Psychiatry Research 272 (2019) 144–148

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Relationship between work functioning and self-reported cognitive complaints in patients with major depressive disorder treated with desvenlafaxine

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ARTICLE INFO

Keywords:
Major depressive disorder
Functional outcomes
Cognitive dysfunction
Cognitive deficits
Work functioning

ABSTRACT

Patients with major depressive disorder (MDD) often report that cognitive difficulties, such as memory problems or poor concentration, interfere with their work functioning. We examined the association between self-reported cognitive complaints and work functioning in employed patients with MDD treated with desvenlafaxine. A sample of 36 adult outpatients with MDD completed subjective cognition (British Columbia Cognitive Complaints Inventory [BC-CCI]) and functioning scales (Sheehan Disability Scale [SDS]; Lam Employment Absence and Productivity Scale [LEAPS]; and Health and Work Performance Questionnaire [HPQ]) before and after 8 weeks of open-label treatment with flexibly-dosed desvenlafaxine (50–100 mg/day). Multiple regression analyses were used to assess the relationship between subjective cognitive measures and work functioning scales. Patients showed significant improvements in clinical, cognitive, and work functioning measures following treatment with desvenlafaxine. A predictive association was found between the BC-CCI and both the SDS and LEAPS, but not with the HPQ, when adjusted for depression severity. Self-report cognitive questionnaires can provide useful information to monitor changes in cognitive functioning over time and to predict improvement in work functioning outcomes.

1. Introduction

Major depressive disorder (MDD) affects more than 300 million people worldwide (World Health Organization, 2017) and is considered a leading cause of work disability (World Health Organization, 2004). Depressed patients miss more days of work (absenteeism) (Adler et al., 2006; Kessler et al., 1999) and report significantly more lost productive time (presenteeism) (Birnbaum et al., 2010; Gilmour and Patten, 2007; Johnston et al., 2009; Stewart et al., 2003) than individuals who are not depressed (Adler et al., 2006; Valenstein et al., 2001). As a result, MDD represents a substantial burden for patients and society (Stewart et al., 2003; Zimmerman et al., 2006).

Cognitive difficulties, which have been recognized as a core feature of MDD, are likely major determinants of decreased work functioning. However, a systematic review (Evans et al., 2014) addressing cognition in MDD found only one previous study that reported significant correlations between objective neuropsychological tests and work functioning measures (Godard et al., 2011). Moreover, a recent open-label study by Lam et al. (2016a) examined the relationship between objectively-measured neurocognitive dysfunction and work functioning before and after treatment with desvenlafaxine and did not find any significant correlations between these measures at baseline or post-treatment (Lam et al., 2016a). In contrast, studies examining subjective cognitive complaints have suggested that the impact of MDD on role functioning at home and in paid employment may be mediated by self-reported cognitive problems and by feelings of embarrassment (Buist-Bouwman et al., 2008). These various lines of evidence suggest that the relationship between cognition and work functioning in MDD may be more complex than expected and that subjective cognitive measures may not only provide clinically useful information but also help us to understand how MDD may lead to reduced work functioning.

To further explore this possibility, we performed secondary analyses

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https://doi.org/10.1016/j.psychres.2018.12.062
Received 23 July 2018; Received in revised form 9 December 2018; Accepted 9 December 2018
Available online 10 December 2018
0165-1781/

of the previous open-label prospective study performed by Lam et al. (2016a). In this study, MDD patients completed clinical and cognitive assessments before and after 8 weeks of standard treatment with flexibly-dosed desvenlafaxine (Lam et al., 2016a), a serotonin and noradrenaline reuptake inhibitor (SNRI) that is effective in treating depressive and functional symptoms (Dunlop et al., 2011; Lam et al., 2016a; Liebowitz et al., 2008; Soares et al., 2009) as well as cognitive dysfunction (Salagre et al., 2017). We used regression analyses to assess the relationship between subjective cognitive measures and work functioning scales. We hypothesized that subjective cognitive complaints would predict work functioning outcomes, independently of depressive symptom severity.

