Using Self-Reported Functioning Measures to Identify Working Patients With Impaired Functional Capacity in Major Depressive Disorder

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METHODOLOGICAL QUESTION

Is it possible to screen for major depressive disorder (MDD) in patients with impairments in functional capacity (FC) through self-reported measures focused on everyday outcomes? This strategy could avoid the risk of censoring patients with higher FC measures due to the ceiling effect and minimize the loss of sample size or statistical power.

INTRODUCTION

- MDD is a chronic and episodic disorder associated with significant impairment in quality of life and psychosocial functioning, including social and occupational/role functioning[1]
- The University of California San Diego Performance-Based Skills Assessment (UPSA) is a performance-based measure of everyday living skills designed to assess FC in patient populations with serious mental illnesses[2]
  - UPSA has been shown to provide clinically relevant information for patient functioning in patients with MDD[2]
  - Ceiling effects could be possible, including in patients with MDD who are currently employed (high-functioning patients)
- The Work Limitations Questionnaire (WLQ) is a self-reported functional measure containing 25 items arranged under four subscales addressing four dimensions of job demands (time, physical, mental/interpersonal, and output demands that measure the on-the-job impact of chronic health problems[3]
- The CONNECT study, a multicenter, phase 3, double-blind, parallel-group, placebo-controlled active-referenced (duloxetine) clinical study, evaluated the effects of vortioxetine, an antidepressant with a mechanism of action thought to be related to its multimodal activity, on cognitive function in adults with MDD (NCT01564862)[4]
  - UPSA was included as a predefined endpoint in the CONNECT study, and 0.9% (n=5) of patients scored at ceiling (score of 100) at baseline[2]
    - Patients with very high UPSA baseline scores have limited to no room to show improvement and achieve a responder status; this necessitates excluding patients with higher baseline UPSA scores from future trials evaluating cognition in MDD
  - In addition, WLQ was performed in the subset of working patients (41.4%); neither vortioxetine nor duloxetine demonstrated clinical efficacy on the WLQ sensitivity index with statistical significance[4]
- The objective of these retrospective post hoc analyses of data from the CONNECT study was to examine if WLQ can be used instead of the UPSA to identify working patients for studies evaluating cognition in MDD so as to exclude those patients who are likely to achieve ceiling scores on the UPSA

METHODS

Population

- Working patients were 18 to 65 years of age and met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of MDD
- Patients had moderate to severe depression, with a Montgomery–Åsberg Depression Rating Scale (MADRS) total score of ≥26 at screening and baseline, and a duration of at least 3 months for the current major depressive episode (MDE)[4]

Assessments

- Objective measures of cognition included the Digit Symbol Substitution Test (DSST)[4]
- Objective and subjective assessments of overall functionality included the UPSA-Brief (UPSA-B) Aligned and the WLQ[4]
  - In the CONNECT study, two versions of the UPSA were used: the full UPSA (5-skill domain UPSA-Validation of Intermediate Measures [UPSA-VIM]) was used in the United States and the UPSA-B, developed with the 2 subtests (financial and communication) that most correlated with the total scores on the 5 subtests in the UPSA-VIM, was used in non-English speaking countries. Both versions yield a total score ranging from 0 to 100. The UPSA-B and recalculated UPSA-VIM raw scores for the finance and communication domains were standardized to 0 to 50 points for each domain, yielding a total score of 0 to 100 for the UPSA-B Aligned
  - The WLQ score presented here is the percent of productivity loss score that converts the weighted sum of the four subscales score to the 0-100 range
  - The threshold for the UPSA-B Aligned scores (baseline UPSA ≤85, >85) was preselected based on the distribution of the UPSA-B Aligned scores at baseline
  - The threshold for the WLQ scores was identified as >13 and ≤13 based on the predefined UPSA-B Aligned baseline scores (≤85, >85)

