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Research paper

Effectiveness of Vortioxetine on Emotional Blunting in Patients with Major Depressive Disorder with inadequate response to SSRI/SNRI treatment

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ABSTRACT

Introduction: Inadequate treatment response and emotional blunting are common challenges with selective serotonin reuptake inhibitors/serotonin-noradrenaline reuptake inhibitors (SSRIs/SNRIs) for major depressive disorder (MDD). We investigated the effectiveness of vortioxetine on emotional blunting in patients with partial response to treatment with SSRIs/SNRIs.

Methods: Patients with MDD who experienced a partial response to SSRI/SNRI monotherapy at adequate dose for ≥6 weeks were switched to 8 weeks of vortioxetine treatment 10-20 mg/day (Study NCT03835715). Key inclusion criteria were Montgomery-Åsberg Depression Rating Scale (MADRS) total score >21 and <29, current major depressive episode <12 months, Oxford Depression Questionnaire (ODQ) total score ≥50, and confirmation of emotional blunting by standardized screening question. Emotional blunting was assessed by ODQ and depressive symptoms by MADRS. Other outcomes assessed included motivation and energy (Motivation and Energy Inventory [MEI]), cognitive performance (Digit Symbol Substitution Test [DSST]), and overall functioning (Sheehan Disability Scale [SDS]).

Results: At week 8, patients (N=143) had improved by -29.8 points ($p<0.0001$) in ODQ total score; 50% reported no emotional blunting in response to standardized screening question. Significant improvements were observed on the DSST, MEI, and SDS at all time points assessed, and 47% of patients were in remission (MADRS total score ≤10) at week 8. The most common treatment-emergent adverse events included nausea, headache, dizziness, vomiting, and diarrhea.

Limitations: No prospective phase before medication switch.

Conclusion: Vortioxetine 10-20 mg effectively improved emotional blunting, overall functioning, motivation and energy, cognitive performance, and depressive symptoms in patients with MDD with partial response to SSRI/SNRI therapy and emotional blunting.

1. Introduction

Major depressive disorder (MDD) is a severe, recurrent, and disabling illness that can be treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). However, approximately 50% of all patients only have a partial response to these therapies in terms of depressive-symptoms resolution (Rush et al., 2006).

In addition, about 50-60% of all patients with MDD treated with SSRIs or SNRIs report some degree of emotional blunting, which may be related to the medication (Goodwin et al., 2017; Read et al., 2014; Bolling and Kohlenberg, 2004). Emotional blunting is a condition characterized by a restriction in emotions, which presents clinically as emotional indifference and detachment, reduced responsiveness, low motivation, and apathy (Price et al., 2009). People with emotional blunting report feeling numb, less able to laugh or cry, unable to enjoy what they used to enjoy, feeling less empathy, and feeling indifference toward others (Sandell and Bornäs, 2017). They often complain about having lost inspiration or passion for creative activities and feeling reduced social responsibility or concern for other people (Sandell and Bornäs, 2017).

Emotional blunting is clinically important as it affects patients'

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functioning in work life, social life, and family life, and thus prevents full functional recovery (Price et al., 2009). For example, patients experiencing emotional blunting may evade or ignore responsibilities, which may result in financial problems or problems at work/school, and they may experience a reduction in the quality of family life or parenting (Price et al., 2009). Emotional blunting has also been identified as a common reason for patients with MDD to stop treatment (Rosenblat et al., 2019). Hence, emotional blunting is burdensome for the patient, and negatively affects health-related quality of life and daily functioning (Price et al., 2009). Functional impairment and residual symptoms such as emotional blunting are important as research has shown that patients with remitted MDD with functional impairment are at higher risk of relapse (IsHak et al., 2013).

