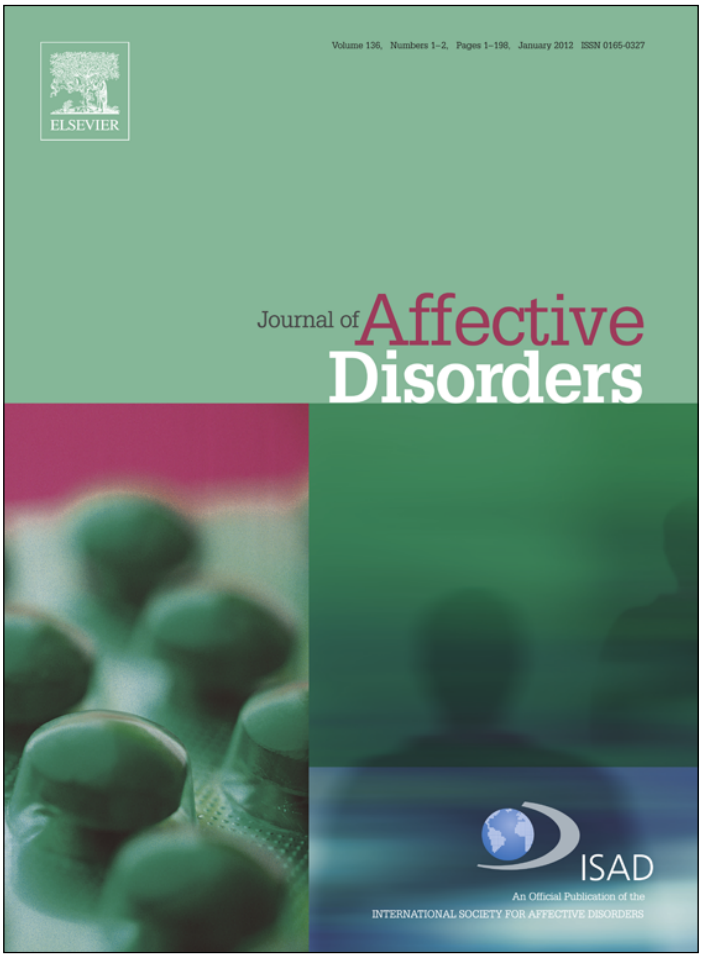

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Research paper

The effects of desvenlafaxine on neurocognitive and work functioning in employed outpatients with major depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is associated with staggering personal and economic costs, a major proportion of which stem from impaired psychosocial and occupational functioning. Few studies have examined the impact of depression-related cognitive dysfunction on work functioning. We examined the association between neurocognitive and work functioning in employed patients with MDD.

Methods: Employed adult outpatients (n=36) with MDD of at least moderate severity ($\geq$23 on the Montgomery Asberg Depression Rating Scale, MADRS) and subjective cognitive complaints completed neurocognitive tests (CNS Vital Signs computerized battery) and validated self-reports of their work functioning (LEAPS, HPQ) before and after 8 weeks of open-label treatment with flexibly-dosed desvenlafaxine 50–100 mg/day. Relationships between neurocognitive tests and functional measures were examined using bivariate correlational and multiple regression analyses, as appropriate. An ANCOVA model examined whether significant change in neurocognitive performance, defined as improvement of $\geq$1 SD in the Neurocognition Index (NCI) from baseline to post-treatment, was associated with improved outcomes.

Results: Patients showed significant improvements in depressive symptom, neurocognitive, and work functioning measures following treatment with desvenlafaxine (e.g., MADRS response=77% and MADRS remission=49%). There were no significant correlations between changes in NCI or cognitive domain subscales and changes in MADRS, LEAPS, or HPQ scores. However, patients demonstrating significant improvement in NCI scores (n=11, 29%) had significantly greater improvement in clinical and work functioning outcomes compared to those without NCI improvement.

Limitations: The limitations of this study include small sample size, lack of a placebo control group, and lack of a healthy comparison group. Our sample also had more years of education and higher premorbid intelligence than the general population.