2. Methods

2.1. Procedures

The design and conduct of the primary study were described in detail previously (Lam et al., 2016a). In brief, it was an open-label study conducted prospectively with patients recruited through the Mood Disorders Centre, a specialized psychiatric clinic in Vancouver, Canada. After confirmation of eligibility, patients provided written informed consent to participate in the study and attended a baseline visit to complete all assessments. The assessments were repeated after 8 weeks of standard treatment with flexibly-dosed desvenlafaxine, 50–100 mg/d. All study activities were approved by the Clinical Research Ethics Board of the University of British Columbia and adhered to the Declaration of Helsinki and the International Conference on Harmonization's standards for Good Clinical Practice.

2.2. Participants

Patients had a diagnosis of MDD by DSM-IV-TR criteria as confirmed by the MINI International Neuropsychiatric Interview (D. V. Sheehan et al., 1998), a score ≥ 23 on the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), and a score ≥ 6 on the British Columbia Cognitive Complaints Inventory (BC-CCI) (Iverson and Lam, 2013) at baseline, indicating the presence of subjective cognitive difficulties. They were employed at the time of testing (paid employment with 15 h/week minimum). Patients were excluded if they had a 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.

A total of 36 subjects completed all measures of interest at baseline and 8 weeks after treatment. The mean age (standard deviation, SD) of these individuals at baseline was 38.7 (11.1) years and their mean years of education was 15.6 (2.1). More than half were women (n = 21; 58.3%), and native English speakers (n = 24, 66.7%). The most frequent psychiatric comorbidities were Generalized Anxiety Disorder (n = 6, 16.7%), and Social Anxiety Disorder (n = 3, 8.3%). Nine (25%) participants met criteria for Dysthymia/Persistent Depressive Disorder.

2.3. Treatment

Treatment consisted of 8 weeks of flexibly-dosed desvenlafaxine [50–100 mg/day (mean desvenlafaxine dose of 74.3 ± 24.6 mg)]. Patients were monitored and received medical care throughout the study, per standard clinical guidelines (Lam et al., 2016b).

2.4. Assessments

Depressive symptom severity and change were evaluated using the MADRS. Response was defined as a ≥50% reduction from baseline in MADRS total score. Remission was defined as MADRS total score ≤10 at the end of the study.

Subjective cognitive functioning was assessed at baseline and following treatment using the BC-CCI, a 6-item self-report questionnaire that assesses difficulties with concentration, memory, trouble expressing thoughts, word finding, and problem-solving over the past seven days (Iverson and Lam, 2013). A four-point scale (0 = not at all, 1 = some, 2 = quite a bit, and 3 = very much) is used to rate each item for a total score range of 0–18; higher scores indicate greater severity of cognitive complaints.

Work functioning was assessed using two measures: the World Health Organization Health and Work Performance Questionnaire (HPQ) (Kessler et al., 2003) and the Lam Employment Absence and Productivity Scale (LEAPS) (Lam et al., 2009). The HPQ is a self-rated questionnaire of work-performance and absenteeism (Kessler et al., 2004, 2003). It includes an item for overall work performance during the past four weeks with a 0-to-10 rating (0 means the “worst possible work performance” a person could have on this job and 10 means “top work performance” on this job), with higher scores indicating better work performance. The HPQ has been extensively validated against objective measures of work productivity (Kessler et al., 2003; Wang et al., 2007). The LEAPS is a self-rated scale of work absence and productivity that includes 7 items rated over the past 2 weeks using a 5-point Likert scale (0–4). A "productivity subscale" sums the scores from the 3 items assessing work functioning and productivity (i.e., doing less work, doing poor quality work, and making more mistakes), with higher scores indicating greater work impairment. The LEAPS has been validated in a sample of 234 patients with MDD (Lam et al., 2009) and has demonstrated sensitivity to change in clinical trials (Lam et al., 2013). Because of its 2-week recall period, the LEAPS is especially appropriate to capture improvements that occur towards the end of an 8-week trial.

