The impact of fatigue and energy on work functioning and impairment in patients with major depressive disorder treated with desvenlafaxine

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Fatigue and low energy are cardinal symptoms of major depressive disorder (MDD) that have an impact on work functioning. Antidepressants with noradrenergic activity have been hypothesized to improve symptoms of fatigue and low energy. We examined the impact of these symptoms on work functioning in patients with MDD treated with the serotonin and noradrenaline reuptake inhibitor, desvenlafaxine. A secondary analysis was carried out from a study of employed adult outpatients ($n = 35$) with MDD and subjective cognitive complaints treated with desvenlafaxine 50–100 mg/day for 8 weeks. Multiple regression analyses modeled improvement in work functioning measures (Lam Employment Absence and Productivity Scale, Health and Work Performance Questionnaire, Sheehan Disability Scale) with measures of fatigue (Patient-Reported Outcomes Measurement Information System Fatigue scale and 20-item Hopkins Symptom Check List Energy scale). Patients showed a significant improvement in Montgomery–Åsberg Depression Rating Scale scores as well as in fatigue and work functioning measures following treatment. Fatigue measures were significantly associated with improvement in some (Lam Employment Absence and Productivity Scale, Sheehan Disability Scale), but not all (Health and Work Performance Questionnaire) work functioning measures, independent of improvement in overall depressive symptoms. The limitations of this study include the small sample size and the lack of a placebo or a comparison group. Fatigue and low energy are important symptoms that are associated with occupational impairment in MDD. Treatments that improve these symptoms are likely to improve work functioning. ***Int Clin Psychopharmacol*** **32:343–349**

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Introduction

Major depressive disorder (MDD) is widely recognized as one of the most disabling medical conditions worldwide (World Health Organization, 2017). The emotional, cognitive, and physical symptoms associated with MDD are particularly impairing for occupational functioning (Kessler *et al.*, 2006; Greer *et al.*, 2010). Among the many symptoms of MDD, fatigue and low energy are commonly experienced and may have particular importance for functional impairment (Demyttenaere *et al.*, 2005; Lam *et al.*, 2013). In a retrospective study, 91% of patients diagnosed with MDD or dysthymia experienced fatigue, and, compared with other depressive symptoms, fatigue was the most predictive of absenteeism and occupational productivity at baseline and the 3-month follow-up (Swindle *et al.*, 2001). In a survey of 164 depressed outpatients, low energy and daytime fatigue interfered more with occupational functioning than other depressive symptoms (Lam *et al.*, 2015). Fatigue may also persist as a residual symptom even when other depressive symptoms have improved (Fava *et al.*, 2014); for example, in one study, 39% of patients in symptom remission continued to experience residual fatigue (Nierenberg *et al.*, 1999). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, after 12 weeks of citalopram treatment, 66% of 2868 patients still had residual symptoms of fatigue/low energy and higher baseline fatigue/energy scores predicted a lower likelihood of symptom remission (Ferguson *et al.*, 2014).

Fatigue and energy loss are terms often used interchangeably, although fatigue is generally defined as the feeling of weariness, tiredness, or lack of energy. The neurobiology of fatigue within MDD is still poorly understood. Various studies have found evidence that depression-related fatigue is associated with dysfunction of neurotransmitters including noradrenaline and dopamine (Blier and Briley, 2011), decreased neuronal activity in the prefrontal cortex (Gold and Chrousos, 1999; MacHale *et al.*, 2000), dysregulation of the hypothalamic–pituitary–adrenal axis (Silverman *et al.*, 2010), and neuroimmune dysfunction including inflammatory cytokines (Miller *et al.*, 2009).

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Given the interest in neurotransmitter dysfunction, some studies have suggested that antidepressants with noradrenergic activity may have greater treatment specificity with fatigue/low energy symptoms compared with agents that selectively affect serotonin (Pae *et al.*, 2007; Blier and Briley, 2011). For example, a pooled analysis of five studies found that bupropion was superior to selective serotonin reuptake inhibitors in reducing fatigue and low energy (Fehnel *et al.*, 2004). Other treatment studies have suggested that serotonin and noradrenaline reuptake inhibitors (SNRIs) have specific effects in reducing fatigue and improving energy. However, there has been significant variability in the assessment of fatigue/energy symptoms in clinical trials. The common clinician-rated symptom scales [e.g. Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979)] used in depression studies have no items specifically addressing fatigue/energy symptoms, although fatigue and low energy may contribute toward the Lassitude item on the MADRS. Patient-rated scales often include only one item [e.g. Personal Health Questionnaire-9 (Kroenke *et al.*, 2001)] for fatigue/energy. Many treatment studies examining fatigue did not use specific measures of fatigue/energy, but instead relied on unvalidated proxy items from the HAM-D and MADRS.