Conclusions: There were no significant correlations between changes in neurocognitive and work functioning measures in this study. However, meaningful improvement in neurocognitive functioning with desvenlafaxine was associated with greater improvement in both mood and occupational outcomes. This suggests that addressing cognitive dysfunction may improve clinical and occupational outcomes in employed patients with MDD. However, the relationship between neurocognitive and work functioning in MDD is complex and requires further study.

1. Introduction

Major Depressive Disorder (MDD) is currently one of the most common medical conditions worldwide (World Health Organization, 2008). People with MDD experience great personal distress, as well as significant impairments in their daily and occupational functioning (Kessler et al., 2006). With onset characteristically in late adolescence and early adulthood, MDD also disproportionately affects young and middle-aged adults in the prime of their working years, and is a leading cause of long-term

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disability and unemployment in this age group (World Health Organization, 2008; Ferrari et al., 2013).

Despite this large burden of disability, many people with MDD maintain gainful employment, though they may experience underemployment (Dooley et al., 2000), miss more hours and days of work (absenteeism) (Alonso et al., 2004), and have difficulty performing to their usual ability (also known as "presenteeism") (Gilmour and Patten, 2007), as compared to their non-depressed peers (Adler et al., 2006; Valenstein et al., 2001). Depression-related presenteeism in the United States contributes to an estimated 200 million lost workdays annually, costing employers between $17 and $44 billion (Stewart et al., 2003). Moreover, impairment in work functioning is a primary concern for patients with MDD; in fact, patients rate functional recovery as a more important treatment outcome than remission of depressive symptoms (Zimmerman et al., 2006).

Cognition is likely a major determinant of work functioning. It is now well recognized that MDD is associated with significant cognitive dysfunction, which in turn can impact functional impairment (Greer and Hatt, 2016; Lam et al., 2014, 2015). A large body of research confirms that patients with MDD perform worse on neuropsychological tests compared to healthy comparison subjects, including information processing speed (Tsourtos et al., 2002), sustained and selective attention (Landrø et al., 2001; Porter et al., 2003), different aspects of learning and memory (Porter et al., 2003; Preiss et al., 2009), and executive function (Gohier et al., 2009; Henry and Crawford, 2005). However, there has been limited study of the relationships between cognitive and psychosocial functioning in MDD. A systematic review identified some studies showing significant correlations between neuropsychological tests and functional outcomes, but others did not find significant associations (Evans et al., 2014).

Problems in cognitive domains, including attention, memory, psychomotor speed, and executive functioning, would be expected to have a significant impact on work functioning (Greer and Hatt, 2016; Lam et al., 2015; McIntyre et al., 2015), but systematic reviews have found that the relationships between cognitive dysfunction and work functioning have not been well-studied (Evans et al., 2013). In particular, there are few studies of the effects of antidepressants on neurocognition (McIntyre et al., 2015) and no studies examining the relationship with functional outcomes, such as work functioning.

Desvenlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI) that has established efficacy in the treatment of MDD (Liebowitz et al., 2008). Desvenlafaxine also has shown efficacy in improving symptom and functional outcomes in employed patients with MDD (Dunlop et al., 2011; Soares et al., 2009). We aimed to examine the relationship of neurocognitive dysfunction on work functioning in patients with MDD before and after treatment with flexibly-dosed desvenlafaxine 50–100 mg/day.

2. Methods

2.1. Participants

Participants were outpatients recruited through the Mood Disorders Center, a specialized psychiatric clinic in Vancouver, Canada. Inclusion criteria for the study were: (1) age 19–55 years, (2) Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR) major depressive episode, (3) current paid employment with a minimum of 15 work hours per week, (4) score $\geq$23 on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), indicating at least moderate severity, and (5) score $\geq$6 on the British Columbia Cognitive Complaints Inventory (BC-CCI) (Iverson and Lam, 2013), indicating the presence of subjective cognitive complaints. Exclusion criteria included lifetime diagnosis of bipolar disorder or other significant primary psychiatric diagnoses, active alcohol or substance abuse or dependence in the past year, 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.

