Assessment in Work productivity and the Relationship with Cognitive symptoms (AtWoRC): Primary analysis from a Canadian open-label study of vortioxetine in patients with Major Depressive Disorder (MDD)

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INTRODUCTION

- Major depressive disorder (MDD) is a multidimensional disease, requiring assessment and treatment of all symptom dimensions including emotional, physical, and cognitive symptoms[1]
- The clinical relevance of cognitive dysfunction in MDD and its role in work-related disability is supported by a large body of evidence[2–9]
- Recent clinical guidelines (2016 Canadian Network for Mood and Anxiety Treatments for the Management of Adults with Major Depressive Disorder) state that recovery from depression involves both relief of symptoms and improvement of functioning[1,10]
- However, systematic reviews show that symptom improvement is only modestly correlated with functional outcomes, and few studies of antidepressants assess functional outcomes[4,7,11–15]
- Treatment of cognitive symptoms may hold the key to meaningful functional improvement, yet there is a lack of understanding of the relationship between cognitive dysfunction and functional impairment in MDD[16]
- Assessment in Work productivity and the Relationship with Cognitive symptoms (AtWoRC) is an interventional, open-label, Canadian study designed to examine the association between cognitive dysfunction and workplace productivity in gainfully employed patients with MDD treated with vortioxetine

OBJECTIVES

Primary Objective

- To describe the association/correlation between change from baseline to week 12 in patient-reported cognitive symptoms (Perceived Deficits Questionnaire for Depression, PDQ-D-20) and work productivity loss (Work Limitations Questionnaire, WLQ) in gainfully employed patients receiving vortioxetine for a Major Depressive Episode (MDE)

Secondary Objectives

- To describe and compare the following outcomes for patients receiving vortioxetine for an MDE at 12 and 52 weeks:
  - Change in cognitive symptoms and performance
    - PDQ-D-20, Digit-Symbol Substitution Test (DSST)
  - Change in symptom and disease severity
    - Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR), Clinical Global Impression – Improvement (CGI-I), Clinical Global Impression – Severity (CGI-S)
  - Change in functioning and work productivity
    - WLQ productivity loss, Sheehan Disability Scale (SDS), Work Productivity and Activity Impairment (WPAI), 12-item World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0)
  - Treatment response rate
    - Change in QIDS-SR of 50% or more from baseline
  - Remission rate
    - QIDS-SR total score of ≤5
- To describe the pharmaco-economic parameters of the whole cohort

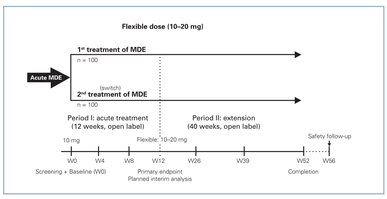
Safety Objective

- To describe the safety and tolerability of vortioxetine in a real-life setting

METHODS

- Interventional study conducted at 26 sites across Canada by 9 psychiatrists and 17 primary care physicians
- To emulate as closely as possible a naturalistic real-life setting, structured investigator-administered interventions and interviews were minimized
- Flexible open-label dosing of vortioxetine of 10–20 mg daily, as per Canadian Product Monograph
- Duration of study is 52 weeks, with safety follow-up at Week 56 and primary endpoint at 12 weeks; study is ongoing
- Patients were classified as having not been treated with another antidepressant (first treatment) or having inadequate response to a previous antidepressant (switch)

Figure 1. Study Design



- PDQ-D-20 assesses self-perceived cognitive difficulties in the areas of prospective memory, retrospective memory, attention/concentration, and planning/organization[17,18]
  - Each of the 20 questions (5 per section) is rated from 0 to 4, with higher scores indicating greater perceived impairment
- WLQ productivity loss reflects proportion of time in the previous 2 weeks that health problems (in this case, MDD) interfered with the ability to work, as measured by 25 items divided into four scales (time management, physical demands, mental-interpersonal demands, output demands)[19,20]
  - Scores are used to calculate the WLQ Index, which is converted to a productivity loss estimate relative to healthy controls (range 0–25%)

Selected Inclusion Criteria:

- Gainfully employed (working ≥20 hours per week) or enrolled full-time in post-secondary studies or vocational training
- Diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5™)
- Current MDE is confirmed by the investigator, with reported duration of the current MDE of at least 3 months
- A baseline score ≥15 on the QIDS-SR
- Reports at least a minimal level of cognitive symptoms as defined by baseline score of ≥30 on the PDQ-D-20

