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Improvements in Workplace Productivity in Working Patients With Major Depressive Disorder

Results From the AtWoRC Study

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Objective: To assess changes in workplace productivity and functioning in an open-label study in working patients receiving vortioxetine (10 to 20 mg/d) for major depressive disorder (MDD). **Methods:** Associations between items in the Work Limitations Questionnaire (WLQ), the Sheehan Disability Scale (SDS), and the Work Productivity and Activity Impairment (WPAI) questionnaire were assessed at 12 and 52 weeks by Pearson correlation coefficients. **Results:** Significant improvements were observed across all domains of workplace productivity and functioning after 12 and 52 weeks' vortioxetine treatment. Strong correlations were seen between improvements in WLQ mental domains and WPAI presenteeism and SDS work/school items. Presenteeism showed stronger correlations with other workplace productivity measures than absenteeism. **Conclusions:** Presenteeism and absenteeism impact productivity in working patients with MDD. Vortioxetine confers long-term benefits across all workplace functioning domains.

Keywords: functioning, major depressive disorder, presenteeism, vortioxetine, workplace productivity

Major depressive disorder (MDD) is one of the most prevalent health problems in the workplace.[1] MDD is associated not only with having to take time off work (absenteeism), but also with reduced productivity when at work (presenteeism).[2] Working patients with MDD experience significant impairments in their work productivity,[2–9] with the impact of MDD on ability to work and workplace productivity appearing to be greater than that of other common mental and physical health disorders.[10–12] Indeed, reduced work productivity accounts for most of the financial costs attributed to MDD.[10,13]

In Canada, the annual prevalence of MDD in the general population in 2012 was reported to be 3.9%, with a lifetime prevalence of MDD of 9.9%.[14] Of the approximately 1.3 million Canadians aged 15 to 65 years who experienced a depressive episode in 2012, more than 1 million were employed.[15] Of these, 83% lost their ability to function fully at work (23% were unable to work due to their depression, 20% worked part time due to their depression, and 40% worked full time but with reduced productivity).

There is strong evidence showing that work is beneficial for physical and mental health and wellbeing.[16] Thus, it is suggested that individuals should be encouraged and supported to remain in or re-enter work when their health condition permits, because work is therapeutic, helps to promote recovery and rehabilitation, leads to better health outcomes, minimizes the negative physical, mental, and social effects of long-term sickness absence, and improves quality of life and general wellbeing.[16] In contrast, unemployment and inability to work (''worklessness'') have been shown to have a detrimental impact on overall health.[16] Worklessness has been shown to be associated with: increased rates of overall mortality, as well as mortality due to suicide and cardiovascular disease[17–19]; increased rates of heart disease,[20] smoking, and lung cancer[21,22]; increased susceptibility to respiratory infections[21]; worse mental health and general wellbeing[23,24]; somatic complaints[25]; and greater use of medical services and disability.[17,18,20–23]

Survey data suggest that most patients with mental health disorders want to work.[26] The Canadian Network for Mood and Anxiety Treatments guidelines for the management of MDD state that recovery from depression involves both relief of symptoms and improvement of all aspects of functioning.[27] Effective antidepressant treatments should therefore not only help get patients with MDD back to work, but also aim to restore patients' functioning at work. In order to achieve functional recovery, all the different symptoms associated with MDD need to be addressed. MDD is a heterogeneous and multidimensional disorder associated with emotional, physical, and cognitive symptoms.[27,28] Cognitive symptoms, in particular, have been negatively associated with long-term functioning in patients with MDD.[29–31]

Vortioxetine is a multimodal antidepressant, approved for the treatment of MDD in adults, that acts as an inhibitor of the serotonin transporter as well as modulating the activity of multiple serotonin receptor subtypes.[32,33] Vortioxetine has been shown to be effective for the treatment of both depressive and cognitive symptoms in patients with MDD in short- and long-term clinical trials.[34–37] The **A**ssessmen**t** in **Wo**rk productivity and the **R**elationship with **C**ognitive symptoms (AtWoRC) study was an interventional, open-label, real-world, Canadian study undertaken to examine the association between patient-reported cognitive symptoms and workplace productivity in working patients with MDD treated with vortioxetine.[38,39] Results of the primary analysis of this study showed a highly significant positive correlation between improvements in cognitive symptoms and improvements in workplace productivity after 12 and

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Clinical Significance: These data from the AtWoRC study provide insight into the degree and nature of workplace impairments experienced by working patients with MDD, in particular the impact of presenteeism on productivity, and show that treatment with vortioxetine confers robust and long-term benefits across a range of workplace productivity and functioning domains.

