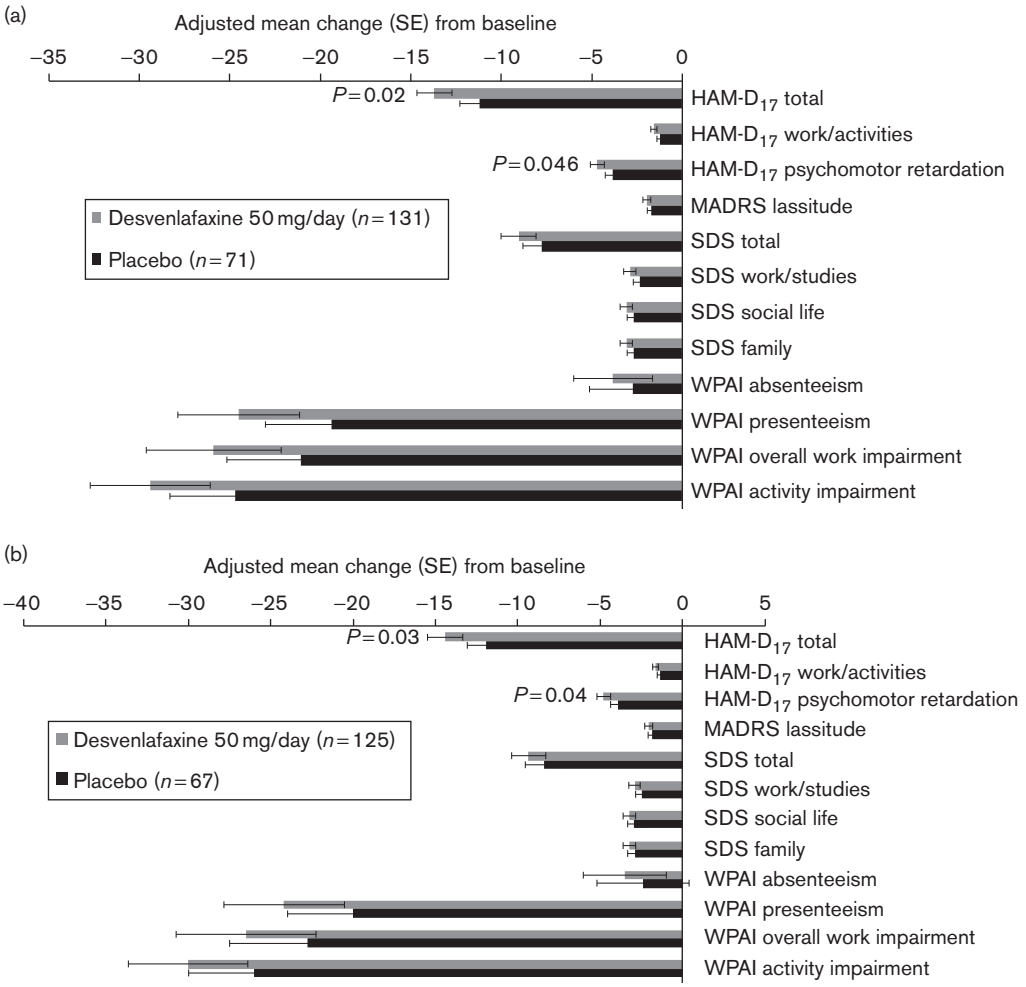
ITT population

In the analysis of baseline predictors of functional improvement in the overall group, baseline HAM-D_{17} total score predicted improvement in HAM-D_{17} psychomotor retardation [parameter estimate (SE): −0.15 (0.04); $P < 0.0001$] and MADRS lassitude [parameter estimate (SE): 0.05 (0.02); $P = 0.03$] at week 12, LOCF. For patients in the desvenlafaxine group, baseline HAM-D_{17} total score predicted improvement in HAM-D_{17} psychomotor retardation [−0.15 (0.05); $P = 0.002$] at week 12, LOCF. For patients in the placebo group, baseline HAM-D_{17} total score predicted improvement in HAM-D_{17} psychomotor retardation [−0.15 (0.06); $P = 0.02$] and MADRS lassitude [0.09 (0.04); $P = 0.03$], and baseline MADRS total score predicted improvement in the SDS total score [−0.57 (0.20); $P = 0.006$] and WPAI activity impairment [−2.15 (0.74); $P = 0.004$] at week 12, LOCF. Baseline characteristics of age, sex, and duration of current depressive episode were not significant predictors of functional improvement in any treatment group.