Selected Exclusion Criteria:

- Score of >69 on the DSST at screening/baseline
- Current diagnosis or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features
- Personality disorder, mental retardation, pervasive development disorder, attention-deficit hyperactivity disorder, organic mental disorders, or mental disorders due to a general medical condition (DSM-5™ criteria)
- Physical, cognitive, or language impairment of such severity as to adversely affect the validity of the data derived from the patient reported outcomes
- The current depressive symptoms are considered by the investigator to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each at the maximum recommended dose (according to Canadian labelling)
- Previously been exposed to vortioxetine

RESULTS

- As of November 2016, 196 eligible patients (97 first treatment, 99 switch) at 26 sites were enrolled, received at least one treatment dose, and attended at least one post-baseline study visit
- Presented here are the 12-week primary analysis results

Table 1. Baseline Patient Demographics and Mean Dose at Week 12

	1st Treatment (n = 107)	Switch (n = 109)	Total (n = 216)
Mean age, years (SD)*	**38.9** (12.7)	**42.7** (12.0)	**40.8** (12.4)
Female gender, % (n)	**69.2** (74)	**69.7** (76)	**69.4** (150)
Caucasian race, % (n)	**92.5** (99)	**95.4** (104)	**94.0** (203)
Mean duration of disease, years (SD)*	**5.9** (6.9)	**10.8** (10.9)	**8.4** (9.4)
Employment type, % (n)			
Employed/independent	**90.7** (97)	**93.6** (102)	**92.1** (199)
Full-time vocational	**3.7** (4)	**1.8** (2)	**2.8** (6)
Full-time post-secondary student	**5.6** (6)	**2.8** (3)	**4.2** (9)
Mean dose of vortioxetine Week 12, mg (SD)	**14.6** (5.0)	**15.8** (5.1)	**15.1** (5.1)

All Patients Treated Set (APTS): All patients with a valid baseline assessment who took at least one dose of study medication.
* Significantly different between groups.

- Switch patients were significantly older than first treatment patients (p = 0.024), and had longer duration of disease (p <0.001)

Table 2. Baseline Clinical Characteristics

Mean Scores at Baseline (Week 0) Mean (SD)	1st Treatment (n = 97)	Switch (n = 99)	Total (n = 196)
PDQ-D-20	**49.7** (12.1)	**49.5** (12.1)	**49.6** (12.0)
QIDS-SR	**18.7** (2.6)	**18.1** (2.8)	**18.4** (2.7)
GAD-7*	**15.5** (4.7)	**14.0** (4.8)	**14.8** (4.8)
CGI-S	**4.1** (0.6)	**4.1** (0.5)	**4.1** (0.5)
WLQ, % productivity loss	**13.0** (4.8)	**13.7** (4.3)	**13.4** (4.6)
WPAI, % overall impairment	**66.0** (23.7)	**69.1** (22.7)	**67.6** (23.2)
SDS	**21.0** (4.8)	**21.0** (5.5)	**21.0** (5.1)
WHODAS	**21.1** (6.8)	**21.0** (7.9)	**21.0** (7.4)
DSST	**47.5** (11.2)	**45.0** (12.1)	**46.2** (11.7)

Full Analysis Set (FAS): All patients from the APTS who attended at least one post-baseline study visit.
GAD-7 = Generalized Anxiety Disorder 7-item scale
* Significantly different between groups.

- Patients had cognitive dysfunction, severe depression, severe anxiety, and functional impairment, with first treatment patients demonstrating a significantly higher degree of anxiety than switch patients (p = 0.034)

Table 3. Primary Endpoint: Association Between PDQ and WLQ Productivity Loss

Partial Correlation Between Change in PDQ-D-20 and Change in WLQ Productivity Loss from Baseline to Week 12 (OC)

Group	n	r	P-value
FAS	196	0.633	<0.001
1st treatment	97	0.671	<0.001
Switch	99	0.584	<0.001

Full Analysis Set (FAS): All patients from the APTS who attended at least one post-baseline study visit.
OC: Observed cases
Controlled for age, sex, baseline PDQ-D-20, baseline WLQ productivity loss, disease duration and disease severity (baseline QIDS-SR, baseline CGI-S)

- Patients who had improved cognitive function following treatment with vortioxetine also had improved workplace productivity

Table 4. Associations Between Assessments at Week 12 (Total FAS, n = 196)