Given the limited information available on the treatment effects of fatigue/energy symptoms on functional outcomes in MDD, we carried out a secondary analysis from a study examining cognition in employed patients with MDD treated with the SNRI desvenlafaxine. Both fatigue/energy and functional outcomes were assessed in this study using several different validated self-report measures. We hypothesized that an improvement in fatigue/energy symptoms would be specifically associated with an improvement in work and social functioning, independent of improvements in depressive severity.

Participants and methods

The University of British Columbia Clinical Research Ethics Board approved all study activities and all participants provided written informed consent. This was a secondary analysis of a study with a primary objective of examining cognition in patients with MDD. The methods have been described previously (Lam *et al.*, 2016a), but in brief, participants were outpatients 19–55 years of age with a diagnosis of a major depressive episode by *Diagnostic and statistical manual of mental disorders*, 4th ed., text revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000) confirmed by the Mini International Neuropsychiatric Interview (Sheehan *et al.*, 1998). Inclusion criteria also included current paid employment (minimum 15 work hours/week), a score on the MADRS of at least 23, and a score on the British Columbia Cognitive Complaints Inventory (Iverson and Lam, 2013) of at least 6 (indicating the presence of subjective cognitive complaints). Exclusion criteria included a lifetime diagnosis of bipolar disorder or other significant primary psychiatric diagnoses, active alcohol or substance abuse or dependence in the past year, a history of significant head trauma, unstable medical comorbidity, treatment-resistant depression (defined as 2 or more failed adequate trials of medication treatment in the current episode), previous lifetime use of desvenlafaxine or electroconvulsive therapy, and use of other concurrent treatments for depression.

Eligible participants on antidepressants were tapered off and medication free for at least 1 week before baseline assessment (5 weeks if they were on fluoxetine). After completing baseline assessments, patients were treated for 8 weeks with desvenlafaxine starting at 50 mg/day. Patients were seen every 2 weeks and the desvenlafaxine dose could be increased to 100 mg/day at week 2 or later at the discretion of the clinic psychiatrist. Hypnotics and sedatives were not permitted. Patients were assessed at baseline and post-treatment with the MADRS and self-rated measures.

Measures

Work functioning was assessed with The Lam Employment Absence and Productivity Scale (LEAPS) (Lam *et al.*, 2009) and the World Health Organization Health and Work Performance Questionnaire (HPQ) (Kessler *et al.*, 2003). The LEAPS is a validated self-report questionnaire developed to assess work functioning and productivity in patients with MDD and has shown sensitivity to change in clinical trials (Lam, 2014). The seven items are rated on a five-point scale of frequency (0 = none of the time, 0%, to 4 = all of the time, 100%). A productivity subscale consists of the sum of three items related to work functioning (making more mistakes, doing poorer quality work, and getting less work done), with total scores ranging from 0 to 9. The HPQ is a comprehensive self-rated questionnaire that assesses illness-related work absence and productivity loss (Kessler *et al.*, 2004; Wang *et al.*, 2007). The HPQ-Overall Work Performance item is rated 0–10, with higher scores indicating better work performance. Functional impairment was also assessed using the Sheehan Disability Scale (SDS) (Leon *et al.*, 1997), a three-item self-report scale querying overall impairment in work, social, and family domains. The SDS-Total score ranges from 0 (no impairment) to 30 (extreme impairment).

Fatigue/low energy was assessed using two self-rated scales: the Fatigue Short Form scale from the National Institutes of Health-sponsored Patient-Reported Outcomes Measurement Information System (PROMIS) (Cella *et al.*, 2010) and the Energy subscale from the 20-item Hopkins Symptom Check List (SCL-20, Simon *et al.*, 1993). The PROMIS Item Bank v1.0 – Fatigue–Short Form 8a scale assesses fatigue experience and functional interference in the past 7 days.

