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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