Scale	PDQ	DSST	QIDS	CGI-I	CGI-S	WLQ	SDS	WPAI	WHODAS
PDQ	1.00	-0.23	0.73	0.50	0.51	0.66	0.69	0.45	0.69
DSST	-0.23	1.00	-0.14	-0.11	-0.22	-0.23	-0.25	-0.15	-0.27
QIDS	0.73	-0.14	1.00	0.50	0.49	0.67	0.73	0.54	0.66
CGI-I	0.50	-0.11	0.50	1.00	0.69	0.50	0.48	0.43	0.43
CGI-S	0.51	-0.22	0.49	0.69	1.00	0.53	0.56	0.45	0.47
WLQ	0.66	-0.23	0.67	0.50	0.53	1.00	0.82	0.72	0.81
SDS	0.69	-0.25	0.73	0.48	0.56	0.82	1.00	0.70	0.84
WPAI	0.45	-0.15	0.54	0.43	0.45	0.72	0.70	1.00	0.63
WHODAS	0.69	-0.27	0.66	0.43	0.47	0.81	0.84	0.63	1.00

Full Analysis Set (FAS): All patients from the APTS who attended at least one post-baseline study visit.
WLQ = WLQ productivity loss score
WPAI = % overall impairment
p <0.05
p <0.001

- Consistent correlation was observed between different assessment scales following 12 weeks of treatment with vortioxetine

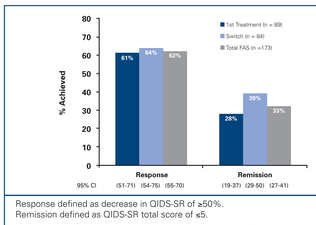
Table 5. Change From Baseline to Week 12: Assessments (OC)

Mean Change From Baseline to Week 12, mean (SD)	1st Treatment (n = 97)	Switch (n = 99)	Total FAS (n = 196)
PDQ-D-20	**-23.7** (17.3)	**-25.5** (15.8)	**-24.6** (16.6)
QIDS-SR	**-9.8** (5.5)	**-10.4** (5.0)	**-10.1** (5.2)
CGI-S	**-1.2** (1.1)	**-1.1** (1.0)	**-1.1** (1.1)
WLQ, % productivity loss	**-6.1** (6.3)	**-7.1** (6.1)	**-6.6** (6.2)
WPAI, % overall impairment	**-31.3** (34.6)	**-34.3** (32.4)	**-32.7** (33.5)
SDS	**-10.2** (9.0)	**-10.8** (8.9)	**-10.5** (8.9)
WHODAS	**-9.9** (9.8)	**-10.1** (8.9)	**-10.0** (9.3)
DSST	**7.8** (11.9)	**10.1** (13.8)	**8.9** (12.9)

Full Analysis Set (FAS): All patients from the APTS who attended at least one post-baseline study visit.
OC: Observed cases
All changes are p <0.0001 (paired t-test) compared to baseline

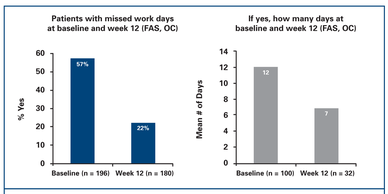
- At 12 weeks, patients treated with vortioxetine showed significant improvement according to all assessments, including measures of cognitive symptoms, disease severity, functional outcomes, work productivity, disability, and objective cognitive performance

Figure 2. Response and Remission at Week 12 (OC)



Response defined as decrease in QIDS-SR of ≥50%.
Remission defined as QIDS-SR total score of ≤5.
Full Analysis Set (FAS): All patients from the APTS who attended at least one post-baseline study visit.
OC: Observed cases

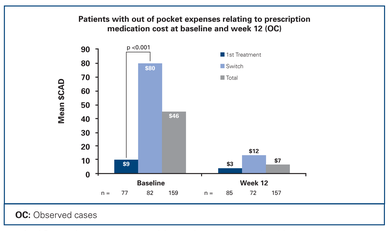
Figure 3. Missed Work Days Related to Depression



Full Analysis Set (FAS): All patients from the APTS who attended at least one post-baseline study visit.
OC: Observed cases

- At 12 weeks, treatment with vortioxetine resulted in fewer patients missing work due to depression; in patients who did miss work, fewer work days were missed than at baseline

Figure 4. Out of Pocket Expenses Related to Depression



OC: Observed cases

- At 12 weeks, treatment with vortioxetine resulted in lower expenses relating to prescription medication in both first treatment and switch patients

Table 6. Most Common Adverse Events (Frequency ≥5% in Total APTS, n = 216)

Event	% (n) Patients
Nausea	27.8 (60)
Headache	12.5 (27)
Insomnia	9.7 (21)
Drug ineffective	7.4 (16)
Nasopharyngitis	6.9 (15)

All Patients Treated Set (APTS): All patients with a valid baseline assessment who took at least one dose of study medication.