2.2. Procedures

Participant recruitment began March 2012 and concluded December 2014. Patients were assessed by a board-certified psychiatrist, which included the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), to confirm the diagnosis. After providing written informed consent, eligible patients attended a baseline visit to complete symptom assessments and self-report scales of work functioning as well as a computerized battery of neurocognitive tests. These assessments were then repeated after 8 weeks of standard treatment with flexibly-dosed desvenlafaxine, 50–100 mg/day. Participants received standard care and were followed in the clinic every 2 weeks or as necessary to monitor adverse effects and to adjust dosing. The University of British Columbia Clinical Research Ethics Board approved all study activities, which were conducted in accordance with the International Conference on Harmonization's standards for Good Clinical Practice.

2.3. Measures

2.3.1. Clinical assessments

Symptom severity and change were evaluated using the clinician-rated MADRS and the Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales (Guy, 1976). Response was defined as $\geq$50% reduction in MADRS score from baseline to post-treatment, while remission was defined as a MADRS score $\leq$10 at post-treatment. Participants also completed the Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR, Rush et al., 2003).

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 demonstrated sensitivity to change in clinical trials (Lam et al., 2014). The 7 items are rated on a 5-point scale of frequency (0=none of the time, 0%, to 4=all of the time, 100%) and LEAPS total scores range from 0 (no impairment) to 28 (extreme impairment). The HPQ is a comprehensive self-rated questionnaire that assesses illness-related work absence and productivity loss. It is one of the few self-rated work functioning scales that is validated against objective measures of work performance in a number of occupations (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.

Global functioning was also assessed with the Sheehan Disability Scale (SDS) (Leon et al., 1997), a 3-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).

2.3.2. Neurocognitive assessments

Neurocognitive functioning was evaluated with Central

Nervous System Vital Signs (CNS VS) (Gualtieri and Johnson, 2006). This computerized battery contains 7 neuropsychological tests, including tests of immediate and delayed verbal and visual memory, Finger Tapping Test, Symbol-Digit Coding Test, Stroop Task, Shifting Attention Test, and a Continuous Performance Test. These tests contribute to 7 cognitive domain scores used in this study: Composite Memory, Psychomotor Speed, Reaction Time, Complex Attention, Cognitive Flexibility, Processing Speed, and Executive Function. A measure of global cognition, the Neurocognition Index (NCI), is calculated as an average of the Composite Memory, Psychomotor Speed, Reaction Time, Cognitive Flexibility, and Complex Attention domain scores. Raw scores are automatically transformed into standard and percentile scores based on an age- and gender-matched normative sample, in which domain scores have a mean of 100 and standard deviation of 15. The NCI and domain scores have been shown to identify neurocognitive impairment in patients with depression (Iverson et al., 2009a) and bipolar disorder (Iverson et al., 2009b).

Patients' subjective cognitive functioning was assessed using the British Columbia Cognitive Complaints Inventory (BC-CCI), a validated 6-item self-report scale measuring perceived difficulties with concentration, memory, trouble expressing thoughts, word finding, slow thinking, and problem solving (Iverson and Lam, 2013).

Intelligence has been shown to account for a significant proportion of the variability on measures of cognitive functioning (Schretlen et al., 2008). The Advanced Clinical Solutions Test of Premorbid Functioning (ACS-TOPF) (Pearson, 2009) was used to estimate the full-scale intelligence quotient (FSIQ) of participants (using the reading score combined with simple demographics).

2.4. Statistical analyses

Changes in outcome scores from baseline to post-treatment were analyzed using two-tailed, paired-samples *t*-tests. Effect sizes were calculated using Cohen's *d* (Cohen, 1988). The relationships between neurocognitive tests and functional measures were initially examined using bivariate correlational analyses, with subsequent multiple regression analyses as appropriate. We used an ANCOVA model including covariates of age, sex, FSIQ and depression improvement (CGI-I scores) to examine whether significant change in neurocognitive performance, defined as improvement of ≥ 1 SD in NCI from baseline to post-treatment, was associated with work functioning outcomes. The ANCOVA model did not violate Levene's test of equality of error variances. We chose the definition of ≥ 1 SD in NCI because it represents cognitive improvement that likely exceeds any practice effects. All analyses were conducted with SPSS v.12 (SPSS Inc., 2003).