Emotional blunting phenotypically overlaps with anhedonia; however the two conditions are not identical (Cao et al., 2019b; Esperidião-Antonio et al., 2017; Loas et al., 1994). Anhedonia is a state of reduced ability to experience feelings of pleasure and is a common symptom of MDD reported in ~75% of patients (Franken et al., 2007; Sternat and Katzman, 2016). Patients with emotional blunting very frequently experience anhedonia but the emotions that are blunted are not limited to pleasure. Several other emotions, including negative emotions, are also blunted or toned down (Price et al., 2009). Emotional blunting and anhedonia have been implicated in disturbances of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways (Pan et al., 2017; Sternat and Katzman, 2016). Anhedonia and impaired reward circuit pathways are associated with a poorer prognosis and suboptimal treatment response (Buckner et al., 2008; Uher et al., 2012; Treadway and Zald, 2011).

The evidence is still not entirely clear with regard to the part played by the disease in emotional blunting compared with the effect of commonly prescribed antidepressants (i.e. as a side-effect) (Read et al., 2014; Goodwin et al., 2017; Price and Goodwin 2009). For SSRIs specifically, research has shown that higher doses are more likely to precipitate emotional blunting (Sansone and Sansone, 2010), which, in some cases, may resolve with lowering the dose. In other cases, the condition does not resolve until the SSRI is discontinued (Sansone and Sansone, 2010). Emotional blunting has been proposed to relate to serotonergic effects in the frontal lobes and/or serotonergic modulation of midbrain dopaminergic systems, which project to the prefrontal cortex (Sansone and Sansone, 2010). By broadly enhancing serotoninergic transmission, SSRI drugs activate gamma-aminobutyric acid (GABA) interneurons, thereby dampening the noradrenergic as well as the dopaminergic input (Blier, 2014).

Given its multimodal mechanism of action as well as pro-cognitive effects, vortioxetine may contribute toward alleviating anhedonia and emotional blunting. In addition to serotonin transporter blockage, vortioxetine displays 5-hydroxytryptamine (5-HT)$_{1A}$ agonism, 5-HT$_3$, 5-HT$_{1D}$, and 5-HT$_7$ antagonism, and 5-HT$_{1B}$ partial agonism (D'Agostino et al., 2015). Agonist activity at 5-HT$_{1A}$ receptors can lead to increased serotonin release and theoretically contribute to additional antidepressant activity. Antagonism at the 5-HT$_3$ receptor is usually associated with regulation of nausea and emesis; however, 5-HT$_3$ receptor blockage in GABAergic interneurons may lead to increases in serotonin, dopamine, norepinephrine, acetylcholine, and histamine (D'Agostino et al., 2015; Stahl, 2013; Stahl et al., 2013). In animal studies, vortioxetine was associated with an increase in extracellular levels of the above neurotransmitters, including dopamine, in several regions of the brain associated with depression, such as the prefrontal cortex and hippocampus (Stahl, 2013).

In a recent study by Cao et al., 2019a in patients with MDD, vortioxetine showed significant effects on depressive symptoms, including anhedonia as measured by the Snaith-Hamilton Pleasure Scale (SHAPS), cognitive performance measured by neuropsychological tests, overall functioning, and health-related quality of life (Cao et al., 2019a). A significant correlation was observed after 8 weeks of therapy between improvement in cognitive performance and performance on the Effort for Expenditure for Rewards Task (EEfRT), an objective measure of anhedonia that specifically evaluates motivation and reward.

Based on the mechanism of action of vortioxetine, we sought to determine whether vortioxetine would be an effective antidepressant in adults with MDD with partial response to SSRI/SNRI treatment who reported emotional blunting.

2. Materials and Methods

In this 8-week, open-label, single-arm study, patients were switched directly from SSRIs and SNRIs to 8 weeks of treatment with vortioxetine (1 week of 10 mg/day followed by 7 weeks of 10-20 mg/day flexible dose).