- Safety and tolerability were consistent with the Canadian product monograph for vortioxetine
- No new safety signals were observed

Table 7. Discontinuation

Reason	1st Treatment (n = 107) % (n) Patients	Switch (n = 109) % (n) Patients	Total (n = 216) % (n) Patients
Withdrew consent	12.1 (13)	15.6 (17)	13.9 (30)
Adverse drug reaction	7.5 (8)	6.4 (7)	6.9 (15)
Inadequate drug effect	2.8 (3)	7.3 (8)	5.1 (11)
Lost to follow-up	4.7 (5)	4.6 (5)	4.6 (10)
Protocol deviation	0.9 (1)	0.9 (1)	0.9 (2)
Lack of drug effect	1.9 (2)	N/A	0.9 (2)
Pregnancy	0.9 (1)	N/A	0.5 (1)
AE related to other drug	N/A	0.9 (1)	0.5 (1)
Rate of Discontinuation			
Discontinued	35.5 (38)	44.0 (48)	39.8 (86)

All Patients Treated Set (APTS): All patients with a valid baseline assessment who took at least one dose of study medication.
N/A = not applicable

CONCLUSIONS

- Patients with depression who were treated with vortioxetine had improvements in cognitive function as well as improved workplace productivity
- After 12 weeks of treatment with vortioxetine, both first treatment and switch patients showed significant improvements in:
  - Cognitive symptoms and performance (PDQ-D-20, DSST)
  - Symptoms and disease severity (QIDS, CGI-S)
  - Work productivity (WLQ, WPAI)
  - Functioning (SDS, WHODAS)
- Improvements were also observed in pharmaco-economics measures, a secondary endpoint of this study
  - Numbers of patients who missed work days and days of work missed decreased from baseline to week 12
  - Out of pocket expenses relating to prescription medication decreased from baseline to week 12, with a larger decrease observed in switch patients
- While the results are in a Canadian context, they demonstrate that depression has a financial impact; it is important to treat MDD to reduce this impact as much as possible
- The safety profile was consistent with previous studies and product monograph
- These results have shown a relationship between change in cognitive symptoms of depression and change in workplace productivity in a Canadian population
  - This suggests that treating cognitive symptoms is important for functional outcomes for patients with depression

REFERENCES

1. Lam RW et al., 2016. Can J Psychiatry; 61(9): 510–523.
2. Veiel HO, 1997. J Clin Exp Neuropsychol; 19(4): 587–603.
3. Goeldner C et al., 2013. Neuropharmacology; 64: 337–346.
4. Lee RS et al., 2012. J Affect Disord; 140(2): 113–124.
5. Hasselbalch BJ et al., 2011. J Affect Disord; 134(1–3): 20–31.
6. Weisenbach SL et al., 2012. Curr Psychiatry Rep; 14(4): 280–288.
7. Buist-Bouwman MA et al., 2008. Acta Psychiatr Scand; 118(6): 451–458.
8. Jaeger J et al., 2006. Psychiatry Res; 145(1): 39–48.
9. McIntyre RS et al., 2013. Depress Anxiety; 30(6): 515–527.
10. Kennedy SH et al., 2016. Can J Psychiatry; 61(9): 540–560.
11. McIntyre RS et al., 2015. CNS Spectr; 20 Suppl 1: 20–30.
12. Campbell S et al., 2004. J Psychiatry Neurosci; 29(6): 417–426.
13. Murrough JW et al., 2011. Neurobiol Learn Mem; 96(4): 553–563.
14. Harmer CJ et al., 2002. Neuropsychologia; 40(9): 1586–1590.
15. Iosifescu DV, 2012. Eur Neuropsychopharmacol; 22 Suppl 3: S499–504.
16. Francomano A et al., 2011. Clinical Neuropsychiatry; 8(6): 354–366.
17. Lawrence C et al., 2013. Prim Care Companion CNS Disord; 15(3): 1–12.
18. Lam RW et al., 2013. Value in Health; 16, QL4 – A330.
19. Lerner D et al., 2004. J Occup Environ Med; 46(6 Suppl): S46–55.
20. Tang K et al., 2011. Arthritis Care Res (Hoboken); 63 Suppl 11: S337–349.

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