Vortioxetine for emotional blunting in patients with major depression and inadequate response to previous antidepressant treatment: the COMPLETE study

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Background

- Major Depressive Disorder (MDD) is a disabling and recurrent illness treated with selective serotonin reuptake inhibitors (SSRIs) or serotonin-noradrenaline reuptake inhibitors (SNRIs).
- However, many patients have inadequate response to these therapies; moreover, almost half of patients treated with an SSRI/SNRI report emotional blunting [1], i.e., restrictions in the full range of emotions that they would normally experience, even during remission.
- Emotional blunting is of clinical importance as it negatively affects daily functioning and health-related quality of life, and thereby the chance of achieving full functional recovery [2].

Objectives

- The main objective of the COMPLETE study (NCT03835715) was to assess the effectiveness of vortioxetine 10–20 mg/day on emotional blunting in patients with MDD who experienced inadequate response to an SSRI or SNRI for their current depressive episode.
- Other outcomes included depressive symptoms, motivation and energy, psychosocial functioning, and cognitive performance.

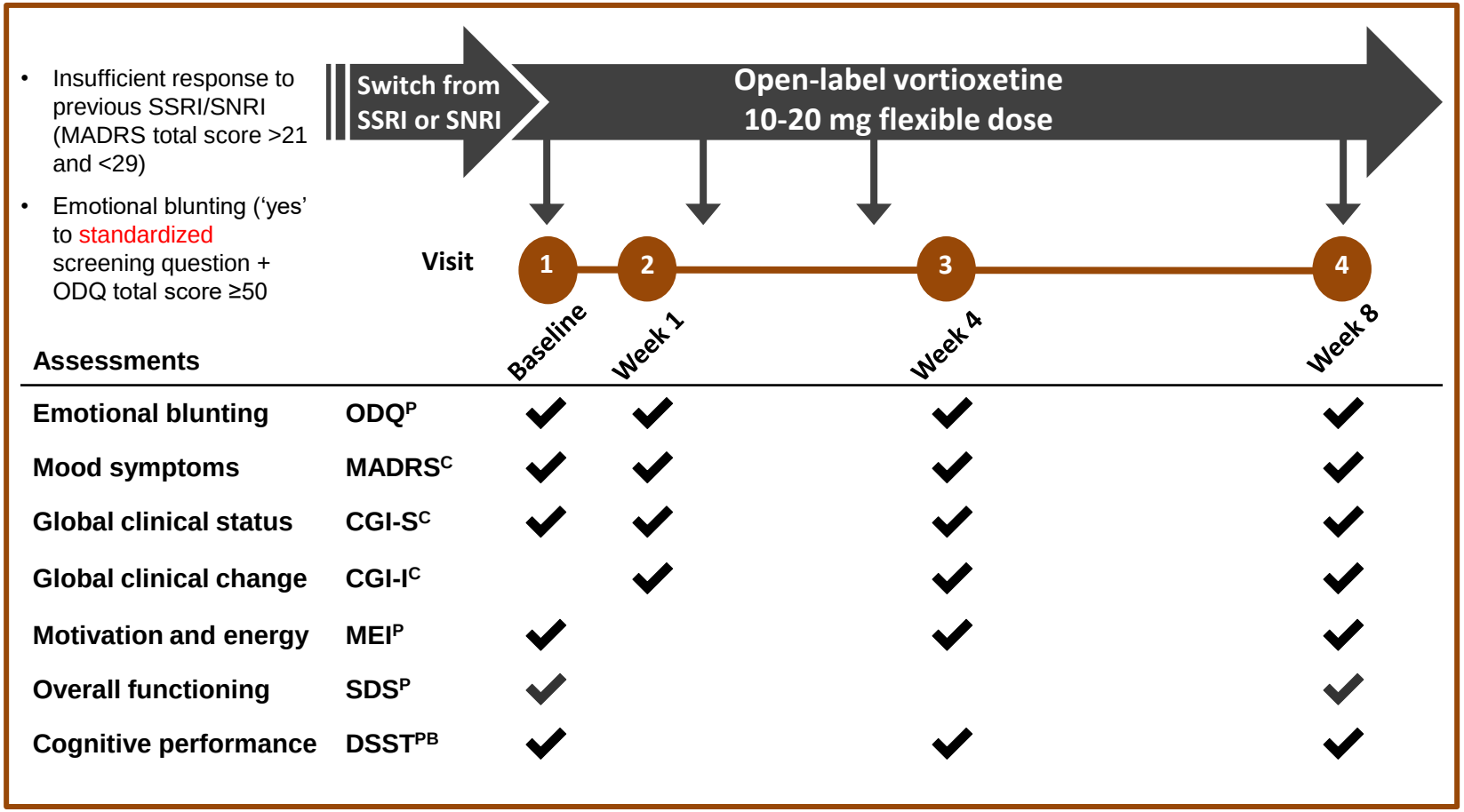
Methods

- This single-arm, open-label study included outpatients ages 18 to 65 years with a primary diagnosis of MDD, a current depressive episode lasting for <12 months, and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score >21 and <29 after ≥6 weeks of monotherapy with an SSRI or an SNRI at an adequate dose.
- Patients further had to experience emotional blunting, as indicated by a screening question and an Oxford Depression Questionnaire (ODQ) total score ≥50, answered yes to a standardized screening question on emotional blunting, and be candidates for a change of medication by their own and the investigator's opinions.