The long-form PROMIS Fatigue item bank consists of 95 items, and was found to be highly correlated with validated fatigue/energy scales, including the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (Yellen *et al.*, 1997) ($r=0.95$, $P<0.001$) and the SF-36 Vitality Scale ($r=0.89$, $P<0.001$) (Ware and Gandek, 1994; Cella *et al.*, 2010). The short form of the PROMIS Fatigue scale used in our study was significantly correlated ($r=0.76$) with the full 95-item bank (Cella *et al.*, 2010). The eight items (e.g. I feel fatigued; How much were you bothered by fatigue, on average; To what degree did your fatigue interfere with your physical functioning) are scored on a Likert scale ranging from 0 (not at all) to 4 (very much), with total scores ranging from 0 to 32.

The SCL Energy scale assesses low energy during the past week and includes five items (trouble concentrating, feeling slow/low energy, feeling everything is an effort, feeling no interest in things, and thinking/speaking/moving slower) scored on a Likert scale with responses ranging from 0 (not at all) to 4 (extremely) and total scores ranging from 0 to 20. For both measures, higher scores indicate greater problems with fatigue and energy. The SCL Energy scale was derived from a factor analysis of the SCL-20 in a sample of 573 patients diagnosed with depression (Swindle *et al.*, 2001). The factor analysis showed four factors corresponding to mood, sleep, energy, and guilt. The five-item SCL Energy scale was correlated significantly ($r=0.64$, $P=0.01$) with the SF-36 Vitality Scale.

Statistical analyses were carried out using SPSS, v.18 (SPSS Inc., 2009). Correlations were calculated using Pearson's correlations and paired *t*-tests were performed on the pre–post outcome data with effect size calculation using Cohen's *d* (Cohen 1988). Generally, effect sizes of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively (Cohen, 1988). A series of multiple regression analyses were carried out with the pre–post change in work or functional measure (LEAPS, HPQ, SDS) as the dependent variable and baseline functional measure, MADRS change, score, and the pre–post change in fatigue measure (PROMIS Fatigue, SCL Energy) as predictor variables. For example, when we examined the relationship between PROMIS Fatigue and LEAPS-Productivity, the dependent variable was the change in LEAPS-Productivity score and the predictor variables were baseline LEAPS-Productivity score, the MADRS change score, and the PROMIS Fatigue change score. For reference, the standardized β coefficient from the regression analysis indicates the strength of the predictor variable, that is, how many standard deviations (SDs) the dependent variable (LEAPS, HPQ, SDS) changed per SD change in the predictor variable (PROMIS Fatigue, SCL Energy).

Results

In the primary study, 55 individuals were screened and eligible, 40 individuals enrolled and completed the baseline assessment, and 36 individuals completed treatment. This analysis is based on the 35 participants who had post-treatment scores on the fatigue/energy measures. Table 1 shows the demographic and clinical characteristics of the sample. Most patients were women ($n=20$, 57%), had recurrent MDD ($n=25$, 71%), and were scheduled to work a mean (SD) of 66.7 (22.2) h in the past 2 weeks. There were no significant differences between men and women on any of the demographic or clinical variables.

Table 2 presents descriptive statistics for the baseline and post-treatment ratings on individual PROMIS scale items. For the item 'how often did you have to push yourself to get things done because of your fatigue?', 30.8% at baseline and 5.6% following treatment reported either often or always. For the item 'how often did you have trouble finishing things because of your fatigue?', 28.2% at baseline and 2.8% following treatment reported either often or always.

Table 3 shows the baseline and post-treatment clinical and functional assessments. At the end of 8 weeks, the mean (SD) desvenlafaxine dose was 74.3 (24.6) mg (50 mg: 18 patients; 100 mg: 17 patients). As reported previously, there were significant improvements in MADRS and functional measures after desvenlafaxine treatment. There were no significant correlations between clinical demographic variables (age, sex, education years, baseline MADRS score) and changes in the LEAPS, HPQ, or SDS. There was also a significant improvement in both PROMIS Fatigue and SCL Energy scales, with large pre–post effect sizes of 1.20 and 1.53, respectively.