Global functioning was assessed using the Sheehan Disability Scale (SDS) (Leon et al., 1997; Sheehan, 1983). The SDS assesses functional impairment in three inter-related domains: work/school, social life, and family life. It consists of three self-rated, 10-point Likert scale response items. The total score ranges from 0 to 30, with higher scores indicating greater psychosocial impairment. In this study, functional response was defined as having an SDS total score ≤12 and functional remission was defined as having an SDS total score <7 at endpoint (Sheehan and Sheehan, 2008).

2.5. Statistical analysis

A regression analysis was performed to determine whether pre to post-treatment changes in BC-CCI scores predict changes in occupational and functional outcomes while adjusting for depression severity (MADRS change scores). A p value of <0.05 was considered statistically significant. Effect sizes were calculated using Cohen's d; generally, values of 0.2, 0.5 and 0.8 are considered small, medium and large effect sizes, respectively (Cohen, 1988). The analysis was performed using IBM SPSS Statistics for Windows, Version 25.0.

3. Results

Descriptive statistics and Cohen's effect sizes for the outcome measures are presented in Table 1. There was a very large change in depression symptom severity after treatment (MADRS, Cohen's d = 2.95). Additionally, there were large improvements in perceived cognitive functioning (BC-CCI, Cohen's d = 1.24) and in self-reported work functioning (HPQ, Cohen's d = 0.73 and LEAPS, Cohen's d = 0.86).

Three separate regression analyses were conducted to determine the

Table 1
Assessments before and after treatment.

	Pre-Treatment (Mean ± SD)	Post-Treatment (Mean ± SD)	Change = [Post-treatment –Pre-treatment] (Mean ± SD)	Cohen's *d*
MADRS	28.55 ± 4.05	10.86 ± 7.94	−17.69 ± 8.57	2.95
BC-CCI	10.56 ± 3.48	5.75 ± 4.29	−4.81 ± 4.57	1.24
HPQ	5.54 ± 1.80	6.94 ± 2.06	1.6 ± 1.80	0.73
LEAPS	5.69 ± 3.45	2.91 ± 3.02	−2.77 ± 3.16	0.86
SDS	20.96 ± 5.15	11.56 ± 8.30	−9.4 ± 9.24	1.40

SD, Standard Deviation; MADRS, Montgomery–Åsberg Depression Rating Scale; BC-CCI, British Columbia Cognitive Complaints Inventory; LEAPS, Lam Employment Absence and Productivity Scale; HPQ, Health and Work Performance Questionnaire; SDS, Sheehan Disability Scale.
For all self-report and clinician-rated scales, lower scores indicate better outcomes, except the HPQ for which higher scores indicate better functioning. For NCI, higher scores represent better performance.

association between pre to post-treatment changes in subjective cognitive measures and occupational outcomes (Table 2). For all analyses, age, gender, and change in subjective measures of cognition (BC-CCI) and clinical symptoms (MADRS) were entered as predictors. In the first analysis, SDS change was entered as the dependent variable. This model explained 60% of the variance in the data [F (4, 35) = 11.63, $p < 0.001$]. Both BC-CCI change ($p = 0.004$) and MADRS change ($p = 0.005$) were significant predictors (Table 2). In the second analysis, LEAPS change was entered as the dependent variable. This model explained 40% of the variance in the data, [F (4, 34) = 5.06, $p = 0.003$]. Only BC-CCI change ($p = 0.012$, $\beta = 0.51$) was a significant predictor (Table 2). In the third analysis, HPQ overall performance change was entered as the dependent variable. This model explained only 11% of the variance in the data and the model was not statistically significant [F (4, 34) = 2.00, $p = 0.12$; Table 2].

4. Discussion

The current study aimed to assess the relationship between subjectively experienced cognitive complaints and self-rated work performance. Using regression analyses, we found that changes in subjective measures of cognition have a predictive association with improvements in self-reported work productivity and global psychosocial functioning, independent of overall depression severity.