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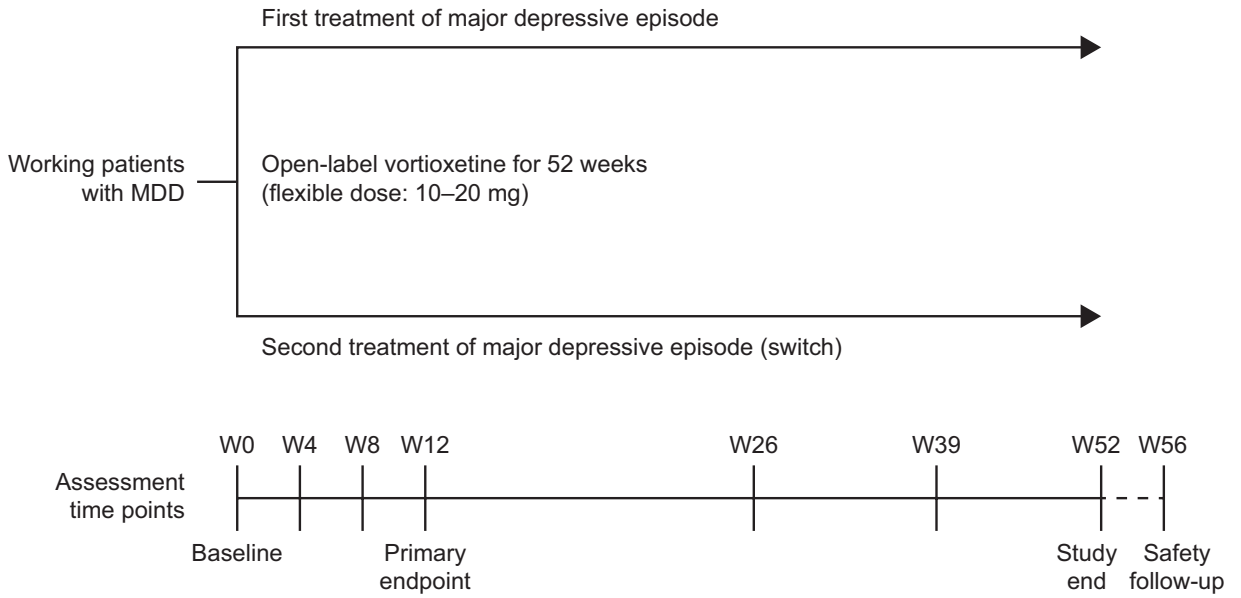

FIGURE 1. Overview of study design. MDD, major depressive disorder; W, week.

52 weeks of vortioxetine treatment, with structural equations model analyses confirming that improvements in cognitive symptoms predicted long-term improvements in functional outcomes even after adjusting for the severity of depressive symptoms.

Here, we present the results of post hoc analyses undertaken to further explore the observed changes from baseline to weeks 12 and 52 across different domains of workplace functioning and work productivity in the AtWoRC study. These results give insight into the nature of workplace impairments experienced by patients with MDD, and characterize improvements in work productivity in a population of working patients treated with vortioxetine.

METHODS

Study Design

AtWoRC (NCT02332954) was an interventional, 52-week, open-label study that enrolled gainfully employed patients with MDD receiving vortioxetine (10–20 mg/d) in a real-world setting in Canada (Fig. 1). The study design and inclusion/exclusion criteria have been reported in detail previously.[38,39] In brief, participants were aged 18 to 65 years and gainfully employed (working at least 20 h/wk) or enrolled full time in post-secondary studies or vocational training, and had a current diagnosis of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition criteria[40] and a current major depressive episode of at least 3 months' duration (confirmed by the study investigator). Participants were also required to have a baseline Quick Inventory of Depressive Symptomatology–self-report score of at least 15 and the presence of cognitive symptoms (defined as a baseline 20-item Perceived Deficits Questionnaire–Depression score of at least 30). Participants were either receiving vortioxetine as their first treatment for the current depressive episode or switching to vortioxetine because of an inadequate response to a previous antidepressant, and had not previously received vortioxetine.