- Patients were switched directly to 8 weeks of open-label vortioxetine (1 week of 10 mg/day followed by 7 weeks of 10-20 mg/day flexible-dose, Fig 1).
- The primary outcome assessment was the Oxford Depression Questionnaire (ODQ), a 26-item, patient-rated scale assessing emotional blunting on four symptom dimensions:
  - General reduction,
  - Positive reduction,
  - Emotional detachment,
  - Not caring.

  An additional subscale assesses antidepressant as cause of emotional blunting.
  A decrease from baseline in ODQ score indicates less emotional blunting.

Methods

Figure 1. Study design



Key exclusion criteria: DSST score >69 at screening/baseline; current diagnosis or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder; personality disorder, mental retardation, pervasive development disorder, attention deficit hyperactivity disorder, organic mental disorders or mental disorders due to a general medical condition; resistance of the current depressive episode to two antidepressant treatments of adequate dose and duration; previous treatment with vortioxetine. [P] Patient-reported; [C] Clinician-rated; [PB] Performance-based. CGI-S/I=Clinical Global Impressions - Severity of Illness/Improvement; DSST=Digit Symbol Substitution Test; MADRS=Montgomery and Åsberg Depression Rating Scale; MEI=Motivation and Energy Inventory; ODQ=Oxford Depression Scale; SDS=Sheehan Disability Scale.

Methods – Statistical approach

- The change from baseline in ODQ total score was analyzed using a mixed model for repeated measurements (MMRM) including site and week as fixed effects, baseline score as a continuous covariate, and baseline score-by-week interaction, based on all available observations.
- Adjusted mean changes from baseline with standard errors (SE) and p-values are reported.
- The relationships between outcomes on ODQ and MADRS, MEI, and SDS scales were explored using partial correlation coefficients and mediation analyses controlling for site and baseline scores.
- Safety and tolerability are reported using descriptive statistics.