To date, few studies have examined the relationship between subjective cognition and work impairment in MDD. Two recent reports focused on patients treated with vortioxetine (Chin et al., 2018; Chokka et al., 2018). Specifically, Chin et al. (2018) assessed 138 patients with MDD (49.6–52.0% were employed during the study period) being initiated on vortioxetine with the self-report Patient Health Questionnaire (PHQ-9), Perceived Deficits Questionnaire-Depression (PDQ-D), a 20-item self-rated cognitive questionnaire (Fehnel et al., 2016), and the Work Productivity and Activity Impairment (WPAI) scale (Reilly et al., 1993) over a 3-month follow up. They observed a reduction in WPAI percentage absenteeism and work productivity loss accompanied by a correlation between scores on the self-rated PHQ-9, PDQ-D, and WPAI. Similarly, Chokka et al. (2018) treated 196 employed MDD patients with vortioxetine for 12 weeks and observed significant correlations between the PDQ-D and productivity loss as assessed with the Work Limitations Questionnaire (Lerner et al., 2001). Although both studies used correlational analyses, so that the independent effect of depressive symptom improvement was not assessed, they provide further support to the hypothesis that subjective cognitive measures are associated with work disability.

Our study adds to the current evidence showing that subjective cognitive complaints, which arise from patients' assessments of their behavior in a variety of environments including the workplace, are associated with work impairment. Specifically, our study shows that change in BC-CCI scores significantly predict functional outcomes 8 weeks after treatment with desvenlafaxine. Change in MADRS scores also played a role in predicting functional outcomes. This result is consistent with previous studies showing that clinical and functional improvements are moderately correlated (Brown et al., 2000; Gadelrab et al., 2010; Kruijshaar et al., 2003; Mohn and Rund, 2016; Rytsälä et al., 2006). However, the contribution of the MADRS change score was significant only when the SDS, but not the LEAPS, was included in the regression model as a dependent variable. The SDS assesses functional impairments in three inter-related domains (work, social life, and family life). The LEAPS, however, includes items that have the most impact on work productivity. Therefore, our study suggests that improvement in depressive symptoms is associated with an overall improvement in patients' psychosocial functioning but not necessarily with specific improvements in work productivity. This may be because improvements in workplace functioning appear to occur more slowly than improvement in depression symptoms during treatment (Dewa et al., 2011; Giller et al., 1988; Mintz et al., 1992; Trivedi et al., 2009; Weissman and Bothwell, 1976). When improvement of perceived cognitive functioning occurred in tandem with improvement in depression symptoms, patients did report improvement in workplace functioning in the present study.

In contrast to the SDS and LEAPS results, no association was found between BC-CCI change scores and HPQ improvement. This result may be related to the instrument recall period, which is the past 4 weeks for the HPQ compared to the past 2 weeks for the LEAPS and the past 7 days for the BC-CCI. The 4-week recall period may not be sensitive to improvements in functional outcomes that take place closer to the end of an 8-week trial.

The main limitation of this study is the small sample size. Additionally, participating subjects may not be entirely representative of typical MDD patients due to exclusion criteria. We also used subjective assessments of global and work functioning, in part due to the challenges in obtaining and validating objective measures (Despiégel et al., 2012). These subjective assessments, although useful

Table 2
Summary of multiple regression analyses determining whether pre- to post- treatment changes in BC-CCI scores predict changes in occupational and functional outcomes (SDS, LEAPS, and HPQ) while adjusting for depression severity (MADRS change scores).

	SDS - Change			LEAPS – Change *(productivity subscale)*			HPQ - Change		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
BC-CCI - Change	0.91	0.30	0.45**	0.35	0.13	0.51*	−0.07	0.09	−0.17
MADRS - Change	0.47	0.16	0.44**	0.07	0.07	0.19	−0.06	0.05	−0.28
Age	0.70	0.10	0.08	0.01	0.04	0.05	0.02	0.03	0.14
Gender	0.19	2.21	0.01	0.04	0.95	0.00	0.08	0.62	0.02
R^2	0.60			0.40			0.21		
F	11.63**			5.06**			2.00		

* $p < 0.05$.
** $p < 0.01$. SE, Standard Error; MADRS, Montgomery–Åsberg Depression Rating Scale; BC-CCI, British Columbia Cognitive Complaints Inventory; LEAPS, Lam Employment Absence and Productivity Scale; HPQ, Health and Work Performance Questionnaire; SDS, Sheehan Disability Scale.

and necessary, may not reflect actual patients' occupational performance. Additionally, both patients and clinicians were aware of treatment assignments, which may have influenced reporting or measurement of the outcome and introduced bias. Limitations aside, these results warrant further investigation into the utility of subjective measures to assess the impact of depression-related cognitive deficits on occupational functioning, monitor changes in cognitive performance over time, and help evaluate treatment effectiveness.