Patients were excluded if they had a diagnosis or history of mania or hypomania, schizophrenia or any other psychotic disorder (including MDD with psychotic features), personality disorder, attention-deficit hyperactivity disorder, mental retardation, pervasive development disorder, organic mental disorders, or mental disorder due to a general medical condition (DSM-5 criteria). Participating patients were not permitted to receive other pharmacotherapy for MDD or other psychoactive medications during the study period. However, as the study was conducted to emulate a naturalistic real-world setting as closely as possible, patients with other comorbidities and concomitant treatments were not excluded from participation.

Ethical approval was obtained from the necessary committees for each study site and all patients provided written informed consent to participate.

Study Assessments

The full range of assessments undertaken in the AtWoRC study have been described in detail previously.[38,39] Patients were assessed at visits at baseline and weeks 4, 8, 12, 26, 39, and 52. Assessments included depression severity, cognitive symptoms and performance, functioning and work productivity, and anxiety symptoms. Self-reported workplace productivity and functioning were assessed using the Work Limitations Questionnaire (WLQ),[41,42] the absenteeism and presenteeism items from the Work Productivity and Activity Impairment (WPAI) questionnaire,[43] the Sheehan Disability Scale (SDS),[44,45] and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0).[46] Table S1 (Supplemental Digital Content, Table 1, http://links.lww.com/JOM/A695) provides an overview of the key features of these four scales.

At each visit, patient compliance with treatment since the previous visit was subjectively assessed by the investigator and the proportion of patients considered compliant (at least 80%) with treatment was calculated. Tablets were not counted; thus, the number of daily vortioxetine doses taken by patients in the study was not assessed.

Statistical Analysis

The population for analysis comprised all patients who met the study inclusion criteria, received at least one dose of vortioxetine, and had a valid baseline assessment and at least one complete post-baseline visit (full analysis population). All analyses were conducted on observed cases; missing data were not replaced. Paired *t* tests were performed to assess changes from baseline to weeks 12 and 52 for the different domains of workplace productivity and functioning. Pearson correlation coefficients were calculated to

assess associations between the different workplace functioning items and subscales. All statistical analyses were performed using R (version 3.5.1).[47] Results of the correlation analyses are presented as correlation plots showing the correlations, as well as scatterplots of individual changes from baseline.

RESULTS

A total of 219 eligible patients were enrolled and received at least one dose of vortioxetine. Of these, 199 patients attended at least one post-baseline visit and were included in this analysis (full analysis population). Baseline demographics and employment status are shown in Table 1. The analysis population was predominantly white (94.5%) and female (69.3%), with a mean age of 40.4 years. Considerable levels of impairment in all domains of workplace functioning and productivity were observed at baseline (Table 2). As might be expected in patients with MDD, impairment in the physical domain of the WLQ was less marked than in domains assessing mental aspects of workplace functioning. The mean vortioxetine dose was 15.3 mg/d at week 12, and 15.2 mg/d at week 52. The proportion of patients considered compliant with treatment by the investigator was 99.0% at week 4, 86.9% at week 12, and 80.9% at week 52. Depending on the scale, the number of patients providing data for analysis was 187 to 199 at baseline, 157 to 177 at week 12, 124 to 145 at week 26, 112 to 128 at week 39, and 109 to 122 at week 52.

Statistically significant improvements from baseline were seen for all measures of workplace functioning and productivity after 12 weeks of vortioxetine treatment, and these improvements were maintained at 52 weeks (Fig. 2 and Table 3; all $P < 0.001$ vs baseline). For the WLQ, pronounced percentage point improvements from baseline to week 52 were seen in the mental domains of time management, output demands, and mental-interpersonal demands (−38.4, −37.6, and −35.4, respectively; all $P < 0.0001$ vs baseline). These changes were greater than for the WLQ physical demands domain (−16.2; $P < 0.0001$ vs baseline), consistent with the profile of baseline impairments in the study population.