Results

- Of 151 patients enrolled, 150 were treated, and 143 were included in the effectiveness analyses. Patients' mean age was 47 years (SD=12), and 105/150 (70.0%) were women (Table 2).
- At baseline, the mean MADRS total score was 25.5 (SD=1.7), and the mean ODQ total score was 89.4 (SD=15.1). Approximately half of patients had an end-dose of 20 mg (Table 3).
- From baseline to week 8, patients improved significantly in ODQ and MADRS scores by -29.8 (SE=1.9; $p<0.0001$) and -13.8 (SE=0.7; $p<0.0001$), respectively, with a significant change in ODQ score seen already at week 1 (Table 4). At week 8, 50% of the patients reported no emotional blunting on the screening question.
- Similarly, DSST, MEI and SDS scores improved significantly, with improvements seen already at the first assessment (Table 4).
- Improvement in ODQ strongly correlated with improvement in MEI (partial $r = -0.778$; $p<0.0001$) and SDS (partial $r = 0.699$; $p<0.0001$), and still moderately after adjustment for improvement in MADRS total score (Fig 4).
- The mediation analysis showed that 63.4% of the change in SDS total score explained by change in ODQ total score was a direct effect of improvement in ODQ after switching to vortioxetine that could not be explained by improvement in MADRS (Fig 5).
- The most common treatment-emergent adverse events (TEAEs; reported by >2%) were nausea, headache, dizziness, vomiting, and diarrhoea; one patient reported a serious adverse event ('abortion missed').

Results

Table 2. Patient flow

	N (%)
Enrolled	151
Treated	150
Completed	131 (87.3)
Analysed (FAS)	143 (95.3)
Discontinued	19 (12.7)
Primary reason for discontinuation	
Adverse event	6
Lost to follow-up	6
Protocol violation	3
Lack of efficacy	2
Withdrawal of consent	1
Other	1

Results

Table 3. Demographic and clinical characteristics

	N (%)
N treated	150
Women	105 (70%)
Mean age (SD), years	47.1 (12.0)
Previous treatment	
SSRI	123 (82.0)
SNRI	27 (18.0)
Mean duration of current episode (SD), weeks	22.3 (12.3)
Range	3 – 56
Number of previous episodes	
0	57 (38.0)
1	34 (22.7)
2+	59 (39.3)
Clinical assessments at baseline	
N (full-analysis set, FAS)	143
ODQ total score	89.4 (15.1)
MADRS total score	25.5 (1.7)
CGI-S score	4.5 (0.6)
MEI total score	44.1 (19.4)
SDS total score	20.8 (4.9)
DSST number of correct symbols	45.4 (13.8)

Results

Table 4. Clinical outcomes (FAS, MMRM)

	Mean change from baseline (SE)		
	Week 1	Week 4	Week 8
ODQ total score	-9.6 (1.6)	-21.2 (1.8)	-29.8 (1.9)
MADRS total score	-3.3 (0.5)	-9.2 (0.6)	-13.8 (0.7)
CGI-S	-0.3 (0.1)	-1.1 (0.1)	-1.8 (0.1)
CGI-I[1]	2.6 (0.1)	2.0 (0.1)	2.0 (0.1)
MEI total score	-	23.5 (2.4)	34.3 (2.8)
SDS total score	-	-	-7.7 (0.9)
SDS Work/School	-	-	-3.2 (0.4)
SDS Social Life	-	-	-2.4 (0.3)
SDS Family/Home	-	-	-2.5 (0.3)
DSST	4.3 (0.9)	-	7.8 (0.9)

$p<0.0001$ for all changes vs baseline. [1]Absolute scores. Negative changes from baseline indicate improvement except for the MEI and the DSST, for which positive changes from baseline indicate improvement. FAS=Full-analysis set; MMRM= mixed model for repeated measurements; SE=Standard error.