Early improvement in the HAM-D_{17} total score at week 2 predicted change at week 12 in HAM-D_{17} psychomotor retardation factor, MADRS lassitude item, SDS total, and WPAI presenteeism, work productivity loss, and activity impairment for desvenlafaxine-treated patients in the ITT population (Table 2). Similarly, improvement in CGI-I and CGI-S total scores at week 2 predicted change at week 12 in all functional outcomes assessed.

Final improvement in depressive symptoms was also correlated with improvement in functional outcomes. In the overall group, improvements from baseline in HAM-D_{17} psychomotor retardation factor, MADRS lassitude, SDS total and item scores, and scores on the four WPAI domains were highly correlated with improvement in the HAM-D_{17} total score at week 12, LOCF [Pearson correlation coefficient (r_s) = 0.141–0.849; $P < 0.0001$, for

Fig. 4



Adjusted mean change (SE) from baseline in functional outcomes at week 12, LOCF in anxious depressed patients treated with desvenlafaxine 50 mg/day or placebo, ITT, and mITT populations. (a) ITT population. (b) mITT population. Anxious depressed patients had a baseline score of at least 7 on the anxiety-somatization factor of the HAM-D_{17}. *P* values were obtained from ANCOVA model including therapy, region, and baseline value as covariates. ANCOVA, analysis of covariance; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.

all measures except WPAI absenteeism ($P = 0.004$); Table 3]. Similar results were observed for desvenlafaxine-treated patients, with improvements in functional outcomes highly correlated with change in HAM-D_{17} (r_s = 0.539–0.848; $P < 0.0001$ for all comparisons), with the exception of WPAI absenteeism, which narrowly missed statistical significance ($r_s = 0.112$; $P = 0.06$). Similar findings were also reported for patients who received placebo [r_s = 0.194–0.846; $P < 0.0001$ for all comparisons with the exception of WPAI absenteeism ($P = 0.02$)].

Improvements from baseline in these functional outcomes were also highly correlated with global clinical improvement as measured by the CGI-I total scores at week 12, LOCF, in the overall, desvenlafaxine, and placebo groups ($P < 0.0001$–0.03; Table 3). Similar correlations were observed with CGI-S total scores at week 12, LOCF ($P < 0.0001$–0.04), with the exception of WPAI absenteeism in the desvenlafaxine group (r_s = 0.100; $P = 0.09$).

mITT population

In the analysis of baseline predictors of functional improvement in the overall group of the mITT population, baseline HAM-D_{17} total score predicted improvement in HAM-D_{17} psychomotor retardation [parameter estimate (SE): −0.16 (0.06); $P = 0.01$]; MADRS lassitude [parameter estimate (SE): 0.08 (0.04); $P = 0.03$]; and WPAI presenteeism [−1.4 (0.62); $P = 0.03$] at week 12, LOCF. For patients in the desvenlafaxine group, baseline HAM-D_{17} total score predicted improvement in

Table 2 Predictive value of percent change in HAM-D_{17}, CGI-I, and CGI-S total score from baseline at week 2 on functional outcomes at week 12 (LOCF)[a]

