The Effect of Vortioxetine on Family Functioning in Adults With Major Depressive Disorder

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BACKGROUND

- Depression causes patients to experience many emotional, cognitive, social, and occupational impairments; in addition, the psychological literature indicates that depression negatively impacts family functioning.[1-7]
- The Depression and Family Functioning Scale (DFFS) was developed to understand and assess the impact of depression on family functioning from the perspectives of patients and their partners.[8]
  - The DFFS Total score is created by summing the 15 item scores (after reverse-scoring items 4, 8, and 12). DFFS Total scores range from 0 to 60, with lower scores reflecting better partner relationship and family functioning.
  - François and colleagues[9] evaluated the psychometric properties of the DFFS and reported that a preliminary working value for the responder threshold defining meaningful DFFS change in a patient population with major depressive disorder (MDD) was between 4.1 and 7.1 points on the 0 to 60 DFFS Total score scale.
- The DFFS was included in REVIVE,[10] a large, randomized, double-blind study of vortioxetine or agomelatine in adults with MDD with an inadequate response to a single course of selective serotonin reuptake inhibitor (SSRI) or serotonin–noradrenaline reuptake inhibitor (SNRI) antidepressant treatment.
  - Montgomery and colleagues[10] reported that vortioxetine was significantly superior to agomelatine with respect to improvements in depression symptoms; health status and disability; and social, occupational, and family functioning at weeks 8 and 12.

OBJECTIVE

- To measure the impact of depression on family functioning from the patient perspective and examine in detail the impact of treatments on family functioning, as well as compare the relationship of family functioning, as measured by the DFFS, to other clinical outcome assessments (COAs) included in REVIVE.[10]

METHODS

Study Design

- Data from REVIVE[10] were analyzed. REVIVE was a randomized, double-blind, flexible-dose, active comparator (agomelatine), 12-week, multicenter study conducted in 14 countries (Austria, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Italy, Lithuania, Poland, Romania, Russia, Spain, Sweden, and the United Kingdom).
- The study population consisted of 501 adults with MDD, according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR),[11] with an inadequate response to a single course of SSRI (citalopram, escitalopram, paroxetine, sertraline) or SNRI (duloxetine, venlafaxine) monotherapy at approved doses for at least 6 weeks prior to the screening visit.
  - Eligible patients were aged 18 to 75 years and were required to have a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥ 22 and item 1 (apparent sadness) score ≥ 3 at screening and baseline visits.
  - Patients were directly switched from their previous treatment by randomization (1:1) to vortioxetine (10 mg-20 mg/day) or agomelatine (25 mg-50 mg/day) for 12 weeks of treatment.
  - Patients were seen at baseline and weeks 1, 2, 3, 4, 8, and 12.

Clinical Outcome Assessments

- In addition to the DFFS, the following COAs were assessed during the study:
  - MADRS[12]
  - Hamilton Anxiety Rating Scale (HAM-A)[13,14]
  - Clinical Global Impression of Severity (CGI-S)[15]
  - Sheehan Disability Scale (SDS)[16,17]: work/school, social life/leisure, and family life/home scores
  - EuroQol-5 Dimensions (EQ-5D)[18,19] index and visual analog scale (VAS)

Table 1. Schedule of COAs

COA	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
DFFS	X					X	X
MADRS	X	X	X	X	X	X	X
HAM-A	X		X		X	X	X
CGI-S	X	X	X	X	X	X	X
SDS	X				X	X	X
EQ-5D	X				X	X	X

Statistical Analyses

- The present analyses were based on the full-analysis set (FAS), comprising all patients who had a valid baseline DFFS Total score and at least one valid postbaseline DFFS Total score.
- DFFS Total scores were estimates from a mixed model for repeated measurement (MMRM), with treatment, week, and site as fixed factors and the baseline DFFS Total score as a covariate. The model also included treatment-by-week and baseline DFFS Total score by-week interactions. An unstructured covariance structure was used to model the within-patient variance, and the estimation method was a restricted maximum likelihood based approach. The same approach was used to estimate the DFFS item scores.
- Patients were stratified into quartiles based on the baseline DFFS Total score, and scores on the other COAs were compared at baseline.
- DFFS Total scores were compared for remitters and nonremitters. Remitters were defined as patients with a MADRS total score ≤ 10.