Results

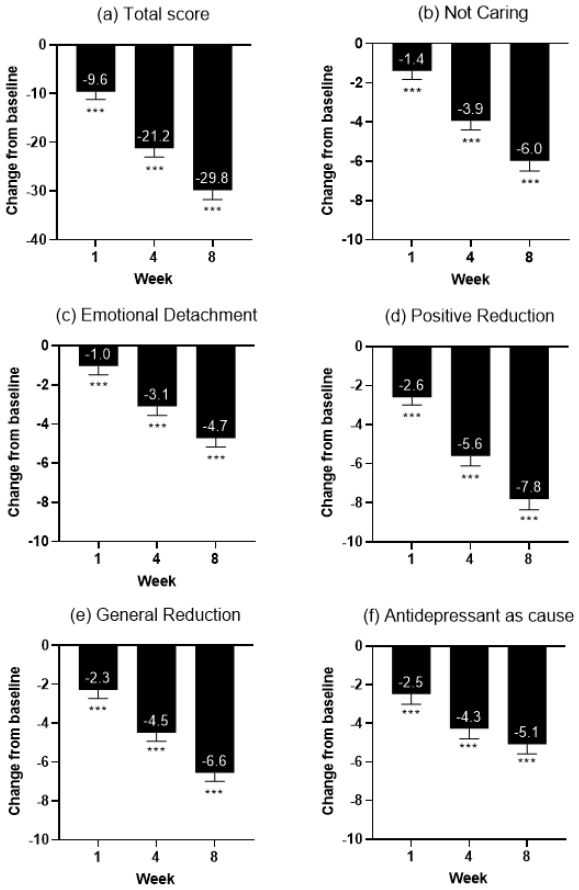
Table 5. Summary of adverse events

	N (%)
Patients treated	150
Patients with TEAEs	71 (47.3)
Patients with serious adverse events	1 (0.7)
Patients with TEAEs leading to discontinuation	6 (4.0)
TEAEs with an incidence >2%	
Nausea	31 (20.7)
Headache	12 (8.0)
Dizziness	10 (6.7)
Vomiting	10 (6.7)
Diarrhea	9 (6.0)
Nightmare	6 (4.0)
Abdominal distension	5 (3.3)
Pruritus	5 (3.3)
Abnormal dreams	4 (2.7)
Pruritus generalized	4 (2.7)

TEAE=Treatment-Emergent Adverse Event.

Results

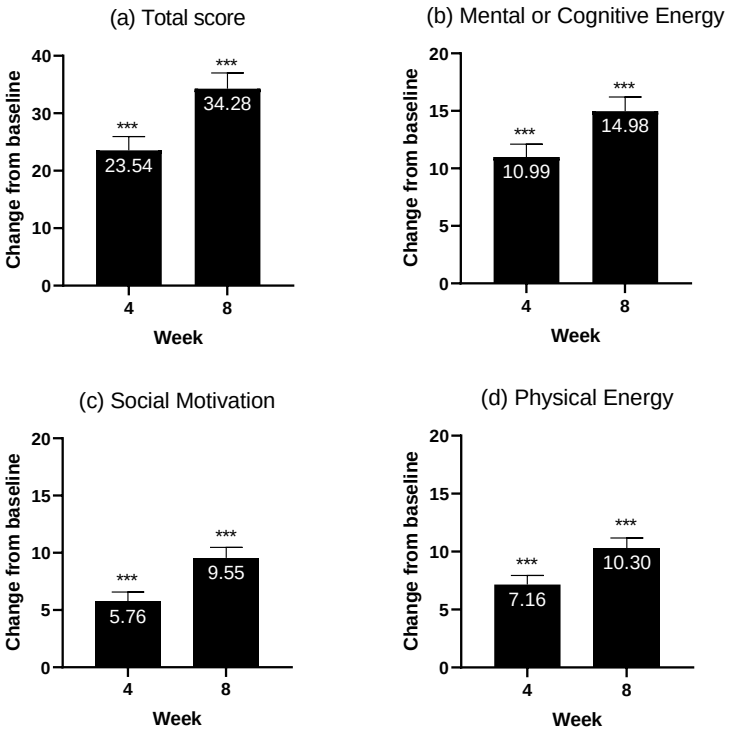
Figure 2. ODQ (FAS, MMRM)