In conclusion, this study found a predictive association between subjective measures of cognition and occupational performance in patients treated with desvenlafaxine. Based on these findings, clinicians may wish to use self-report cognitive questionnaires to assess the possible contribution of cognitive difficulties to functional disability. Future studies should incorporate larger sample sizes and longer duration of treatment. In addition, it will be important to assess the relationships between other subjective cognitive measures and functional scales, to determine whether our results are generalizable to other measures.

Conflicts of interest and sources of funding

This study was funded by an investigator-initiated grant from Pfizer Canada. The sponsor had no role in the design, conduct, analysis or publication of the study. CTRN: NCT01468610.

RWL has received research support or consulting/speaking honoraria from: Asia-Pacific Economic Cooperation, AstraZeneca, Bristol-Myers Squibb, Canadian Institutes of Health Research, Canadian Depression Research and Intervention Network, Canadian Network for Mood and Anxiety Treatments, Johnston and Johnston, Lundbeck, Lundbeck Institute, Mochida, Movember Foundation, Pfizer, Servier, St. Jude Medical, Takeda, University Health Network Foundation, VGH Foundation, and UBC Institute of Mental Health/Coast Capital Savings. VCE received salary support from the investigator-initiated grant. GLI has received research support or honoraria from: Alcohol Beverage Medical Research Council, AstraZeneca Canada, Canadian Institutes of Health Research, Lundbeck Canada, Pfizer Canada, Rehabilitation Research and Development (RR&D) Service of the US Department of Veterans Affairs, and the US Department of Defense. He has also received research support from test publishing companies in the past, including PAR, Inc., ImPACT® Applications Systems, and CNS Vital Signs. He receives royalties for one neuropsychological test (Wisconsin Card Sorting Test-64 Card Version). LNY is on speaker/advisory boards for, or has received research grants from: AstraZeneca, Bristol Myers Squibb, CIHR, CANMAT, Eli Lilly, GlaxoSmithKline, Janssen, The Michael Smith Foundation for Health Research, Pfizer, Servier and the Stanley Foundation. CR, ML, EMT, TC and CW have no disclosures to report.

References

Adler, D.A., McLaughlin, T.J., Rogers, W.H., Chang, H., Lapitsky, L., Lerner, D., 2006. Job performance deficits due to depression. Am. J. Psychiatry 163, 1569–1576.

Birnbaum, H.G., Kessler, R.C., Kelley, D., Ben-Hamadi, R., Joish, V.N., Greenberg, P.E., 2010. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. Depress. Anxiety 27, 78–89.

Brown, C., Schulberg, H.C., Prigerson, H.G., 2000. Factors associated with symptomatic improvement and recovery from major depression in primary care patients. Gen. Hosp. Psychiatry 22, 242–250.

Buist-Bouwman, M.A., Ormel, J., de Graaf, R., de Jonge, P., van Sonderen, E., Alonso, J., 2008. Mediators of the association between depression and role functioning. Acta Psychiatr. Scand. 118, 451–458.

Chin, C.N., Zain, A., Hemrungrojn, S., Ung, E.K., Kwansanit, P., Au Yong, K.C., 2018. Results of a real-world study on vortioxetine in patients with major depressive disorder in South East Asia (REVIDA). Curr. Med. Res. Opin. 34, 1975–1984.

Chokka, P., Bougie, J., Rampakakis, E., Proulx, J., 2018. Assessment in Work Productivity kand the Relationship with Cognitive Symptoms (AtWoRC): primary analysis from a Canadian open-label study of vortioxetine in patients with major depressive disorder (MDD). CNS Spectr. 1–10.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Lawrence Erlbaum Associates, Mahwah, NJ, USA.