3. Results

3.1. Demographics and clinical characteristics

Of 55 individuals who were screened and eligible for the study, 40 enrolled and completed baseline assessment. Table 1 shows demographic and clinical characteristics of the sample. The mean estimated FSIQ score was significantly higher than the general population mean of 100 (single sample t-test, two-tailed, $t(35)=8.14$, $p<0.001$). There were no significant differences between men and women on any of the demographic or clinical variables.

Most patients (n=32, 78%) had experienced previous depressive episodes while fewer (n=8, 22%) were experiencing their first episode. The most frequent psychiatric comorbidities secondary to the diagnosis of MDD were Dysthymia/Persistent Depressive Disorder (n=9), Generalized Anxiety Disorder (n=7), and Social Anxiety Disorder (n=4).

Table 1
Demographic and clinical characteristics of patients at baseline, n=40.

Women:Men, %	55:45
Age (SD), years	39.0 (10.8)
Single Episode:Recurrent, %	22:78
Patients with comorbidities, %	58
Estimated FSIQ, mean (SD)	109.1 (6.7)
Education level, mean (SD) years	15.7 (2.1)
Hours scheduled to work in the past 2 weeks, mean (SD)	66.1 (22.1)

SD, standard deviation; FSIQ, full scale intelligence quotient.

3.2. Clinical and functional assessments at baseline and post-treatment

Table 2 shows the clinical and functional assessments at baseline and post-treatment. At baseline, patients had moderate severity of depression and moderate impairments in work functioning. A total of 36 patients completed the 8-weeks of treatment with a mean (SD) desvenlafaxine dose of 74.3 (24.6) mg (50 mg: 18 patients; 100 mg: 17 patients; 50 mg alternating with 100 mg: 1 patient). Three patients (7.5%) discontinued treatment because of adverse events (insomnia; nausea; nausea, diarrhea, and headache) and one (2.5%) was lost to follow up.

At the post-treatment evaluation, all the depressive symptom and functional outcomes had significantly improved. There were large and clinically significant improvements in symptom ratings (*d*'s=1.81–2.99) and work functioning (*d*'s=0.89–1.35). Clinical response and remission rates were high, with 28 (78%) patients achieving MADRS-defined response and 17 (47%) achieving remission.

3.3. Neurocognitive assessments at baseline and post-treatment

Table 2 shows the neurocognitive performance at baseline and post-treatment. At baseline, patients had scores significantly below age- and sex-matched normative scores on the NCI (single-sample t-test, two tailed, $t(36)=-2.4$, $p=0.02$) and the Complex Attention domain ($t(34)=-2.7$, $p=0.01$). There was also a non-significant trend towards lower scores on Cognitive Flexibility ($t(36)=-1.9$, $p=0.057$).

At post-treatment, there was significant improvement in the NCI (paired-samples *t*-test, $t(36)=3.2$, $p=0.003$, $d=0.43$) and significant improvement in all the cognitive domains with medium effect sizes, except Composite Memory ($t(34)=-0.7$, *ns*) and Reaction Time ($t(35)=1.8$, *ns*). Most patients showed improvement in NCI, but 2 patients (5.4%) showed worsening of NCI ≥ 1 SD.

Before treatment, all patients had some degree of perceived cognitive impairment, as measured by the BC-CCI. There was a significant improvement in perceived cognitive functioning following treatment ($t(35)=6.03$, $p<0.001$, $d=1.09$).

3.4. Relationships between functional and neurocognitive assessments

There were no significant correlations between the work functioning scales (LEAPS total score and HPQ-Overall) and the NCI, or the individual cognitive domains, either at baseline or at post-treatment. There also were no significant correlations in the change scores from baseline to post-treatment between the work functioning scales and the NCI or cognitive domains. There were significant correlations between the change in SDS total score and changes in the NCI ($r=-0.36$, $p=0.029$), Cognitive Flexibility domain ($r=-0.35$, $p=0.036$), and Complex Attention domain ($r=-0.40$, $p=0.021$). However, in the multiple regression model,

Table 2
Assessments at baseline and post-treatment.