RESULTS

Patient Characteristics

- The FAS comprised 376 patients. There were no clinically relevant differences between treatment groups in demographic or patient characteristics at baseline (Table 2).

Impact of Treatments on Family Functioning

- Figure 1 shows average DFFS Total scores by treatment group at baseline, week 8, and week 12.
  - DFFS Total scores improved from baseline to weeks 8 and 12 for both treatment groups, indicating improvements in family functioning and partner relationship.
  - The mean DFFS Total score at baseline was 28.99 in the agomelatine group and 29.25 in the vortioxetine group.
    - At week 8, the mean DFFS score was 21.41 in the agomelatine group and 18.50 in the vortioxetine group. The mean difference between vortioxetine and agomelatine was –2.92 (95% CI: –4.77 to –1.06; $P = 0.0021$; FAS, MMRM).
    - At week 12, the mean DFFS score was 18.33 in the agomelatine group and 15.78 in the vortioxetine group. The mean difference between vortioxetine and agomelatine was –2.54 (95% CI: –4.55 to –0.53; $P = 0.0134$; FAS, MMRM).
- Figure 2 shows the average scores on each DFFS item by treatment group at baseline.
  - The following DFFS items had scores > 2, reflecting domains more severely impacted by depression:
    - Avoid talking about specific topics with your partner because of your depression?
    - Were you and your partner able to resolve disagreements or disputes between the two of you?
    - Withdrawn, even when spending time with your partner or other family members?
    - Depression interfered with your sexual relationship?
    - Depression interfered with feelings of intimacy toward your partner?
    - Depression interfered with ability to take care of household chores or responsibilities?
  - The only item with an average < 1 at baseline was "Did your partner intervene in arguments between you and other family members?"
- Figure 3 displays the average change in DFFS item scores from baseline to week 8, and Figure 4 displays the average change in DFFS item scores from baseline to week 12.
  - Certain DFFS items showed improvements between baseline and week 8, with further improvements at week 12.
  - These improvements were greater for vortioxetine compared with agomelatine, except for item 4 at week 8 and items 5 and 13 at week 12; however, patterns were similar in both treatment groups.
  - The following items showed the greatest improvement:
    - Avoid talking about specific topics with your partner because of your depression?
    - Withdrawn, even when spending time with your partner or other family members?
    - Depression interfered with ability to take care of household chores or responsibilities?
  - The following items, related to disagreements and arguments, had the lowest improvement:
    - Did you and your partner argue?
    - Were you and your partner able to resolve disagreements or disputes?
    - Did your partner intervene in arguments between you and other family members?

Relationship of Family Functioning to Other COAs

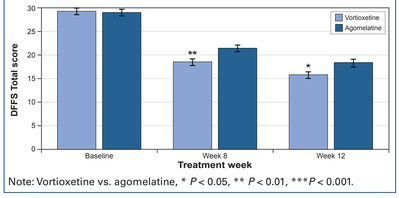
- Patients were stratified into DFFS Total score quartiles defined at baseline, and baseline scores on the other COAs were compared (Table 3).
  - Worse DFFS Total scores were significantly associated with worse functioning (SDS) and health status (EQ-5D). Similar patterns were observed for MADRS and CGI-S ratings.
  - DFFS Total scores were compared for remitters (n = 142 at week 8 and n = 183 at week 12) and nonremitters (n = 233 at week 8 and n = 121 at week 12). Remitters, defined as patients with a MADRS total score ≤ 10, averaged 13.25 at week 8 and 11.37 at week 12; nonremitters averaged 24.25 at week 8 and 23.25 at week 12 (Figure 5).