Statistical Analyses

- The analysis were conducted on the full analysis set that comprised all randomized patients who received ≥1 dose of study medication and had ≥1 valid post-baseline assessment of the primary efficacy variable (DSST). The analysis endpoints include:
  - Change from baseline to week 8 between vortioxetine and placebo in DSST performance score using analysis of covariance (ANCOVA) in observed cases (OC)
  - Change from baseline in the four WLQ scale scores and percentage of productivity loss score after 8 weeks of treatment using ANCOVA (OC)
  - Change from baseline in the UPSA-B Aligned after 8 weeks of treatment analyzed using ANCOVA (OC)

RESULTS

Patients

- This analysis included 528 patients with moderate to severe MDD and a subset of patients (n=207) who had been employed at least 14 days before baseline (working patients) and completed the WLQ
  - Baseline demographics and clinical characteristics of the CONNECT study have been reported elsewhere[4]
  - Baseline characteristics of the subset of working patients (n=207) were similar to those of the study population [**Table 1**]

Table 1. Baseline Characteristics of the Subset of Working Patients (n=207)

Sex, n (%)	
Female	134 (64.8)
Male	73 (35.3)
Race, n (%)	
White	192 (92.8)
Black	13 (6.28)
Asian	1 (0.5)
American Indian or Alaska Native	1 (0.5)
Age (years), mean (SD)	43.81 (11.76)

SD, standard deviation.

Analyses

- **Distribution of UPSA-B Aligned and DSST Scores by Employment Status**
  - Working patients had higher UPSA-B Aligned scores (FC) at baseline than patients who were not working (79.83 vs 77.49; p=0.049) [**Table 2**] and showed a statistically significant treatment-related improvement for vortioxetine relative to placebo on the UPSA-B Aligned (4.12; p=0.005), while the improvement difference in non-working patients was not statistically significant (2.18; p=0.071)
  - Working patients had higher DSST scores at baseline, indicating better performance than those who were not working (45.19 vs 41.02; p<0.001) [**Table 2**]; patients who were working showed a numerically lower treatment-related improvement for vortioxetine relative to placebo on the DSST (1.01; p=0.403) than patients who were not working (2.66, p=0.008)

Table 2. Baseline UPSA-B Aligned and DSST Scores by Employment Status

	Employment	n	Mean (SD)	Range
UPSA-B Aligned	Working	207	79.83 (12.26)	43-100
	Not working	321	77.49 (13.93)	28-100
DSST	Working	207	45.19 (11.40)	18-72
	Not working	321	41.03 (12.32)	5-69

DSST, Digit Symbol Substitution Test; SD, standard deviation; UPSA-B, University of California San Diego Performance-Based Skills Assessment-Brief.

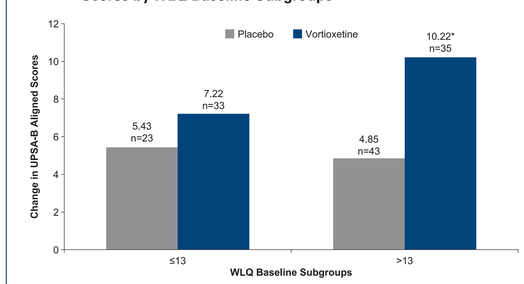
- **Distribution of UPSA-B Aligned Scores by WLQ Baseline Subgroups**
  - Working patients who had WLQ scores >13 (n=123), indicating greater impairment, had lower baseline UPSA-B Aligned scores than those with WLQ scores ≤13 (n=84) (78.46 vs 81.83; p=0.052) [**Table 3**]. However, patients with WLQ scores >13 showed larger treatment-related improvements on the UPSA-B Aligned (5.37-point improvement on vortioxetine vs placebo, p=0.018) as compared to those with lower impairment, with WLQ scores ≤13 (1.79-point improvement on vortioxetine relative to placebo, p>0.05) [**Figure 1**]
- **Distribution of DSST Scores by WLQ Baseline Scores**
  - The threshold for WLQ (>13 and ≤13) was applied to categorize the working population in the CONNECT study and determine their baseline DSST scores and change from baseline
  - Among working patients, scores >13 on the WLQ (n=123) were associated with lower scores on the DSST compared with the WLQ ≤13 group (n=84) (43.59 vs 47.54; p=0.014) [**Table 3**]
  - Patients with greater impairments on the WLQ showed a numerically larger treatment-related improvement on the DSST: a 2.66-point improvement on vortioxetine relative to placebo, while patients with lower impairments on the WLQ had a 0.11-point improvement on the DSST [**Figure 2**]