	Baseline (n=40)	Post-treatment (n=36)	Paired samples t-test, pre-post treatment	Cohen's d
Clinical assessments mean score (SD)				
MADRS	28.5 (4.0)	10.9 (8.0)	$t(35)=12.4$, $p<0.001$	2.99
QIDS-SR	16.2 (3.6)	8.4 (5.1)	$t(35)=7.8$, $p<0.001$	1.81
CGI severity	4.3 (0.6)	2.3 (1.1)	$t(35)=9.9$, $p<0.001$	2.39
LEAPS total	15.7 (5.4)	7.6 (6.7)	$t(34)=7.0$, $p<0.001$	1.35
HPQ-overall	5.5 (1.9)	7.1 (1.7)	$t(34)=-5.3$, $p<0.001$	0.89
SDS total	21.1 (5.0)	11.6 (8.3)	$t(35)=6.1$, $p<0.001$	1.45
Neurocognitive assessments mean standard score (SD)				
Neurocognition index	95.6 (11.2)	100.3 (10.8)	$t(35)=3.2$, $p=0.003$	0.43
Composite memory	98.7 (14.8)	97.1 (19.0)	$t(34)=-0.7$, $p=0.47$	0.10
Processing speed	98.9 (15.8)	107.2 (13.3)	$t(35)=4.3$, $p<0.001$	0.57
Executive function	96.2 (16.9)	104.8 (12.6)	$t(35)=3.8$, $p=0.001$	0.58
Reaction time	96.9 (15.2)	100.6 (15.8)	$t(35)=1.8$, $p=0.074$	0.24
Psychomotor speed	96.7 (16.5)	102.8 (13.6)	$t(35)=2.9$, $p=0.006$	0.40
Complex attention	91.8 (18.2)	100.0 (13.5)	$t(33)=2.7$, $p=0.011$	0.51
Cognitive flexibility	94.2 (17.5)	103.5 (13.2)	$t(35)=4.0$, $p<0.001$	0.60

SD, standard deviation; MADRS, Montgomery Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Rated; LEAPS, Lam Employment Absence and Productivity Scale; HPQ-Global, Health and Work Performance Questionnaire, Global Work Performance, SDS-Total, Sheehan Disability Scale; BC-CCI, British Columbia Cognitive Complaints Inventory; ns, not significant.
For all self-report and clinician-rated scales, lower scores indicate better outcomes, except the HPQ-Overall, for which higher scores indicate better functioning. For CNS-Vital Signs, higher scores represent better performance.

these factors were no longer significant when age, sex, and FSIQ were entered as covariates.

Of the 36 participants with valid NCI change data, 11 (31%) had significant improvement in neurocognitive performance, defined as ≥ 1 SD improvement in NCI from baseline to post-treatment. As expected, there was a significant difference in the NCI change scores between groups ($F(1,31)=22.21$, $p<0.001$) (Fig. 1). The NCI-improved group also had significantly better outcomes than the group without NCI improvement (Fig. 1). Specifically, the NCI-improved group had greater improvement in MADRS scores ($F(1,31)=6.20$, $p=0.018$, $d=0.66$) and QIDS-SR scores ($F(1,31)=11.80$, $p=0.002$, $d=1.10$). Even when adjusting for depression improvement using CGI-I scores, the NCI-improved group showed significant improvement in the work functioning measures, LEAPS total scores ($F(1,31)=12.46$, $p=0.001$, $d=1.01$) and HPQ-Overall scores ($F(1,31)=5.22$, $p=0.029$, $d=0.65$).