Despiégel, N., Danchenko, N., François, C., Lensberg, B., Drummond, M.F., 2012. The use and performance of productivity scales to evaluate presenteeism in mood disorders. Value Health 15, 1148–1161.

Dewa, C.S., Thompson, A.H., Jacobs, P., 2011. The association of treatment of depressive episodes and work productivity. Can. J. Psychiatry 56, 743–750.

Dunlop, B.W., Reddy, S., Yang, L., Lubaczewski, S., Focht, K., Guico-Pabia, C.J., 2011. Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo. J. Clin. Psychopharmacol. 31, 569–576.

Evans, V.C., Iverson, G.L., Yatham, L.N., Lam, R.W., 2014. The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. J. Clin. Psychiatry 75, 1359–1370.

Fehnel, S.E., Forsyth, B.H., Dibenedetti, D.B., Danchenko, N., François, C., Brevig, T., 2016. Patient-centered assessment of cognitive symptoms of depression. CNS Spectr. 21, 43–52.

Gadelrab, H.F., Cabello, M., Vieta, E., Valle, J., Leonardi, M., Chatterji, S., 2010. Explaining functional outcomes in depression treatment: a multilevel modelling approach. Disabil. Rehabil. 32, S105–S115.

Giller, E., Bialos, D., Riddle, M.A., Waldo, M.C., 1988. MAOI treatment response: multiaxial assessment. J. Affect. Disord. 14, 171–175.

Gilmour, H., Patten, S.B., 2007. Depression and work impairment. Health Rep. 18, 9–22.

Godard, J., Grondin, S., Baruch, P., Lafleur, M.F., 2011. Psychosocial and neurocognitive profiles in depressed patients with major depressive disorder and bipolar disorder. Psychiatry Res 190, 244–252.

Iverson, G.L., Lam, R.W., 2013. Rapid screening for perceived cognitive impairment in major depressive disorder. Ann. Clin. Psychiatry 25, 135–140.

Johnston, K., Westerfield, W., Momin, S., Phillippi, R., Naidoo, A., 2009. The direct and indirect costs of employee depression, anxiety, and emotional disorders – an employer case study. J. Occup. Environ. Med. 51, 564–577.

Kessler, R.C., Ames, M., Hymel, P.A., Loeppke, R., McKenas, D.K., Richling, D.E., 2004. Using the World Health Organization Health and Work Performance Questionnaire (HPQ) to evaluate the indirect workplace costs of illness. J. Occup. Environ. Med. 46, S23–S37.

Kessler, R.C., Barber, C., Beck, A., Berglund, P., Cleary, P.D., McKenas, D., 2003. The World Health Organization Health and Work Performance Questionnaire (HPQ). J. Occup. Environ. Med. 45, 156–174.

Kessler, R.C., Barber, C., Birnbaum, H.G., Frank, R.G., Greenberg, P.E., Rose, R.M., 1999. Depression in the workplace: effects on short-term disability. Health Aff. 18, 163–171.

Kruijshaar, M.E., Hoeymans, N., Bijl, R.V., Spijker, J., Essink-Bot, M.L., 2003. Levels of disability in major depression: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J. Affect. Disord. 77, 53–64.

Lam, R.W., Iverson, G.L., Evans, V.C., Yatham, L.N., Stewart, K., Tam, E.M., 2016a. The effects of desvenlafaxine on neurocognitive and work functioning in employed outpatients with major depressive disorder. J. Affect. Disord. 203, 55–61.

Lam, R.W., Kennedy, S.H., Parikh, S.V., MacQueen, G.M., Milev, R.V., Ravindran, A.V., 2016b. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: introduction and methods. Can. J. Psychiatry 61, 506–509.

Lam, R.W., Michalak, E.E., Yatham, L.N., 2009. A new clinical rating scale for work absence and productivity: validation in patients with major depressive disorder. BMC Psychiatry 9, 78.

Lam, R.W., Parikh, S.V., Ramasubbu, R., Michalak, E.E., Tam, E.M., Axler, A., 2013. Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. Br. J. Psychiatry 203, 358–365.