The regression models (Table 4) all showed significant associations between the predictor variables and the functional outcome measures. In general, there was a strong significant association between the three predictor variables and the various functional outcome measures, as reflected in medium to large R^2 values. The changes in functional outcomes were all significantly and independently associated with changes in MADRS scores, with standardized β (which reflects the relative predictive strength of the predictor variables) ranging from 0.296 for the LEAPS to 0.441 for the HPQ. As hypothesized, changes in both fatigue/energy scales significantly and independently predicted change in the functional measures too. For example, fatigue/energy predicted changes in the LEAPS ($\beta=0.371$ for SCL Energy; 0.314 for

Table 1 Demographic and clinical characteristics of patients at baseline ($n=35$)

Women : men (%)	57 : 43
Age [mean (SD)] (years)	39.2 (10.9)
Single episode : recurrent (%)	29 : 71
Education level [mean (SD)] (years)	15.6 (2.1)
Hours scheduled to work in the past 2 weeks [mean (SD)]	66.7 (22.2)

Table 2 Baseline and post-treatment ratings on the PROMIS fatigue scale

	Baseline ratings			Post-treatment ratings		
PROMIS Item Bank v1.0 – Fatigue–Short Form 8a	Mean	SD	Moderate + (%)	Mean	SD	Moderate + (%)
1: I feel fatigued	3.08	1.22	51.3	1.83	1.36	16.7
2: I have trouble starting things because I am tired	2.72	1.21	30.8	1.61	1.34	8.3
3: How run-down did you feel on average?	2.97	1.11	38.5	1.81	1.21	11.1
4: How fatigued were you on average?	2.90	1.17	35.9	1.78	1.35	13.9
5: How much were you bothered by your fatigue on average?	2.92	1.26	43.6	1.56	1.30	8.3
6: To what degree did your fatigue interfere with your physical functioning?	2.51	1.34	25.6	1.44	1.34	8.3
7: How often did you have to push yourself to get things done because of your fatigue?	2.82	1.14	30.8	1.78	1.24	5.6
8: How often did you have trouble finishing things because of your fatigue?	2.72	1.19	28.2	1.56	1.21	2.8
Mean item score	3.00	0.98	NA	1.69	1.20	NA

The responses (scoring) for items 1–6 are as follows: not at all (1), a little bit (2), somewhat (3), quite a bit (4), or very often (5); and for items 7 and 8 are: never (1), rarely (2), sometimes (3), often (4), and always (5).
Moderate + = quite a bit or very often for items 1–6, and often or always for items 7 and 8.

Table 3 Assessments at baseline and post-treatment ($n = 35$)

Assessments	Baseline [mean (SD)]	Post-treatment [mean (SD)]	Pre–post change [mean (SD)]	Paired-samples *t*-test, pre–post-treatment	Cohen's *d*
MADRS	28.37 (3.95)	10.86 (8.05)	−17.51 (8.63)	$t(34) = 12.01$, $P < 0.001$	2.93
LEAPS-Productivity	5.69 (3.45)	2.91 (3.02)	−2.77 (3.16)	$t(34) = 5.18$, $P < 0.001$	0.86
HPQ-Overall	5.54 (1.80)	7.14 (1.70)	1.59 (1.83)	$t(34) = -5.25$, $P < 0.001$	0.91
SDS-Total	20.70 (4.98)	11.49 (8.41)	−9.59 (9.31)	$t(34) = 5.86$, $P < 0.001$	1.38
SDS-Work	6.41 (2.18)	3.37 (2.93)	−3.15 (3.05)	$t(34) = 5.96$, $P < 0.001$	1.19
PROMIS Fatigue	24.03 (7.83)	13.57 (9.65)	−10.46 (11.26)	$t(34) = 5.49$, $P < 0.001$	1.20
SCL Energy	13.03 (3.67)	6.23 (5.19)	−6.80 (5.95)	$t(34) = 6.03$, $P < 0.001$	1.53

For all measures, lower scores indicate better outcomes, except the HPQ-Overall, for which higher scores indicate better functioning.
HPQ-Overall, Health and Work Performance Questionnaire, Overall Work Performance; LEAPS, Lam Employment Absence and Productivity Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; PROMIS Fatigue, Patient-Reported Outcomes Measurement Information System, Item Bank v1.0 – Fatigue–Short Form 8a; SCL Energy, Symptom Check List 20-item, Energy scale; SDS-Total, Sheehan Disability Scale, Total score; SDS-Work, Sheehan Disability Scale, Work item.

PROMIS Fatigue) and SDS-Work scales ($\beta = 0.243$ for SCL Energy; 0.345 for PROMIS Fatigue), even after adjusting for improvement in the MADRS. For the SDS-Total score change, the standardized β of the energy and fatigue measures was larger than that of the MADRS (0.427 vs. 0.355 for SCL Energy; 0.482 vs. 0.361 for PROMIS Fatigue), suggesting a greater predictive effect for fatigue/energy compared with overall depression severity. This was not the case for the HPQ, however, in which neither fatigue/energy scale predicted changes in HPQ-Overall performance.