4. Discussion

At baseline, this sample of employed outpatients with MDD had moderate severity of depression and moderate impairment in global and work functioning. They also had perceived cognitive impairment and mild impairment in neurocognitive performance, with significantly lower scores for the composite NCI and the Complex Attention domain compared to age- and sex-matched normative scores. It should be noted that our patient sample had more years of education and higher intelligence than the general population, hence neurocognitive functioning would be expected to be higher in the patient group than the normative sample, and it is likely that individual impairment would be greater than indicated by simple comparison to the normative scores. Regardless, these results are consistent with many studies showing cognitive impairment in patients with MDD during an acute depressive episode (Iverson et al., 2011, 2009a; Iverson and Lam, 2013; Landrø et al., 2001; Porter et al., 2003; Rock et al., 2013; Snyder, 2013).

Eight weeks of open-label treatment with desvenlafaxine 50–100 mg resulted in significant improvement in all clinical outcomes, including both clinician-rated (MADRS, CGI-I) and patient-rated (QIDS-SR) measures, and all functional outcomes (SDS, LEAPS, HPQ). Patients also had significant improvements in perceived cognitive functioning (BC-CCI) and neurocognitive performance (composite NCI and all cognitive domains except Composite Memory and Reaction Time). These results are consistent with data from a subset of patients that underwent neuropsychological testing during a placebo-controlled study of desvenlafaxine in employed patients with MDD (Reddy et al., 2016). The desvenlafaxine-treated patients (n=52) had significant improvement after 12 weeks of treatment in composite measures representing quality of working memory and speed of working memory, but not in

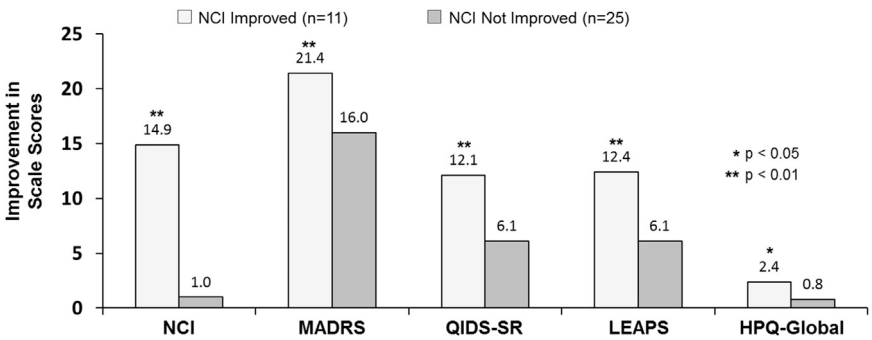

Fig. 1. Comparing groups stratified by significant improvement on the CNS-Vital Signs Neurocognition Index. Bars represent pre-post treatment change scores. Groups are stratified: NCI Improved= ≥ 1 SD improvement in NCI from baseline to post-treatment; NCI Not Improved= <1 SD improvement in NCI from baseline to post-treatment. NCI, Neurocognition Index; MADRS, Montgomery Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Rated; LEAPS, Lam Employment Absence and Productivity Scale; HPQ-Overall, Health and Work Performance Questionnaire, Overall Work Performance.

attention (Reddy et al., 2016). There was also significant improvement in measures of executive function including the Trail Making Test and Stroop Test. However, differences compared to the placebo-treated group (n=29) were found only for 'quality of working memory,' a composite score of numeric and spatial working memory tasks (Reddy et al., 2016). Of note is that a recently published meta-analysis (which did not include any studies of desvenlafaxine) found significant positive effects of antidepressants on cognitive domains of psychomotor speed and delayed recall, but not on cognitive control or executive function (Rosenblat et al., 2016).

The main objective of this study was to determine the association between neurocognition and work functioning in working outpatients with MDD, before and after treatment with desvenlafaxine. We did not find any significant correlations between neurocognitive and work functioning measures at baseline or at post-treatment. Our systematic review (Evans et al., 2013) of studies examining this question found only one previous study in patients with MDD (Godard et al., 2011). In that study, work functioning was assessed in 16 depressed patients with MDD with the work subscale of the Longitudinal Interval Follow-up Evaluation, Range of Impaired Functioning Tool (LIFE-RIFT) (Leon et al., 1999), and neurocognitive performance was assessed with tests from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001), CogitEx-II (Laplante and Baruch, 1999) and the Continuous Performance Test-Second Edition (CPT-II) (Conners and MHS Staff, 2000). Significant correlations were found between LIFT-RIFT work subscale scores and scores on neuropsychological tests of attention, executive function, and verbal memory. However, it should be noted that the Godard study had fewer patients than ours (16 versus 40, respectively), and that their sample was older and had fewer years of education. Other antidepressant studies have shown improvement in both cognition and work functioning, such as with vortioxetine (Mahableshwarkar et al., 2015) and the previously-described study with desvenlafaxine (Reddy et al., 2016), but did not specifically examine the relationship between the two.