The study included outpatients aged 18-65 years with a primary diagnosis of MDD (per Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) and a current depressive episode of less than 12 months' duration. Patients who had a clinically inadequate (i.e. partial) response (based on the investigators' clinical judgement of the type and severity of symptoms) to an SSRI or SNRI monotherapy at approved doses for at least 6 weeks before the screening visit (SSRIs: escitalopram, paroxetine, and sertraline; SNRIs: duloxetine and venlafaxine) were eligible. A Montgomery-Åsberg Depression Rating Scale (MADRS) total score >21 and <29 (moderate to severe depression), and an Oxford Depression Questionnaire (ODQ) (Price et al., 2012) total score ≥50 (substantial emotional blunting) at baseline were required for inclusion. In addition, all patients had to respond "Yes" to the "gold standard" standardized screening question on emotional blunting developed by Price et al (2012): "*Emotional effects vary, but may include, for example, feeling emotionally 'numbed' or 'blunted' in some way; lacking positive emotions or negative emotions; feeling detached from the world around you; or 'just not caring' about things that you used to care about. Have you experienced such emotional effects during the last 6 weeks?*". All patients had to be candidates for a change of medication by their own and the investigator's opinions.

Patients with current primary psychiatric diagnoses other than MDD or abuse of any substance within 6 months before the beginning of the study were excluded, as were patients with inadequate response to two previous antidepressant treatment courses of adequate dosage and duration. Other key exclusion criteria included mental retardation, pregnancy, and risk of suicide.

The study was conducted between February 2019 and February 2020 at a total of 23 sites in France, Spain, Italy, and Lithuania in accordance with the principles of Good Clinical Practice (ICH, 2016) and the Declaration of Helsinki (World Medical Association, 2002), and was approved by the local ethics committees of each study site. Eligible patients provided written informed consent before participating in any study procedure. The study is registered at ClinicalTrials.gov (NCT03835715).

2.1. Assessments

Clinical and safety assessments were conducted at baseline [except for the Clinical Global Impression (CGI)-Improvement (CGI-I), see below] and at weeks 1, 4, and 8. A safety follow-up was conducted approximately 4 weeks after the last visit.

2.2. Clinical Assessments

Emotional blunting was assessed using the patient-reported ODQ (Price et al., 2012), a novel, patient-reported, 26-item rating scale assessing five dimensions of emotional blunting: not caring (NC), emotional detachment (ED), positive reduction (PR), general reduction (GR), and antidepressant as cause (AC). The questionnaire comprises three sections: Section 1 (12 items) evaluates the experience of emotional blunting during the past week; Section 2 (8 items) compares the experience of emotional blunting during the past week to the

experience of emotional blunting before their depression; and Section 3 (6 items) assesses the patient's perception of a relationship between the current antidepressant medication and emotional blunting, as well as whether this effect had affected adherence to treatment. Single items are rated on a 5-point Likert scale ranging from 1 (disagree) to 5 (agree) and summed into scores for each dimension and a total score (possible total score range: 26-130). Higher values on the ODQ reflect higher levels of emotional blunting.

To supplement the assessment of the effect of vortioxetine on emotional blunting, patients were also asked the same single "gold standard" screening question on emotional blunting at week 8.

Other outcomes assessed included depressive symptoms as rated by clinicians using the MADRS (Montgomery and Asberg, 1979); possible total score range 0-60 with higher scores indicating worse symptom severity. The 5-item MADRS anhedonia subscale score, which is based on the following MADRS items: 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel), was also pre-specified for analysis (Cao et al., 2019a). Clinicians further evaluated overall severity and improvement/worsening of illness using the CGI-Severity of Illness (CGI-S) and the CGI-I (not assessed at baseline) (Busner and Targum, 2007)). CGI-S/I scores range from 1 ('Normal – not at all ill'/'Very much improved') to 7 ('Among the most extremely ill patients'/'Very much worsened'). Other patient-reported outcomes included the Motivation and Energy Inventory (MEI) (Fehnel et al., 2013) assessing social motivation and mental and physical energy (possible score range: 0-144), higher scores indicating higher levels of motivation and energy, and the Sheehan Disability Scale (SDS) (Sheehan et al., 1996) in which patients rate their functional impairment in terms of work/school, social life, family life/home responsibilities. The sum of the three SDS items yields a total score (possible range 0-30), with higher scores indicating worse functioning. Cognitive functioning was assessed using the Digit Symbol Substitution Test (DSST; 90 s test period) (Wechsler, 1997), a performance-based measure of cognitive processing skills involving attention, processing speed, and executive function. The DSST score was calculated as the number of correct symbols (possible range 0-133), higher scores indicating better cognitive performance.