TABLE 1. Baseline Patient Demographics and Employment Status

Characteristic	Total ($n = 199$)
Age (yrs), mean ± SD	40.4 ± 12.6
Female, % (*n*)	69.3 (138)
White, % (*n*)	94.5 (188)
Time since MDD diagnosis (yrs), mean ± SD	8.3 ± 9.5
Vortioxetine dose at week 52 (mg/d), mean ± SD	15.2 ± 5.1
Highest level of education, % (*n*)	
High school or less	38.7 (77)
College	38.7 (77)
University	13.1 (26)
Postgraduate	4.5 (9)
Missing	5.0 (10)
Employment type, % (*n*)	
Employed/independent	92.0 (183)
Full-time vocational training	2.5 (5)
Full-time post-secondary student	4.5 (9)
Missing	1.0 (2)
Occupation, % (*n*)	
Manufacturing	4.0 (8)
Professional	8.0 (16)
Service staff	11.6 (23)
Sales	11.6 (23)
Clerical	13.6 (27)
Healthcare	8.5 (17)
Agriculture	0.5 (1)
Construction	5.0 (10)
Other	29.1 (58)
Missing	8.0 (16)

MDD, major depressive disorder; SD, standard deviation.

TABLE 2. Assessment Scores at Baseline

Assessment	*n*	Mean ± SD	Observed Min–Max
PDQ-D-20	199	49.7 ± 12.1	30–78
QIDS-SR	199	18.4 ± 2.6	14–25
WLQ, % productivity loss	186	13.4 ± 4.6	1.8–24.2
Time management	196	57.8 ± 22.2	5–100
Physical demands	187	30.8 ± 21.9	0–100
Mental-interpersonal demands	195	52.5 ± 19.6	0–100
Output demands	194	52.9 ± 23.9	0–100
WPAI, % total work loss	189	68.0 ± 23.3	0–100
Absenteeism	189	22.2 ± 28.5	0–100
Presenteeism	192	61.5 ± 22.8	0–100
SDS, total score	199	21.0 ± 5.1	0–30
Work/school	198	6.63 ± 2.28	0–10
Family life/home responsibilities	199	7.16 ± 2.10	0–10
Social life/leisure	199	7.29 ± 1.97	0–10
WHODAS 2.0	199	21.0 ± 7.4	2–45

n, number of patients with available data; PDQ-D-20, 20-item Perceived Deficits Questionnaire–Depression; QIDS-SR, Quick Inventory of Depressive Symptomatology–self-report; *n*, number of patients with available data; SD, standard deviation; SDS, Sheehan Disability Scale; WHODAS, 12-item World Health Organization Disability Assessment Schedule 2.0; WLQ, Work Limitations Questionnaire; WPAI, Work Productivity and Activity Impairment.

After 52 weeks of vortioxetine treatment, improvements in all WLQ domains showed strong correlations with improvement in WPAI presenteeism (*r*, 0.54 to 0.61; Fig. 3). For improvements in the SDS work/school item, stronger correlations were seen with improvements in WLQ mental work functioning domains (mental-interpersonal demands, time management, and output demands; *r*, 0.56 to 0.62) than with the WLQ physical demands domain ($r = 0.49$). WPAI presenteeism consistently showed stronger correlations with other measures of workplace productivity (ie, SDS work/school and the overall WLQ productivity loss score) than did WPAI absenteeism ($r \geq 0.69$ vs $r \leq 0.32$).

The pattern of correlation between the different measures of workplace functioning at week 12 was similar to that observed at week 52, although correlations including WLQ physical demands were generally lower at week 12 and correlations including WPAI absenteeism were generally higher at week 12 (Figure S1, Supplementary Digital Content 2, http://links.lww.com/JOM/A696). After 12 weeks of vortioxetine treatment, higher correlations were seen with improvements in WLQ mental work functioning domains than with the WLQ physical demands domain (*r*, 0.59 to 0.61 vs 0.29), and WPAI presenteeism consistently showed stronger correlations with other measures of workplace productivity (ie, SDS work/school and the overall WLQ productivity loss score) than did WPAI absenteeism ($r \geq 0.68$ vs $r \leq 0.45$).

As expected, strong correlations were seen between improvements in cognitive and depressive symptoms and improvements in most measures of workplace productivity and functioning at both week 12 and week 52; however, correlations were less marked with the WLQ physical demands and WPAI absenteeism domains.