Although both neurocognitive and work functioning measures significantly improved with desvenlafaxine treatment, there were no significant correlations between their respective change scores from baseline to post-treatment. While change in the SDS, a measure of global functioning, was significantly correlated with changes in the composite NCI and the cognitive domains of Cognitive Flexibility and Complex Attention, these associations were no longer significant after adjusting for age, sex, and premorbid intelligence. Together with the baseline and post-treatment results, these findings suggest that the effects of neurocognition on functioning may be more complex than expected. For example, it is possible that these relationships are nonlinear, or that the impact of neurocognitive impairment on work functioning may be moderated by the type of work, interpersonal conflicts at work, individual coping styles, psychosocial support, socio-economic status, and other factors. There may also be complex mediational relationships between baseline cognitive functioning and drug response in specific cognitive domains that impact work functioning outcomes (Woo et al., 2016; Wykes et al., 2012).

Finally, while change scores were not significantly correlated, clear improvement in the NCI was associated with better treatment outcomes. There is currently no consensus on what constitutes a clinically significant change in neurocognitive assessments, and different measures are used in studies, such as reliable change indices and standardized regression models. In this study, we defined a clinically meaningful change as ≥ 1 SD in the composite NCI, which can be considered a large effect size. The NCI-improved group (n=11, 29%) had significantly greater improvement in both clinical and work functioning measures. The improvement in work functioning was apparent even when adjusting for depression improvement. This suggests a direct effect of neurocognitive improvement on work functioning rather than an indirect effect via mood improvement.

4.1. Limitations

The limitations of this study include a small sample size and a lack of a placebo control group, so we cannot exclude practice effects on the cognitive tests. In addition, there was no healthy comparison group, although we examined age- and sex-matched normative scores. Our sample was recruited from a single specialist clinic in an urban center, potentially limiting generalizability, and had more years of education and a higher premorbid intelligence than the average population, potentially obscuring meaningful individual cognitive and/or work functioning impairments. The sample was also middle-aged and had recurrent depressive episodes; given that neurocognitive dysfunction is apparent even in younger, first-episode patients (Lee et al., 2012), it will be important to investigate treatment-related cognitive and functional changes in younger people with MDD. Some change in performance on CNS-Vital Signs is expected due to practice effects. Practice effects could therefore account for a substantial amount of the improvement, at least on some of the domain scores. The cognitive test battery used in our study has been shown to have adequate test-retest reliability in healthy subjects (Gualtieri and Johnson, 2006; Cole et al., 2013), but it remains unclear whether reliability data can be extrapolated to patient samples. The treatment duration of 8 weeks, while sufficient to demonstrate changes in mood, may not be long enough to demonstrate meaningful changes in cognitive and occupational functioning with desvenlafaxine. Finally, the functional measures, although commonly used in depression studies, were all based on patient self-report and may be subject to bias.

5. Conclusions

Depressed employed patients with MDD who report perceived cognitive complaints show mild impairment in neurocognitive performance. Treatment with 8 weeks of flexibly-dosed desvenlafaxine 50–100 mg/day led to significant improvement in clinical, functional, and neurocognitive measures. There were no significant correlations between measures of neurocognitive and work functioning at baseline, at post-treatment, or in change during treatment. Clinically significant improvement in neurocognitive performance, however, was associated with better treatment outcomes, which illustrates the importance of addressing cognitive dysfunction in the treatment of working patients with MDD. However, the relationship of neurocognitive impairment to work functioning in depression is complex and requires further study.

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