Table 2. Patient Characteristics at Baseline (FAS)

Characteristic	Vortioxetine (n = 189)	Agomelatine (n = 187)	Total (N = 376)
Age (years), mean (SD)	47.13 (11.9)	45.43 (12.1)	46.28 (12.0)
Sex, n (%)			
Male	44 (23.3)	51 (27.3)	95 (25.3)
Female	145 (76.7)	136 (72.7)	281 (74.7)
Marital status, n (%)			
Single	30 (15.9)	31 (16.6)	61 (16.2)
Married or living as couple	132 (69.8)	125 (66.8)	257 (68.4)
Divorced/separated	19 (10.1)	22 (11.8)	41 (10.9)
Widowed	3 (1.6)	4 (2.1)	7 (1.9)
Missing	5 (2.6)	5 (2.7)	10 (2.7)
Number of children in household, mean (SD)	0.76 (1.0)	0.82 (1.2)	0.79 (1.1)
Median, minimum-maximum, n	0, 0-7, 183	0, 0-9, 182	0, 0-9, 365
Employment status, n (%)			
Full-time work or school	97 (51.3)	96 (51.3)	193 (51.3)
Nonworking spouse	8 (4.2)	11 (5.9)	19 (5.1)
Other	8 (4.2)	3 (1.6)	11 (2.9)
Part-time work or school	14 (7.4)	22 (11.8)	36 (9.6)
Retired	29 (15.3)	23 (12.3)	52 (13.8)
Unemployed	28 (14.8)	27 (14.4)	55 (14.6)
Missing	5 (2.6)	5 (2.7)	10 (2.7)
This is patient's first depressive episode, n (%)	46 (24.3)	55 (29.4)	101 (26.9)

SD = standard deviation.

Figure 1. Mean DFFS Total Scores by Treatment Group at Baseline, Week 8, and Week 12 (FAS, MMRM)



Note: Vortioxetine vs. agomelatine, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 2. Mean DFFS Item Scores at Baseline, by Treatment Group (FAS)

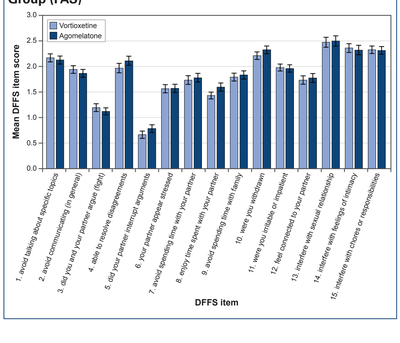
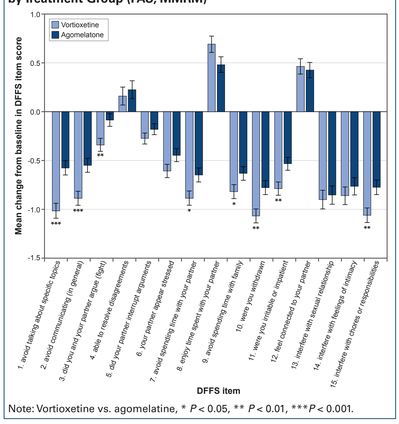
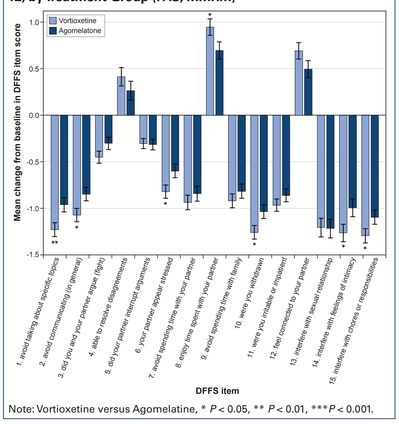


Figure 3. Mean Change in DFFS Item Scores, Baseline to Week 8, by Treatment Group (FAS, MMRM)



Note: Vortioxetine vs. agomelatine, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 4. Mean Change in DFFS Item Scores, Baseline to Week 12, by Treatment Group (FAS, MMRM)



Note: Vortioxetine versus Agomelatine, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

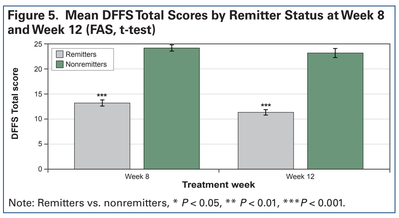
Table 3. COAs by DFFS Total Score Quartiles at Baseline