DISCUSSION

In this study in working patients with MDD, robust and significant improvements were observed across domains and items

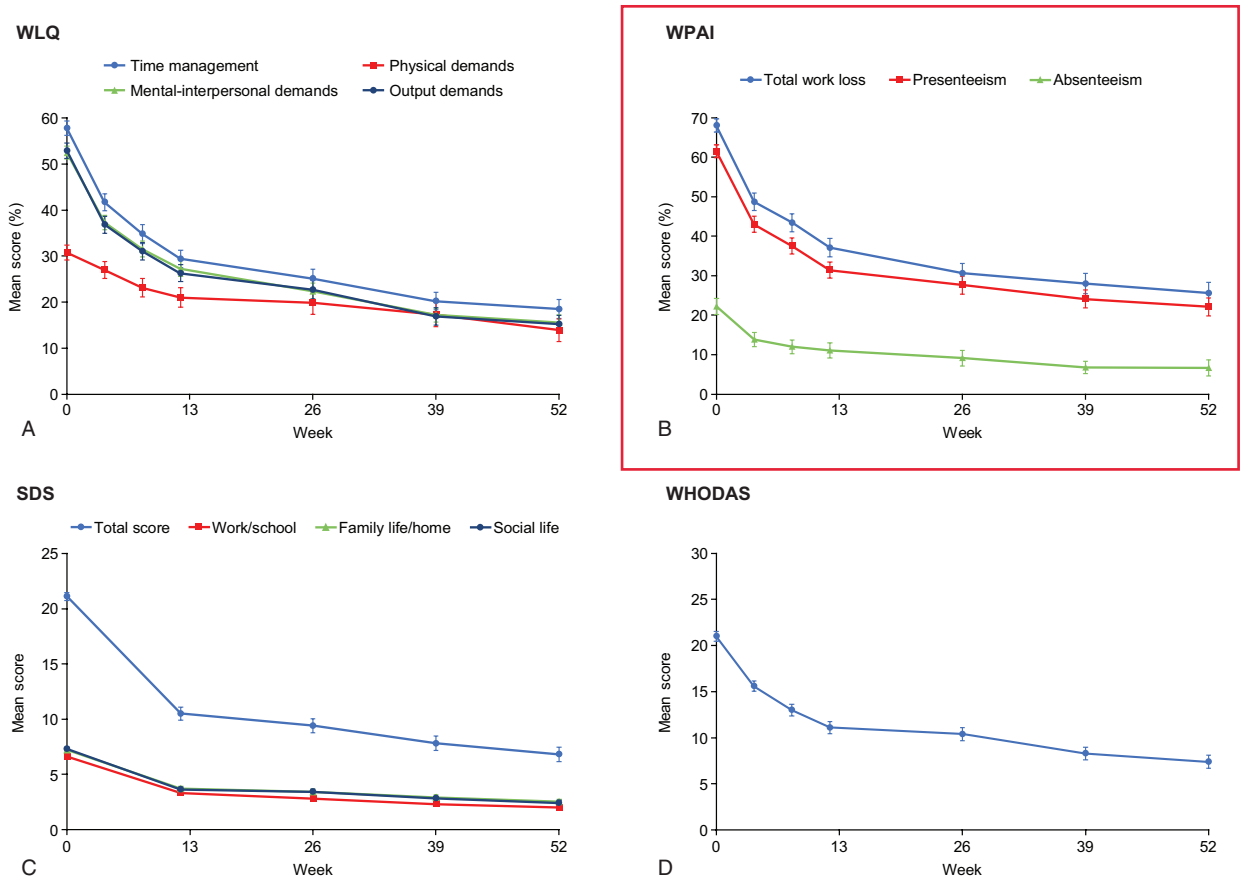

FIGURE 2. Mean (standard error) workplace productivity and functioning scores over the 52 weeks of vortioxetine treatment. Number of patients providing data: 187 to 199 at baseline, 157 to 177 at week 12, 124 to 144 at week 26, 112 to 127 at week 39, and 109 to 122 at week 52. Error bars represent one standard error of the mean. SDS, Sheehan Disability Scale; WHODAS, 12-item World Health Organization Disability Assessment Schedule 2.0; WLQ, Work Limitations Questionnaire; WPAI, Work Productivity and Activity Impairment.

assessing different aspects of workplace functioning and productivity after 12 weeks of vortioxetine treatment, with these improvements maintained to 52 weeks. The most pronounced improvements were seen in domains related to mental rather than physical workplace functioning, reflecting the profile of functional impairments in the patient population at baseline. The level of impairment at baseline in WLQ domains related to mental workplace functioning seen in the present study was notably higher (ie, worse) than that