Discussion

Desvenlafaxine has established efficacy in the treatment of MDD (Liebowitz *et al.*, 2008) and has also been shown to improve functional outcomes (Soares *et al.*, 2009). In our study, treatment with desvenlafaxine significantly improved both fatigue/energy symptoms and work functioning in employed patients with MDD. This improvement was independent of an improvement in overall depression severity. These results add to the still-small database of information on the effects of antidepressants on work functioning and on moderators and mediators of functional improvement. For example, a systematic review and meta-analysis of effects of antidepressants on occupational functioning in patients with MDD (Evans *et al.*, 2016) found only one study, involving desvenlafaxine as treatment (Dunlop *et al.*, 2011), that specifically examined a sample of employed patients. The meta-analysis, which included studies with patients unselected for employment status, antidepressants were found to be significantly superior to placebo in improving SDS-Work scores at 8 weeks, with a mean difference of 0.73 and a standardized mean difference of 0.28, representing small effects (Evans *et al.*, 2016). A subset analysis of SNRI medications found a similar mean difference and standardized mean difference of 0.72 and 0.28, respectively, also favoring active treatment over placebo. The pre–post changes found in that meta-analysis with active drug are consistent with the improvement found in the SDS-Work item in our study.

Interestingly, in a secondary analysis of Dunlop *et al.*'s (2011) study, desvenlafaxine was found to improve symptom and functional outcomes in patients with MDD with baseline low energy, but not in those with normal energy (Lam, 2014). In that study, however, a validated measure of energy was not used; instead, energy was assessed using several items from the HAM-D.

This study examined fatigue/energy using two validated measures that have been used in depression studies. One study using the PROMIS Fatigue scale examined data from individuals recruited through a random sampling method to ensure that the sample was representative of the general population (Junghaenel *et al.*, 2011). The average

Table 4 Summary of multiple regression analyses

	R^2	Adjusted R^2	*B*	SE *B*	β	*P*
Outcome: LEAPS-Productivity change						
Model 1	0.701	0.673				
Baseline LEAPS-Productivity			−0.567	0.090	−0.619	<0.0001
MADRS change			0.108	0.046	0.296	0.024
SCL Energy change			0.197	0.066	0.371	0.005
Model 2	0.686	0.655				
Baseline LEAPS-Productivity			−0.584	0.093	−0.638	<0.0001
MADRS change			0.131	0.044	0.357	0.005
PROMIS Fatigue change			0.088	0.033	0.314	0.013
Outcome: HPQ-Overall change						
Model 1	0.489	0.440				
Baseline HPQ-Overall			−0.550	0.131	−0.551	<0.0001
MADRS change			−0.092	0.034	−0.441	0.011
SCL Energy change			0.008	0.050	0.028	0.868
Model 2	0.489	0.439				
Baseline HPQ-Overall			−0.555	0.129	−0.555	<0.0001
MADRS change			−0.089	0.032	−0.426	0.009
PROMIS Fatigue change			0.000	0.024	0.003	0.986
Outcome: SDS-Work change						
Model 1	0.541	0.498				
Baseline SDS-Work			−0.450	0.168	−0.330	0.012
MADRS change			0.150	0.055	0.423	0.010
SCL Energy change			0.630	0.394	0.243	0.120
Model 2	0.591	0.553				
Baseline SDS-Work			−0.475	0.159	−0.348	0.005
MADRS change			0.139	0.048	0.390	0.007
PROMIS Fatigue change			0.094	0.036	0.345	0.014
Outcome: SDS-Total change						
Model 1	0.645	0.611				
Baseline SDS-Total			−0.396	0.201	−0.221	0.058
MADRS change			0.383	0.144	0.355	0.012
SCL Energy change			3.361	1.076	0.427	0.004
Model 2	0.705	0.678				
Baseline SDS-Total			−0.451	0.179	−0.251	0.017
MADRS change			0.389	0.122	0.361	0.003
PROMIS Fatigue change			0.400	0.093	0.482	<0.0001

β, standardized β; *B*, unstandardized β; HPQ-Overall, Health and Work Performance Questionnaire, Overall Work Performance; LEAPS, Lam Employment Absence and Productivity Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; PROMIS fatigue, Patient-Reported Outcomes Measurement Information System, Item Bank v1.0 – Fatigue–Short Form 8a; R^2, variance; SCL-20 energy, Symptom Check List, 20-item, Energy scale; SDS-Total, Sheehan Disability Scale, Total score; SDS-Work, Sheehan Disability Scale, Work item; SE *B*, standard error of β.