***p<0.0001. Negative changes from baseline indicate improved emotional blunting.

Results

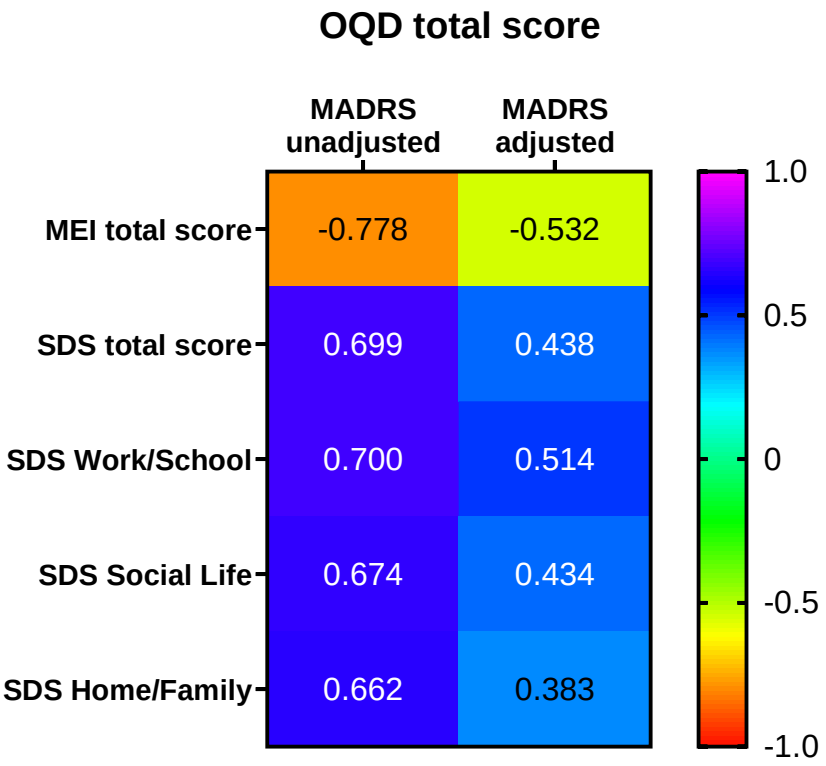
Figure 3. MEI (FAS, MMRM)



***p<0.0001. Positive changes from baseline indicate higher motivation and energy.

Results

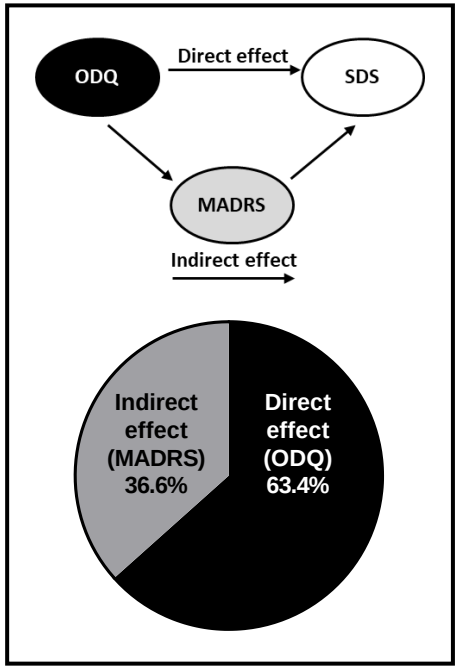
Figure 4. Partial correlations[1] (FAS)



p<0.0001 for all changes vs baseline. [1]Adjusted for site and baseline scores.

Results

Figure 5. Mediation analysis: Total, direct, and indirect effects (FAS)



Conclusion

- In patients with MDD who experienced inadequate depressive symptom resolution and emotional blunting after treatment with an SSRI/SNRI, 50% reported absence of emotional blunting after only 8 weeks of treatment with vortioxetine 10 or 20 mg
- Improvements in emotional blunting were significant already at week 1; with continuous progressive and significant improvement observed at week 4 and 8.
- Similarly, patients improved across all other endpoints, including motivation and energy, cognitive performance, depressive symptoms and overall functioning.
- Improvement in emotional blunting was associated with better functional outcome as well as better energy and motivation, independently of improvement in depressive symptoms.
- Depressive symptom resolution was reported in 47% of patients (higher than previous studies [~40%][3])
- Vortioxetine was well tolerated with no new safety signals.

References

[1] Goodwin GM, et al. J Affect Disord. 2017; 221: 31-35.

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