2.3. Safety and Tolerability Assessments

Adverse events (AEs) were recorded based on nonleading questioning from investigators (e.g. 'How do you feel?') or their observations, or patients' spontaneous reporting. Qualified personnel coded AEs using the lowest level term according to MedDRA® (Medical Dictionary for Regulatory Activities; version 14.0). Discontinuation-emergent events were evaluated after recording of AEs at baseline and at week 1 using the Discontinuation-Emergent Signs and Symptoms checklist (DESS) (Rosenbaum et al., 1998), a 43-item clinician-rated checklist designed to evaluate symptoms (e.g., agitation, insomnia, fatigue, dizziness) after a patient has stopped antidepressant therapy (whether due to non-compliance or completion of treatment). An event was considered discontinuation-emergent and scored 1 point if reported for the first time or, if previously reported, it worsened. The DESS total score is calculated as the total number of discontinuation-emergent events.

2.4. Statistical Analysis

The efficacy-analysis set comprised all patients who met the study inclusion criteria, received at least one dose of vortioxetine, and had at least one valid post-baseline ODQ assessment. Analyses were conducted on observed cases; missing data were not replaced. The safety-analysis set included all patients who received at least one dose of vortioxetine.

The primary endpoint assessing the mean change from baseline to week 8 in ODQ total score was analyzed using a mixed model for repeated measurements (MMRM) including site and week as fixed effects, the baseline score as a continuous covariate, and the baseline score-by-week interaction, based on all available observations. Because the AC domain of the ODQ specifically asks about the role of the antidepressant in emotional blunting, the analysis was conducted with and without including the score for this domain in ODQ total score. Standard errors and p-values from tests of whether estimated changes from baseline are different from zero are reported. The same methodology was used for all other continuous endpoints, except CGI-I, for which analysis was based on the absolute value, and using the CGI-S baseline score in the MMRM. For the SDS, if the work/school single item was not available, this item was imputed using the mean of the Social and Family single item scores to calculate the total score (Florea et al., 2017). Categorical endpoints, reported as percentages, included: the standardized screening question on emotional blunting at week 8 (yes/no); response, defined as $\geq$50% decrease in MADRS total score; and remission, defined as MADRS total score $\leq$10.

To assess the change from baseline in ODQ total score not explained by a change in MADRS total score, the primary analysis was repeated with the additional inclusion of the MADRS total score at baseline and the change from baseline as covariates and with/without adjustment for the change in MADRS total score.

Partial correlation and mediation analyses were performed to investigate the relationships between change in ODQ total score and MEI and SDS. The pairwise associations between the changes from baseline to week 8 were described using partial correlation coefficients controlling for site and baseline scores for the relevant scales. To assess the extent to which these associations might be explained by MADRS improvement, analyses were also repeated with the effects of MADRS total score at baseline and the change from baseline to week 8 removed. A mediation analysis was performed post hoc to estimate how much of the change from baseline to week 8 in SDS total score explained by a change in ODQ total score was mediated by change in MADRS total score. The analysis included fitting three models; the first model estimating the *total effect* of change in ODQ on change in SDS; the second model confirming a relationship (*total effect*) between ODQ and MADRS; and the third model estimating *direct* and *indirect* (mediated) *effects* of ODQ total score and MADRS total score, respectively, on SDS total score. All models included site and SDS, ODQ, and MADRS total scores at baseline.

AEs and DESS total score (at baseline and week 1) were summarized using descriptive statistics.