			HAM-D_{17} at week 2		CGI-I at week 2		CGI-S at week 2	
Functional outcome[b]	Treatment group	*n*	*F* value	*P* value	*F* value	*P* value	*F* value	*P* value
ITT population								
HAM-D_{17} psychomotor retardation factor	Overall	388	86.41	<0.0001	53.79	<0.0001	37.77	<0.0001
	Desvenlafaxine	258	64.94	<0.0001	46.64	<0.0001	28.46	<0.0001
	Placebo	130	17.22	<0.0001	6.65	0.01	6.74	0.01
MADRS lassitude	Overall	357	60.66	<0.0001	43.51	<0.0001	38.03	<0.0001
	Desvenlafaxine	242	50.61	<0.0001	38.00	<0.0001	24.13	<0.0001
	Placebo	115	11.14	0.001	6.29	0.01	12.55	0.0006
SDS total	Overall	388	41.18	<0.0001	39.41	<0.0001	29.37	<0.0001
	Desvenlafaxine	258	44.00	<0.0001	34.37	<0.0001	28.51	<0.0001
	Placebo	130	2.94	0.08	5.41	0.02	2.41	0.12
WPAI absenteeism	Overall	383	4.25	0.04	4.10	0.04	3.22	0.07
	Desvenlafaxine	256	3.45	0.06	6.29	0.01	4.79	0.03
	Placebo	127	0.94	0.33	0.01	0.91	0.02	0.89
WPAI presenteeism	Overall	384	22.52	<0.0001	20.34	<0.0001	6.98	0.009
	Desvenlafaxine	256	25.81	<0.0001	16.25	<0.0001	10.89	0.001
	Placebo	128	0.58	0.45	2.85	0.09	0.33	0.57
WPAI overall work impairment	Overall	381	23.52	<0.0001	22.29	<0.0001	9.15	0.003
	Desvenlafaxine	255	28.79	<0.0001	19.80	<0.0001	14.80	0.0002
	Placebo	126	0.37	0.54	2.27	0.13	0.43	0.51
WPAI activity impairment	Overall	385	28.26	<0.0001	24.47	<0.0001	22.24	<0.0001
	Desvenlafaxine	256	39.24	<0.0001	26.41	<0.0001	22.83	<0.0001
	Placebo	129	0.35	0.56	1.35	0.25	1.45	0.23
mITT population								
HAM-D_{17} psychomotor retardation factor	Overall	281	74.82	<0.0001	50.40	<0.0001	36.05	<0.0001
	Desvenlafaxine	188	49.25	<0.0001	34.43	<0.0001	21.10	<0.0001
	Placebo	93	18.45	<0.0001	11.35	0.001	11.52	0.001
MADRS lassitude	Overall	259	51.36	<0.0001	35.87	<0.0001	28.29	<0.0001
	Desvenlafaxine	178	39.14	<0.0001	23.44	<0.0001	17.24	<0.0001
	Placebo	81	9.72	0.003	10.03	0.002	9.43	0.003
SDS total	Overall	281	42.33	<0.0001	39.49	<0.0001	27.53	<0.0001
	Desvenlafaxine	188	42.22	<0.0001	31.97	<0.0001	24.10	<0.0001
	Placebo	93	2.41	0.124	5.64	0.02	2.29	0.13
WPAI absenteeism	Overall	276	4.12	0.04	2.77	0.10	1.20	0.27
	Desvenlafaxine	186	2.09	0.15	3.64	0.06	1.64	0.20
	Placebo	90	1.68	0.20	0.04	0.85	0.14	0.71
WPAI presenteeism	Overall	277	27.53	<0.0001	21.96	<0.0001	7.75	0.006
	Desvenlafaxine	186	23.23	<0.0001	11.46	0.0009	6.33	0.01
	Placebo	91	2.57	0.11	8.46	0.005	0.39	0.53
WPAI overall work impairment	Overall	274	29.49	<0.0001	24.22	<0.0001	9.61	0.002
	Desvenlafaxine	185	27.59	<0.0001	15.58	0.0001	9.13	0.003
	Placebo	89	1.76	0.19	6.19	0.01	0.17	0.68
WPAI activity impairment	Overall	278	37.75	<0.0001	29.48	<0.0001	24.62	<0.0001
	Desvenlafaxine	186	41.43	<0.0001	22.68	<0.0001	18.19	<0.0001
	Placebo	92	1.53	0.22	4.89	0.03	4.40	0.04

CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent-to-treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent-to-treat; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.

[a]Regression model: change in functional assessment at week 12, LOCF = % change of HAM-D at week 2.

[b]HAM-D_{17} psychomotor retardation factor = items 1, 7, 18, and 14 of HAM-D_{17}; MADRS lassitude = item 7 of MADRS.

HAM-D_{17} psychomotor retardation [−0.19 (0.08); $P = 0.01$] and WPAI presenteeism [−1.5 (0.74); $P = 0.04$] at week 12, LOCF. For patients in the placebo group, baseline HAM-D_{17} total score predicted improvement in MADRS lassitude [0.17 (0.07); $P = 0.03$], and baseline MADRS total score predicted improvement in SDS total score [−0.67 (0.25); $P = 0.01$] and WPAI activity impairment [−2.07 (0.94); $P = 0.03$] at week 12, LOCF. Baseline characteristics of age, sex, and duration of current depressive episode were not significant predictors of functional improvement in any treatment group.

In the mITT population, early improvement in the HAM-D_{17} total score at week 2 predicted change at week 12 in HAM-D_{17} psychomotor retardation factor, MADRS lassitude item, SDS total, and WPAI presenteeism, work productivity loss, and activity impairment for desvenlafaxine-treated patients (Table 2). Similarly, improvement in CGI-I and CGI-S total scores at week 2 predicted change at week 12 in all functional outcomes assessed, with the exception of WPAI absenteeism, in the desvenlafaxine treatment group.