COA	DFFS < 23 Mean (SD) n	DFFS 23-28 Mean (SD) n	DFFS 29-35 Mean (SD) n	DFFS ≥ 36 Mean (SD) n
MADRS Total Score*	26.97 (3.5) 93	28.83 (4.1) 75	29.39 (3.9) 99	29.67 (4.4) 109
HAM-A*	19.35 (5.0) 93	21.29 (5.1) 75	21.58 (6.4) 99	22.72 (6.4) 109
CGI-S*	4.23 (0.5) 93	4.29 (0.6) 75	4.41 (0.5) 99	4.66 (0.7) 109
SDS Total Score*	14.66 (5.6) 77	19.31 (4.5) 61	20.25 (4.1) 79	21.68 (4.1) 95
SDS Family Score*	4.82 (2.2) 93	6.37 (1.9) 75	6.48 (1.6) 99	7.41 (1.4) 109
SDS Social Score*	4.84 (2.2) 93	6.55 (1.9) 75	6.80 (1.6) 99	7.16 (1.8) 109
SDS Work Score*	4.86 (2.3) 77	6.41 (2.0) 61	6.81 (1.8) 79	7.11 (1.7) 95
EQ-5D index*	0.68 (0.19) 93	0.58 (0.27) 75	0.53 (0.27) 99	0.44 (0.27) 109
EQ-5D VAS*	56.86 (16.8) 93	48.63 (16.7) 75	44.72 (17.3) 99	37.25 (18.1) 109

* $P < 0.05$.

Note: The DFFS, MADRS, CGI-S, HAM-A, and SDS are scored such that higher scores indicate worse outcomes; the EQ-5D index and VAS are scored such that higher scores indicate better outcomes.

Figure 5. Mean DFFS Total Scores by Remitter Status at Week 8 and Week 12 (FAS, t-test)



Note: Remitters vs. nonremitters, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

DISCUSSION

- The DFFS was developed as a measure of partner relationship and family functioning[8] according to the methods and standards outlined in the European Medicines Agency's reflection paper[20] and the Food and Drug Administration's guidance on patient-reported outcomes.[21] The DFFS was specifically intended to gather important information not typically captured in clinical practice or research to facilitate a more comprehensive evaluation of treatments in patients with MDD.[8] In this study:
  - DFFS Total scores showed improvements in family functioning and partner relationship from baseline to weeks 8 and 12, with the vortioxetine treatment group demonstrating significantly greater improvement compared with the agomelatine group ($P \leq 0.05$).
  - All DFFS item scores showed improvement at weeks 8 and 12, with the vortioxetine treatment group generally improving more than the agomelatine group, with half of the items showing a statistically significant improvement for vortioxetine compared with agomelatine.
  - The quartile analyses showed that higher (worse) DFFS Total scores were significantly associated with impaired functioning on the SDS and worse health status on the EQ-5D. Worse DFFS Total scores were also significantly associated with more severe depression symptoms as assessed by the MADRS and CGI-S.
    - Interestingly, the mean score difference between the quartiles was close to the estimated value of meaningful change (4-7 points), the preliminary DFFS responder threshold determined by François and colleagues,[9] and appeared to separate patients on functioning and health status.
  - The difference between remitters and nonremitters was at least 11 DFFS points, approximately 1.5 to 3 times the estimated value of meaningful change on the DFFS (4-7 points), suggesting a major impact of remission status on family functioning and partner relationship.

LIMITATIONS

- Although the efficacy of vortioxetine was established in REVIVE because it was more effective than agomelatine, the absence of a placebo group complicates the inference as to whether the less effective treatment, agomelatine, was efficacious.
- The exclusion of patients with other comorbid disorders (with the exception of generalized anxiety disorder and social anxiety disorder), patients at risk of suicide or younger than 18 years, and pregnant women means that results cannot be confidently generalized to these groups.

CONCLUSIONS

- This study builds on previous research, providing evidence that vortioxetine is significantly superior to agomelatine with respect to improvements in family functioning and partner relationships, as well as social and occupational functioning, health status, and depression symptoms.
- Depressed patients with impaired family functioning were characterized by worse overall functioning, health status, and depression symptoms, suggesting that attention should be given to family functioning of depressed patients.

REFERENCES

Please see handout for complete reference list.

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