Reported p-values are nominal (not multiplicity controlled), and significance refers to nominal $p<0.05$. Analyses were conducted using SAS (version 9.4) statistical software.

3. Results

3.1. Patient Flow and Baseline Characteristics

Of 151 patients enrolled, 150 were treated, of whom 131 (87.3%) completed treatment and 143 (95.3%) were included in the analyses (7 patients did not provide post-baseline data). A total of 19 patients discontinued the study; the primary reasons were AE (6 patients [4.0%]), loss to follow-up (6 patients [4.0%]), lack of efficacy (2 patients [1.3%]), protocol violation (3 patients [2.0%]), withdrawal of consent (1 patient [0.7%]), and "Other reason" (1 patient [0.7%]). Patients' mean age was 47 years (standard deviation [SD]=12), and 105 (70.0%) were women (Table 1). The mean MADRS total score at baseline was 25.5 (SD=1.7) and the mean ODQ total score was 89.4 (SD=15.1). Most patients (82.0%) were switched from an SSRI at the beginning of the study, most commonly escitalopram, while 18.0% were switched from an SNRI, mostly venlafaxine (Table 1). At week 1, the dose was increased from 10 mg/day to 20 mg/day in 38 patients. At the next scheduled visit (week 4), of these 38 patients, two patients had withdrawn, 33 maintained a 20 mg/day dose, and in three patients the dose was reduced to 10 mg/day; the dose was increased from 10 mg/day to 20 mg/day in a further 38 patients. Approximately half of the patients (51.4%) were receiving

20 mg/day vortioxetine at week 8, and the mean dose was 15.3 mg/day.

3.2. Clinical Assessments of Emotional Blunting

At week 8, the mean change from baseline in ODQ total score was -29.8 [standard error (SE)=1.9; p <0.0001)], and with significant changes seen from week 1 (Table 2; Fig 1). Significant changes were seen across all ODQ subdomains, ranging from -7.8 (SE=0.6; p<0.0001) (PR) to -4.7 (SE=0.5; p<0.0001) (ED) at week 8. The change from baseline in the AC domain was -5.1 (SE=0.5); omitting the subscale score for this domain from the total score in the primary analysis resulted in a change from baseline to week 8 of -24.7 (SE=1.6) points. At week 8, 50% of all patients reported no emotional blunting in answer to the "gold standard" standardized screening question. On the MADRS anhedonia factor score, a significant effect was observed from week 1 (-2.2; p<0.0001), increasing to week 4 (-5.9; p<0.0001) and week 8 (-8.9; p<0.0001).

3.3. Other Clinical Assessments

Improvements in motivation and energy, assessed using the MEI, were substantial and significant from week 4 and across all subdomains – cognitive and mental energy, social motivation, and physical energy (Table 2; Fig 2). Significant improvement in the cognitive performance (DSST) score was observed at week 1 (4.3; p<0.0001) and increased by week 8 (7.8; p<0.0001) (Table 2). Significant improvements from baseline to week 8 in overall functioning, as measured by the SDS, were observed for the total score as well as the single items, most pronouncedly in the work/school domain (Table 2). Overall depressive symptom resolution, as measured by the MADRS total score, improved significantly from week 1 (-3.3; p<0.0001) and continuously increased to week 8 (-13.8; p<0.0001). The rates of response and remission at week 8, as measured by the MADRS, were 61.8% and 46.6%, respectively.

Repeating the primary analysis with additional correction for baseline and change from baseline in MADRS total score showed that only 23% of the total variation in the change from baseline to week 8 in the ODQ total score could be explained by the change in MADRS score.

3.4. Partial Correlation and Mediation Analyses

The partial correlation analyses showed that the changes from baseline to week 8 in ODQ total score and SDS total score were strongly and positively correlated (r=0.653; p<0.0001; Table 3). Further, change in ODQ was negatively correlated with change in MEI total score (r=-0.775; p <0.0001), i.e., improvement in emotional blunting was associated with better outcomes in functioning outcome as well as energy and motivation. After adjustment for improvement in MADRS total score, these associations were still of moderate strength and highly significant, with a partial r of 0.438 between changes in ODQ and SDS (p<0.0001) and of -0.532 between ODQ and MEI (p<0.0001) (Table 3).