Similar to results in the ITT population, the final improvement in depressive symptoms was also correlated with improvement in functional outcomes for patients in the mITT population. In the overall group, improvements from baseline in HAM-D_{17} psychomotor retardation factor, MADRS lassitude, SDS total and item scores, and scores on the four WPAI domains were highly

Table 3 Correlations between change in HAM-D_{17}, CGI-I, and CGI-S total scores and functional outcome scores from baseline to week 12 (LOCF), ITT population

		Correlation with change in HAM-D_{17} total score		Correlation with change in CGI-I total score		Correlation with change in CGI-S total score	
Functional outcome[a]	*n*	r_s	*P* value	r_s	*P* value	r_s	*P* value
HAM-D_{17} psychomotor retardation factor							
Overall	427	0.849	<0.0001	0.719	<0.0001	0.720	<0.0001
Desvenlafaxine	285	0.848	<0.0001	0.709	<0.0001	0.739	<0.0001
Placebo	142	0.846	<0.0001	0.730	<0.0001	0.674	<0.0001
MADRS lassitude							
Overall	390	0.652	<0.0001	0.623	<0.0001	0.663	<0.0001
Desvenlafaxine	265	0.661	<0.0001	0.631	<0.0001	0.663	<0.0001
Placebo	125	0.629	<0.0001	0.600	<0.0001	0.662	<0.0001
SDS total							
Overall	427	0.597	<0.0001	0.591	<0.0001	0.580	<0.0001
Desvenlafaxine	285	0.612	<0.0001	0.603	<0.0001	0.614	<0.0001
Placebo	142	0.560	<0.0001	0.563	<0.0001	0.511	<0.0001
SDS item 1 (work/studies)							
Overall	427	0.533	<0.0001	0.532	<0.0001	0.508	<0.0001
Desvenlafaxine	285	0.554	<0.0001	0.550	<0.0001	0.546	<0.0001
Placebo	142	0.471	<0.0001	0.480	<0.0001	0.417	<0.0001
SDS item 2 (social life)							
Overall	427	0.546	<0.0001	0.534	<0.0001	0.544	<0.0001
Desvenlafaxine	285	0.539	<0.0001	0.526	<0.0001	0.566	<0.0001
Placebo	142	0.561	<0.0001	0.549	<0.0001	0.503	<0.0001
SDS item 3 (family)							
Overall	427	0.539	<0.0001	0.536	<0.0001	0.521	<0.0001
Desvenlafaxine	285	0.562	<0.0001	0.553	<0.0001	0.548	<0.0001
Placebo	142	0.495	<0.0001	0.506	<0.0001	0.471	<0.0001
WPAI absenteeism							
Overall	422	0.141	0.0037	0.175	0.0003	0.128	0.009
Desvenlafaxine	283	0.112	0.06	0.167	0.005	0.100	0.09
Placebo	139	0.194	0.02	0.182	0.03	0.173	0.04
WPAI presenteeism							
Overall	423	0.523	<0.0001	0.478	<0.0001	0.439	<0.0001
Desvenlafaxine	283	0.557	<0.0001	0.476	<0.0001	0.490	<0.0001
Placebo	140	0.435	<0.0001	0.466	<0.0001	0.320	<0.0001
WPAI overall work impairment							
Overall	420	0.504	<0.0001	0.492	<0.0001	0.452	<0.0001
Desvenlafaxine	282	0.541	<0.0001	0.493	<0.0001	0.503	<0.0001
Placebo	138	0.406	<0.0001	0.472	<0.0001	0.329	<0.0001
WPAI activity impairment							
Overall	424	0.555	<0.0001	0.514	<0.0001	0.498	<0.0001
Desvenlafaxine	283	0.614	<0.0001	0.546	<0.0001	0.551	<0.0001
Placebo	141	0.431	<0.0001	0.445	<0.0001	0.392	<0.0001

CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent-to-treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; r_s, Pearson correlation coefficient; SDS, Sheehan Disability Scale; WPAI, Work Productivity and Impairment Questionnaire.
[a]HAM-D_{17} psychomotor retardation factor = items 1, 7, 18, and 14 of HAM-D_{17}; MADRS lassitude = item 7 of MADRS.

correlated with improvement in the HAM-D_{17} total score at week 12, LOCF [Pearson correlation coefficient (r_s) = 0.130–0.860; $P < 0.0001$ for all measures except WPAI absenteeism ($P = 0.02$)]. For desvenlafaxine-treated patients in the mITT population, improvements in functional outcomes highly correlated with change in HAM-D_{17} [$r_s = 0.538$–0.860; with the exception of WPAI absenteeism, which was not significant ($r_s = 0.09$; $P = 0.18$)]. Similar findings were also observed for patients who received placebo ($r_s = 0.424$–0.857; $P < 0.0001$ for all comparisons), with the exception of WPAI absenteeism, which was only borderline significant ($P = 0.07$).