Table 3. Baseline UPSA-B Aligned and DSST Scores by WLQ Subgroups

	WLQ Sub-groups	n	Mean (SD)	Range
Baseline UPSA-B Aligned	≤13	84	81.83 (11.78)	43-100
	>13	123	78.46 (12.43)	44-100
Baseline DSST	≤13	84	47.54 (11.10)	23-69
	>13	123	43.59 (11.37)	18-72

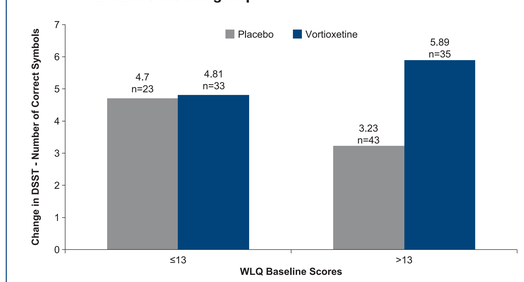
DSST, Digit Symbol Substitution Test; SD, standard deviation; UPSA-B, University of California San Diego Performance-Based Skills Assessment-Brief; WLQ, Work Limitations Questionnaire.

Figure 1. LS Mean Change From Baseline to Week 8 in UPSA-B Aligned Scores by WLQ Baseline Subgroups



*p<0.05.
LS, least-squares; UPSA-B, University of California San Diego Performance-Based Skills Assessment-Brief; WLQ, Work Limitations Questionnaire.

Figure 2. LS Mean Change From Baseline to Week 8 in DSST Scores by WLQ Baseline Subgroups



DSST, Digit Symbol Substitution Test; LS, least-squares; WLQ, Work Limitations Questionnaire.

CONCLUSIONS

- In the CONNECT study, working patients who also scored higher on FC measures showed larger overall treatment responses than non-working patients regardless of their scores on the FC measures
- This retrospective, post hoc analyses of data from the CONNECT study showed that among working patients with depression, a self-reported measure of workplace productivity can identify those with lower performance-based FC
- Including patients who have WLQ scores >13 may bypass the risk of censoring patients because of ceiling effects on the UPSA-B Aligned, minimizing a loss of sample size and overcoming the potential loss of study power
- This study further showed that the WLQ cut-off score of 13 also helped identify patients with higher impairments in DSST scores who also showed larger improvements with vortioxetine treatment
- The use of WLQ to identify patients for studies evaluating cognition in MDD and to avoid the exclusion of patients who are likely to achieve ceiling scores on the UPSA-B Aligned is limited to working patients
- Limited conclusions may be drawn from this study due to its small sample size and use of post hoc analyses
- Duloxetine was not included in these analyses because it was not significantly different from placebo on the UPSA in the CONNECT study[4]

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DISCLOSURES

VM is a full-time employee of Takeda Development Center Americas, Inc., and holds shares in Takeda and GSK. WZ and RX are full-time employees of Takeda Development Center Americas, Inc. PDH has served as a consultant to Akili, Allergan, Boehringer Ingelheim, Forum Pharmaceuticals, Genentech, Lundbeck Pharmaceuticals, Otsuka America, Roche Pharma, Sanofi, Sunovion, Takeda Pharmaceuticals, and Teval for the past 3 years.

REFERENCES

1. Lam RW, Filteau MJ, Milev R. Clinical effectiveness: the importance of psychosocial functioning outcomes. *J Affect Disord*. 2011;132:S9-S13.

2. Harvey PD, Jacobson W, Zhong W, et al. Determination of a clinically important difference and definition of a responder threshold for the UCSD performance-based skills assessment (UPSA) in patients with major depressive disorder. *J Affect Disord*. 2017;213:105-111.

3. Lerner D, Amick BC III, Rogers WH, Malspeis S, Bungay K, Cynn D. The work limitations questionnaire. *Med Care*. 2001;39:72-85.

4. Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology*. 2015:40:2025-2037.