The mediation analysis further 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 improved depressive symptoms (MADRS), which accounted for 36.6% of the effect on SDS total score ([Suppl] Fig 3).

3.5. Safety and Tolerability

A total of 71 patients (47.3%) reported a treatment-emergent AE (TEAE) (Table 4). The most common TEAEs (reported by >5%) were nausea, headache, dizziness, vomiting, and diarrhea; one patient reported a serious AE ('abortion missed'). No patients died during the study. Six patients discontinued the study due to TEAEs; TEAEs leading to withdrawal in ≥2 patients comprised vomiting, nausea, and diarrhea. The mean DESS total score was 1.9 (SD=3.8) at baseline and 2.2 (SD=4.2) at week 1.

Table 1
Demographic and clinical characteristics.

Demographic and clinical characteristics	No. of patients (%)
Treated patients (N)	150
Women	105 (70)
Mean age (SD), years	47.1 (12.0)
Country	
Spain	67 (44.7)
France	49 (32.7)
Lithuania	20 (13.3)
Italy	14 (9.3)
Previous treatment	
SSRI	123 (82.0)
Escitalopram	63 (42.0)
Paroxetine	26 (17.3)
Sertraline	21 (14.0)
Citalopram	13 (8.7)
SNRI	27 (18.0)
Venlafaxine	17 (11.3)
Duloxetine	10 (6.7)
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	28 (18.7)
3+	31 (20.7)
Clinical assessments at baseline, mean (SD)	
N (FAS)	143
ODQ total score	89.4 (15.1)
MADRS total score	25.5 (1.7)
CGI-S score	4.5 (0.6)
MEI	44.1 (19.4)
SDS	20.8 (4.9)
DSST	45.4 (13.8)

CGI-S=Clinical Global Impression-Severity of Illness; DSST=Digit Symbol Substitution Test; FAS=full analysis set; MADRS=Montgomery-Åsberg Depression Rating Scale; MEI=Motivation and Energy Inventory; ODQ=Oxford Depression Questionnaire; SD=standard deviation; SDS=Sheehan Disability Scale; SNRI=serotonin-noradrenaline reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Table 2
Effect of vortioxetine on emotional blunting, motivation/energy, cognitive performance, depressive symptoms, and overall functioning (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)
MADRS anhedonia factor score	-2.2 (0.3)	-5.9 (0.4)	-8.9 (0.4)
CGI-S	-0.3 (0.1)	-1.1 (0.1)	-1.8 (0.1)
CGI-I[a]	3.4 (0.1)	2.6 (0.1)	2.0 (0.1)
MEI total score	-	23.5 (2.4)	34.3 (2.8)
Mental or cognitive energy	-	11.0 (1.1)	15.0 (1.2)
Social motivation	-	5.8 (0.8)	9.6 (0.9)
Physical energy	-	7.2 (0.8)	10.3 (0.9)
SDS total score	-	-	-7.7 (0.9)
Work/school	-	-	-3.2 (0.4)
Social life	-	-	-2.4 (0.3)
Family/home	-	-	-2.5 (0.3)
DSST	4.3 (0.9)	-	7.8 (0.9)

p<0.0001 for all changes vs baseline.
CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity of Illness; DSST=Digit Symbol Substitution Test; FAS=full analysis set; MADRS=Montgomery-Åsberg Depression Rating Scale; MEI=Motivation and Energy Inventory; MMRM=mixed model for repeated measurements; ODQ=Oxford Depression Questionnaire; SDS=Sheehan Disability Scale; SE=standard error.
[a] Absolute scores.