Discussion

This post-hoc analysis of data from a large, randomized, placebo-controlled study (Dunlop *et al.*, 2011) prospectively evaluated the effects of treatment with the SNRI desvenlafaxine on functional outcomes in employed patients with MDD. For patients in the ITT population, treatment with desvenlafaxine 50 mg/day for 12 weeks significantly improved measures of occupational and physical functioning, as evident from improvements in HAM-D_{17} item 7 work/activities, HAM-D_{17} psychomotor retardation factor, and WPAI presenteeism scores. Patients in the mITT population, a population with more severe MDD (baseline HAM-D_{17} total score ≥ 20), experienced significant improvements in occupational, physical, and social functioning, as indicated by improvements in HAM-D_{17} psychomotor retardation factor, WPAI presenteeism, and WPAI activity impairment scores.

The improvements in functional outcomes observed in this secondary analysis expand on the findings of the primary study (Dunlop *et al.*, 2011) and are consistent with the results of other desvenlafaxine studies. A pooled analysis of individual patient data ($n = 2913$) from nine

placebo-controlled studies of desvenlafaxine versus placebo showed significant improvements in SDS total and individual item scores, the HAM-D_{17} work/activities item, and the MADRS lassitude item (Soares *et al.*, 2009). In contrast to this 12-week trial of employed patients with MDD, the pooled analysis included 8-week studies of patients with MDD whose employment status was not specified.

These results are also consistent with other antidepressant trials assessing functional outcomes (Kocsis *et al.*, 2002; Szegedi *et al.*, 2003; Trivedi *et al.*, 2010; Dunlop *et al.*, 2011; Oakes *et al.*, 2012). In an analysis of two phase 4 clinical trials using similar protocols and comparable patient populations, the SNRI duloxetine showed superiority to placebo in improving HAM-D_{17} item 7 work/activities scores at week 8 (primary end point) in one trial ($P < 0.001$), but narrowly missed statistical significance in the second trial ($P = 0.051$) (Oakes *et al.*, 2012). Long-term, maintenance therapy (18 months) with the selective serotonin reuptake inhibitor sertraline significantly improved psychosocial and physical functioning in patients with chronic major and double depression, as measured by change from maintenance-phase baseline in scores on the Social Adjustment Scale – Self-Report, Medical Outcomes Study 36-Item Short-Form Health Survey, and Longitudinal Interval Follow-up Evaluation ($P \leq 0.001$–0.02). The study also showed that long-term antidepressant treatment with sertraline was required to sustain improvements in functioning as cessation of treatment resulted in rapid decline of functional symptoms (Kocsis *et al.*, 2002). Using a comparable study design, Trivedi *et al.* (2010) reported significant improvements in multiple domains of functioning, including quality of life ($P = 0.004$–0.013), work functioning ($P = 0.007$–0.010), and interpersonal functioning ($P = 0.004$–0.048), following long-term, maintenance treatment (1 and 2 years) with the SNRI venlafaxine versus placebo.

Key strengths of this secondary analysis include the randomized study design, the large population of prospectively identified adults who were gainfully employed, and the duration of antidepressant treatment. It is important to note that functional improvement often lags behind depressive symptom improvement, even in patients who have achieved response or remission (Papakostas, 2009). In addition, a systematic review of depression treatment studies, including both pharmacotherapy and psychotherapy trials, found that functional outcomes were not always significantly correlated with changes in symptom scales (McKnight and Kashdan, 2009). In this secondary analysis, improvements in functioning were observed with 12 weeks of desvenlafaxine treatment and improvements in functional outcomes were highly correlated with improvement in depressive symptoms across treatment groups. These data suggest that improvement in depressive symptoms and functional outcomes occurs together. This conclusion is also consistent with a 10-study pooled analysis of desvenlafaxine versus placebo in samples of patients with MDD ($n = 3530$) of indeterminate occupational status, in which improvement in HAM-D_{17} scores at 8 weeks were significantly correlated with improvement in scores on the SDS and the World Health Organization Well-Being Index (Guico-Pabia *et al.*, 2012; World Health Organization, 2012).