Leon, A.C., Olfson, M., Portera, L., Farber, L., Sheehan, D.V., 1997. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int. J. Psychiatry Med. 27, 93–105.

Lerner, D., Amick, B.C., Rogers, W.H., Malspeis, S., Bungay, K., Cynn, D., 2001. The work limitations questionnaire. Med. Care 39, 72–85.

Liebowitz, M.R., Manley, A.L., Padmanabhan, S.K., Ganguly, R., Tummala, R., Tourian, K.A., 2008. Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder. Curr. Med. Res. Opin. 24, 1877–1890.

Mintz, J., Mintz, L.I., Arruda, M.J., Hwang, S.S., 1992. Treatments of depression and the functional capacity to work. Arch. Gen. Psychiatry 49, 761–768.

Mohn, C., Rund, B.R., 2016. Neurocognitive profile in major depressive disorders: relationship to symptom level and subjective memory complaints. BMC Psychiatry 16, 108.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Reilly, M.C., Zbrozek, A.S., Dukes, E.M., 1993. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 4, 353–365.

Rytsälä, H.J., Melartin, T.K., Leskelä, U.S., Lestelä-Mielonen, P.S., Sokero, T.P., Isometsä, E.T., 2006. Determinants of functional disability and social adjustment in major depressive disorder: a prospective study. J. Nerv. Ment. Dis. 194, 570–576.

Salagre, E., Solé, B., Tomioka, Y., Fernandes, B.S., Hidalgo-Mazzei, D., Garriga, M., 2017. Treatment of neurocognitive symptoms in unipolar depression: a systematic review and future perspectives. J. Affect. Disord. 221, 205–221.

Sheehan, D.S., 1983. The Anxiety Disease. Charles Scribner & Sons, New York, USA, pp. 151.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., 1998. The Mini International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), S22–S33.

Sheehan, K.H., Sheehan, D.V., 2008. Assessing treatment effects in clinical trials with the Discan metric of the Sheehan Disability Scale. Int. Clin. Psychopharmacol. 23, 70–83.
Soares, C.N., Kornstein, S.G., Thase, M.E., Jiang, Q., Guico-Pabia, C.J., 2009. Assessing the efficacy of desvenlafaxine for improving functioning and well-being outcome measures in patients with major depressive disorder: a pooled analysis of 9 double-blind, placebo-controlled, 8-week clinical trials. J. Clin. Psychiatry 70, 1365–1371.
Stewart, W.F., Ricci, J.A., Chee, E., Hahn, S.R., Morganstein, D., 2003. Cost of lost productive work time among US workers with depression. JAMA 289, 3135–3144.
Trivedi, M.H., Corey-Lisle, P.K., Guo, Z., Lennox, R.D., Pikalov, A., Kim, E., 2009. Remission, response without remission, and nonresponse in major depressive disorder: impact on functioning. Int. Clin. Psychopharmacol. 24, 133–138.
Valenstein, M., Vijan, S., Zeber, J.E., Boehm, K., Buttar, A., 2001. The cost-utility of screening for depression in primary care. Ann. Intern. Med. 134, 345–360.
Wang, P.S., Simon, G.E., Avorn, J., Azocar, F., Ludman, E.J., McCulloch, J., 2007. Telephone screening, outreach, and care management for depressed workers and impact on clinical and work productivity outcomes: a randomized controlled trial. JAMA 298, 1401–1411.
Weissman, M.M., Bothwell, S., 1976. Assessment of social adjustment by patient self-report. Arch. Gen. Psychiatry 33, 1111–1115.
World Health Organization, 2004. The World Health Report 2004: Changing history, Annex Table 3: Burden of Disease in DALYs By Cause, Sex, and Mortality Stratum in WHO Regions, Estimates For 2002. World Health Organization, Geneva.
World Health Organization, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization, Geneva.
Zimmerman, M., McGlinchey, J.B., Posternak, M.A., Friedman, M., Attiullah, N., Boerescu, D., 2006. How should remission from depression be defined? The depressed patient's perspective. Am. J. Psychiatry 163, 148–150.