4. Discussion

In this study, patients with MDD who experienced inadequate depressive symptom resolution and emotional blunting after treatment with an SSRI or SNRI reported significant improvement in emotional blunting, overall functioning, motivation and energy, cognitive performance, and depressive symptoms after 8 weeks of treatment with vortioxetine 10-20 mg/day. At the end of the study, 50% of the patients did not report emotional blunting versus 100% at the beginning of the study, and nearly half of the patients were in remission for their core depressive symptoms. A positive effect on emotional blunting was observed after just 1 week of treatment. Mediation analysis indicated that 64% of the effect of emotional blunting on functional outcome was a direct effect and not mediated by improvement in depressive symptoms. The improvement in emotional blunting with vortioxetine treatment was strongly and significantly correlated with improvements in motivation and energy, and overall functioning.

As mentioned, emotional blunting and anhedonia are not identical conditions and their clinical presentation differs in important aspects. The term 'anhedonia' primarily refers to the inability to experience pleasure (Rizvi et al 2016). Anhedonia is a core diagnostic feature of a major depressive episode and patients with anhedonia may have a diagnosis of MDD even if the 'depressed mood' criterion is not met (American Psychiatric Association APA, 2013). Patients with emotional blunting very frequently experience anhedonia but the emotions that are blunted are not limited to pleasure and include several other emotions, including negative emotions. By contrast, patients with anhedonia are very well able to experience negative emotions, the perception of which is heightened rather than blunted. This may explain why several antidepressants, including some SSRIs, have shown beneficial effects on measures of anhedonia during a major depressive episode but, at the same time, they have also shown the ability to cause emotional blunting (Goodwin et al., 2017; Cao et al., 2019b). Indeed, many antidepressants are able to ameliorate the inability to experience pleasure and to reduce the intensity of negative emotions (Nutt et al., 2007). However, the same antidepressants may cause emotional blunting, in that they reduce the ability to experience physiological negative emotions (i.e. going to a funeral and crying, feeling sad when something bad happens) and, at the