Early improvement in depressive symptoms also predicted final improvements in functional outcomes for patients who received treatment with desvenlafaxine. Many studies have shown that early improvement in depressive symptoms, within the first 2 weeks, is associated with, and predictive of, the final symptom response (Lam, 2012). However, there have been fewer studies on whether early improvement in symptoms also predicts improvement in functional outcomes. To our knowledge, this is the first study to examine this issue. We found that improvement at 2 weeks, as assessed by the HAM-D_{17}, CGI-I, and CGI-S, was highly predictive of improvements in all functional outcomes at 12 weeks.

The ITT results of this study also found improvement in functioning in subgroups of patients with low energy and anxious depression. Low energy and anxiety are depressive symptoms that may be especially impairing of work functioning. In a survey of employed patients with MDD, anergia and tension were identified by 66 and 54%, respectively, of depressed patients as significantly interfering with their occupational functioning (Lam *et al.*, 2012). A study of primary care patients with depression also found that fatigue/low energy was the symptom that best predicted occupational impairment (absenteeism and reduced work productivity), both at baseline and after 3 months of naturalistic treatment (Swindle *et al.*, 2001). In that study, the severity of depression was not specified. In contrast, in the mITT analysis in this study, which included more severely depressed patients at baseline, the normal-energy subgroup (defined as baseline HAM-D_{17} psychomotor retardation factor score < 9) also showed significant improvement with desvenlafaxine in several occupational outcomes. Hence, it is important to note that functional outcomes, including several work outcomes, improved significantly with desvenlafaxine treatment in both normal-energy and low-energy subgroups.

The limitations of this study must be acknowledged. The study population did not include individuals who were unemployed or who had mild symptoms of depression. Moreover, patients included in this study represent a population with very limited or no comorbid medical conditions or concomitant medication use; therefore, the ability to generalize these results to typical outpatients may be limited. We did not correct for multiple comparisons in the statistical analysis; thus, the positive results should be considered preliminary until replication. Finally, a fixed dose of 50 mg desvenlafaxine was used. Although clinical studies have not consistently found better response rates with higher doses of desvenlafaxine,

it is possible that individual patients could benefit from a higher dose (e.g. 100 mg/day), specifically with respect to some clinical and functional outcomes.

Conclusion

Treatment with desvenlafaxine 50 mg/day for 12 weeks significantly improved HAM-D_{17} work/activities, HAM-D_{17} psychomotor retardation, and WPAI presenteesim scores from baseline in patients with MDD. In addition, desvenlafaxine 50 mg/day significantly improved functional outcomes in subgroups of patients with lower energy (HAM-D_{17} psychomotor retardation and SDS work/studies item) or anxious depression (HAM-D_{17} psychomotor retardation). Early improvement in depressive symptoms predicted improvements in functional outcomes for patients who received desvenlafaxine 50 mg/day, and improvement in functional outcomes highly correlated with improvement of depressive symptoms across treatment groups.

Return to normal functioning is an important goal of antidepressant therapy (Zimmerman *et al.*, 2006); however, the impact of treatment on functional outcomes has yet to be fully determined. Patient response and remission, on the basis of specific cut-off scores on symptom severity scales, are often the primary focus of antidepressant trials, but may not reflect the most important clinical outcomes (Oakes *et al.*, 2012). Clinical trials of antidepressant therapies should include assessments of functional impairment as an outcome measure of treatment success in patients with MDD (Bech, 2005; McKnight and Kashdan, 2009; Greer *et al.*, 2010; Langlieb and Guico-Pabia, 2010; Lam *et al.*, 2011).

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Conflicts of interest

Raymond W. Lam: Grant/Research Support: Bristol-Myers Squibb, Canadian Institutes of Health Research, Canada Psychiatric Association Foundation, Litebook Company, Lundbeck, Pfizer, St Jude Medical, UBC Institute of Mental Health/Coast Capital Savings. Speaker Honoraria: AstraZeneca, Canadian Psychiatric Association, Canadian Network for Mood and Anxiety Treatments, Lundbeck, Lundbeck Institute, Mochida, Pfizer, Servier. Consultant: AstraZeneca, Bristol Myers Squibb, Canadian Network for Mood and Anxiety Treatments, Eli Lilly, Litebook Company Ltd (unpaid), Lundbeck, Pfizer, Takeda.

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Ming-Ann Hsu, Rana Fayyad, and Matthieu Boucher are Pfizer employees.

Christine Guico-Pabia is a former Pfizer employee.

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