TABLE 3. Change from Baseline to Weeks 12 and 52 in Workplace Productivity and Functioning Scores (Full Analysis Population, Observed Cases)

	Week 12		Week 52	
Assessment	***n***	**Mean ± SD**	***n***	**Mean ± SD**
WLQ				
Time management	170	−28.4 ± 29.2	116	−38.4 ± 27.2
Physical demands	156	−10.2 ± 27.7	110	−16.2 ± 29.6
Mental-interpersonal demands	169	−24.8 ± 25.8	117	−35.4 ± 22.9
Output demands	167	−27.5 ± 30.6	116	−37.6 ± 27.0
WPAI				
Absenteeism	151	−10.7 ± 34.1	104	−12.7 ± 31.2
Presenteeism	158	−30.3 ± 31.9	109	−39.2 ± 32.3
SDS				
Work/school	172	−3.35 ± 3.34	118	−4.47 ± 3.19
Family life/home responsibilities	177	−3.49 ± 3.20	122	−4.57 ± 3.38
Social life/leisure	177	−3.58 ± 3.21	122	−4.74 ± 3.30
WHODAS 2.0	177	−10.1 ± 9.61	122	−13.3 ± 10.1

Significant improvements ($P < 0.001$, paired t test) versus baseline were found for all outcomes at week 12 and week 52.

n, number of patients with available data; SD, standard deviation; SDS, Sheehan Disability Scale; WHODAS, 12-item World Health Organization Disability Assessment Schedule 2.0; WLQ, Work Limitations Questionnaire; WPAI, Work Productivity and Activity Impairment.

FIGURE 3. Results of correlation analysis of change from baseline to week 52 between the different workplace productivity and functioning domains (observed cases). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Scatterplots are shown on the upper right side of the correlation plot, with corresponding Pearson correlation coefficients on the lower left side (darker values indicate greater correlation coefficients). int, interpersonal; PDQ-D-20, 20-item Perceived Deficits Questionnaire–Depression; QIDS-SR, Quick Inventory of Depressive Symptomatology–self-report; SDS, Sheehan Disability Scale; WHODAS, 12-item World Health Organization Disability Assessment Schedule 2.0; WLQ, Work Limitations Questionnaire; WPAI, Work Productivity and Activity Impairment.

reported in patients with other chronic medical conditions, such as rheumatoid arthritis or osteoarthritis; however, the level of impairment in the WLQ physical demands domain was similar or less pronounced.[48,49] WLQ subscale scores observed at baseline were also considerably higher than scores previously reported for working patients with MDD and individuals without depression.[50,51] However, after 52 weeks of vortioxetine treatment in the present study, scores approached those reported for individuals without depression in these earlier studies.[50,51]

Considerable improvements in levels of absenteeism and presenteeism were also observed in the study population over the 52 weeks of vortioxetine treatment. As in other recent studies,[8,52,53] we found presenteeism to have a stronger association with workplace productivity (as determined by WLQ domains and the SDS work/school item) than absenteeism in working patients with MDD. This was not unexpected, as patients may be reluctant to disclose their diagnosis to their employer or unwilling to take prolonged sick leave because of economic considerations and concerns about job security. Financial costs associated with presenteeism have been shown to be five to 10 times higher than those associated with absenteeism in patients with MDD.[8] Presenteeism due to MDD in the workplace may manifest as an inability to concentrate, increased likelihood of making mistakes, and difficulty establishing good working relationships with coworkers. The mean WPAI presenteeism score reported in the AtWoRC study population at baseline (61.5%) was considerably higher than previously reported in employed patients with depression initiating antidepressant treatment (35.9%)[54]; however, these scores were similar in the two populations after 6 months of treatment (27.6% and 25.2%, respectively). The magnitude of presenteeism in patients with MDD also appears greater than that reported in patients with chronic physical health conditions, including rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.[55–58]

Improvements in self-reported functioning, as assessed by the SDS work/school, social life/leisure, and family life/home responsibilities domains and the WHODAS scale, were also seen after 12 weeks of vortioxetine treatment and were maintained at 52 weeks. These scales capture a broader range of health-related outcomes than the other measures of functioning and workplace productivity used in this study. As with the other measures of productivity and functioning, mean scores on the SDS work/school item and the WHODAS scale after 52 weeks of vortioxetine treatment in the present study were similar to previously reported normative scores.[45,59] This suggests that most patients may have returned to pre-morbid levels of functioning and quality of life.