item score (SD) on the PROMIS Fatigue scale was 2.16 (0.87) for the general population sample ($n=666$), 2.7 (0.9) for those with a diagnosis of depression ($n=136$), and 3.4 (0.7) for those currently experiencing depression ($n=38$) (Junghaenel *et al.*, 2011). These results are similar to those in our depressed sample in which the average item PROMIS Fatigue score was 3.0 (0.98) before treatment and 1.7 (1.2) after treatment with desvenlafaxine. In another sample of 573 depressed patients, the SCL Energy scale was found to have higher correlations with occupational impairment, as measured by the Work Limitation Questionnaire (Lerner *et al.*, 2001), than the other SCL-20 factors (mood, sleep and guilt) identified by factor analysis (Swindle *et al.*, 2001). In addition, there were significant correlations between change in the SCL Energy scale and work productivity gains on the Work Limitation Questionnaire (e.g. percent effectiveness at work, $r=-0.35$; output demands, $r=0.51$; time management, $r=0.61$; interpersonal demands, $r=0.46$; all $P=0.01$, two tailed) in depressed patients at the 3-month follow-up after naturalistic treatment with various antidepressants (Swindle *et al.*, 2001).

In our study, we found that fatigue/energy symptoms improved by 44 and 52% over the course of 8 weeks of antidepressant treatment, as measured on the PROMIS Fatigue scale and the SCL Energy scale, respectively. Improvement in fatigue/energy was associated significantly with functional improvement in some work functioning measures (LEAPS-Productivity, SDS-Work), but not on others (HPQ), and this appears to be independent of improvement in depression severity, as assessed by the MADRS.

The discrepant HPQ results may be because of the different assessment periods for the scale (4 weeks, vs. 1 or 2 weeks for the others), thus under-representing improvement in work functioning experienced later in treatment. Improvements on functional outcome measures may occur more slowly than changes in symptoms of depression assessed on rating scales, suggesting that a study period of more than 8 weeks may be required to capture the full extent of functional improvement (Soares *et al.*, 2009). Nonetheless, after treatment with desvenlafaxine for 8 weeks, work functioning improved by 49% as measured by both the LEAPS-Productivity and the

SDS-Work subscales. Given that clinical response is often defined as a reduction of at least 50% on a given symptom scale, the fact that we have found similar improvements in work functioning in our 8-week study, on both the LEAPS-Productivity and the SDS-Work subscales, is encouraging.

Our results with desvenlafaxine are also consistent with other studies of fatigue/energy in SNRIs. Venlafaxine (Hewett *et al.*, 2009, 2010) and levomilnacipran (Thase *et al.*, 2016) were shown to improve scores on the Motivation and Energy Inventory (Fehnel *et al.*, 2004) compared with placebo. Levomilnacipran also improved fatigue symptoms compared with placebo (Freeman *et al.*, 2016). In secondary analyses of a randomized trial in which patients were treated with reboxetine (a noradrenaline reuptake inhibitor) or citalopram, there was no evidence of a difference in their efficacy in treating fatigue as a symptom of depression, but reboxetine might have been more effective in treating depression in individuals who had higher levels of pretreatment fatigue (Bould *et al.*, 2012). Randomized clinical trials will be needed to determine whether there is a differential response of fatigue/energy to SNRIs versus non-SNRI antidepressants, and the impact on functional outcomes.

Our study has several important methodological limitations. First, this was an open-label study – we did not have a placebo condition or a comparator drug condition. Second, the sample size was relatively small. Third, the sample was enriched to include only those individuals who were employed. We did not include those who were severely ill and functionally disabled, and thus our results cannot be generalized to a broader population of adults with MDD. Finally, fatigue is a common residual symptom of MDD (Fava *et al.*, 2014). The present study could not investigate the effect of desvenlafaxine on fatigue as a residual symptom because of its short-term design (8 weeks).

Conclusion

Occupational impairment is a significant concern for patients and society, given the economic burden of depression. Depressed employed patients with MDD have significant fatigue/energy symptoms that are significantly improved with 8 weeks of treatment with the SNRI desvenlafaxine 50–100 mg. The improvement in occupational and social functioning is predicted by improvement in fatigue/energy, even when adjusted for improvement in overall depression severity. These findings indicate that fatigue/energy are important symptoms to target during MDD treatment to ensure optimal functional recovery.

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Conflicts of interest

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