Our findings are in keeping with a recent systematic review showing that antidepressant treatment generally improves measures of workplace functioning and productivity in patients with MDD.[60] In the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, early improvements in work productivity in employed patients with MDD were associated with higher remission rates at 3 and 7 months.[61] However, impairments in workplace functioning and productivity have been shown to persist in patients with MDD even after remission of mood symptoms.[62,63] Cognitive symptoms have also been shown to persist longer than depressive symptoms in patients with MDD and can persist even in patients who achieve remission of mood symptoms.[64–66] Furthermore, cognitive symptoms appear to have a direct negative impact on work productivity measures in patients with MDD, particularly presenteeism.[67] Such findings suggest that treatments that target both mood and cognitive symptoms may further improve functional outcomes and workplace productivity in patients with MDD. Antidepressant treatments may improve cognitive symptoms to some extent when improving mood symptoms; to date, however, only vortioxetine has been shown to have robust and direct effects on cognition.[33,35,37]

Results of the primary analysis of the AtWoRC study showed highly significant positive correlations between improvements in cognitive symptoms and improvements in workplace productivity after 12 and 52 weeks of vortioxetine treatment.[38,39] Results of structural equations model analyses confirmed that the observed improvements in cognitive symptoms predicted long-term improvements in functional outcomes, even after adjusting for the severity of depressive symptoms.[39] In the present analysis of data from the AtWoRC study, strong correlations were seen between improvements in cognitive symptoms and the majority of measures of workplace productivity and functioning at 52 weeks, although correlations were less marked with the WLQ physical demands and WPAI absenteeism domains. This is not unexpected since mental health conditions typically have less physical impact than conditions such as arthritis, in which physical impairment appears more closely associated with levels of absenteeism.[55,56] However, it should also be noted that some patients reported no or only very low-level impairment in these domains at baseline (ie, scoring at floor level). This leaves limited room for improvement on the specific domains and may shrink correlations of changes from baseline towards zero.

Reduced workplace productivity and functioning associated with MDD imposes a significant economic burden.[10,13] In Canada, the annual economic impact of MDD was estimated to be CAN$32.3 billion in 2016.[15] Results of a pharmacoeconomic analysis has shown that the observed improvements in cognitive symptoms and workplace productivity in working patients with MDD treated with vortioxetine in the AtWoRC study have a substantial economic impact, resulting in a mean financial gain for the employer of CAN$110.64 per patient per week (2017 costs).[68] This translates into potential savings of CAN$4550 per patient for the Canadian economy over the 52 weeks of treatment, after factoring in the cost of therapy.

A major strength of the AtWoRC study is that it was undertaken in a real-world setting and was specifically designed to examine the association between cognitive symptoms and functioning in a population exclusively comprising working patients with MDD. Furthermore, data were collected using several measures of workplace functioning and productivity, permitting detailed analysis of the associations between different workplace functioning outcomes. Patient-reported outcome measures were used to assess disease severity and impact from the patient's own perspective. Use of patient-reported outcomes is in keeping with awareness of the limitations of clinical symptom-based measures in assessing recovery from mental illness in a way that is meaningful to patients, as well as reflecting the general move towards increased patient involvement in treatment decisions.[69–72]

Potential limitations include the open-label study design and the lack of a control group or active comparator. A limitation related to the study being conducted to mimic a real-world setting is that treatment adherence was only assessed subjectively by the investigators. Furthermore, patients with other medical conditions or receiving cognitive behavioral therapy were not excluded. However, given that the AtWoRC study was undertaken to assess long-term changes in symptoms and workplace productivity in working patients with MDD treated with vortioxetine and not to draw conclusions about the comparative effectiveness of vortioxetine with other treatments, the single-cohort, real-world study design was appropriate. Although the enrolled population comprised two distinct groups of patients (first treatment and switching), the population was not stratified for this analysis. However, this was considered justified as results of the previous analysis showed comparable mean change from baseline to week 52 between the two patient groups for all outcome measures.[39] Correlations between changes from baseline to weeks 12 and 52 were also similar in the two patient groups.[38,39]

In summary, results of the AtWoRC study highlight the impact of presenteeism in addition to absenteeism on workplace productivity in working patients with MDD, and show that vortioxetine confers robust and long-term benefits across workplace functioning domains in a real-world setting.

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