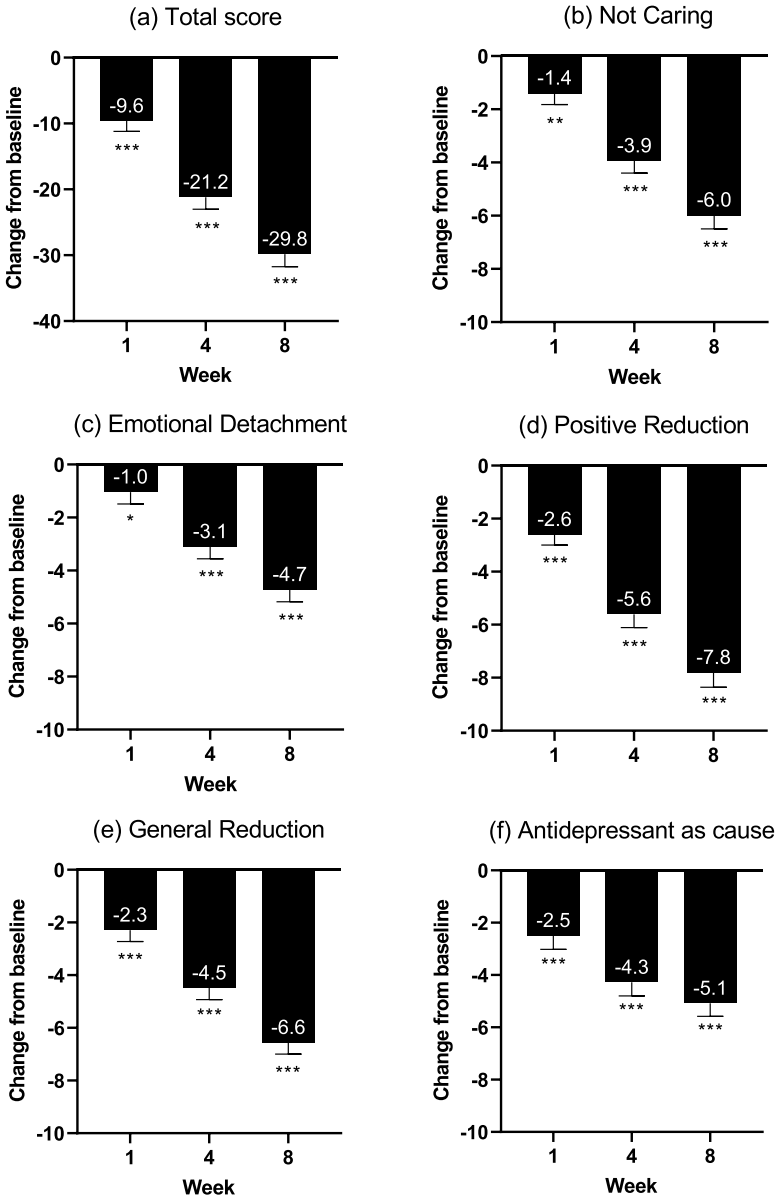

Fig. 1. Changes from baseline in Oxford Depression Questionnaire: (a) Total score and (b-e) subdomains (full analysis set, mixed model for repeated measurements). *p<0.05; **p<0.001; ***p<0.0001.

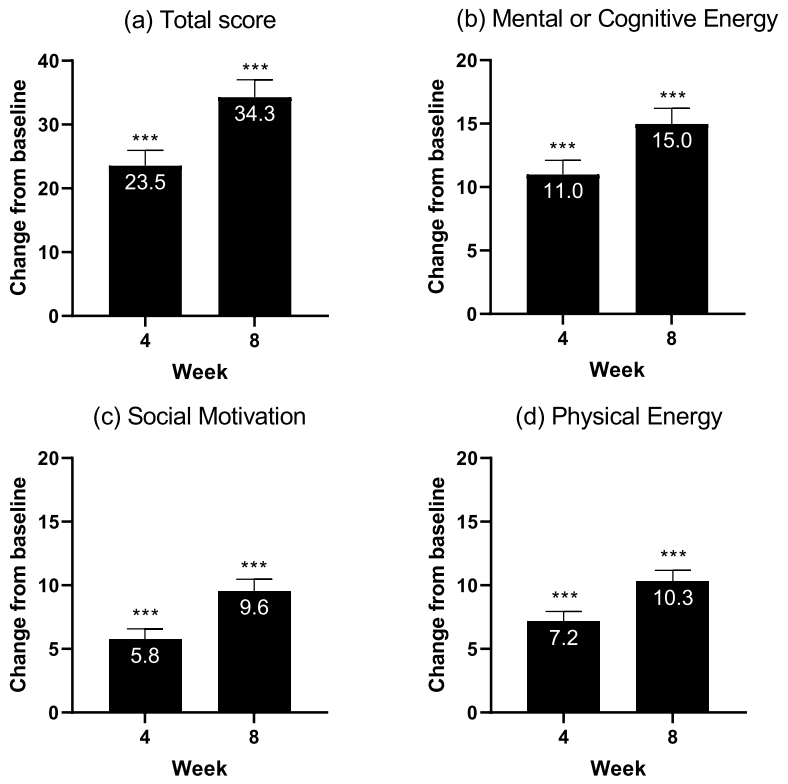

Fig. 2. Changes from baseline in Motivation and Energy Inventory: (a) Total score and (b-d) subdomains (full analysis set, mixed model for repeated measurements). ***p<0.0001.

same time, they 'stabilize' positive emotions, flattening them in a range that is better than the intensity experienced during depression but is not normal. Hence, patients may be improved in their ***anhedonia***, i.e. they are no longer tormented by excessive negative emotions or unable to experience pleasure, but they are ***emotionally blunted***, e.g. in their creativity, in their ability to enjoy and engage in things, and in their reactivity to life events.

The mechanism by which vortioxetine is efficacious in adults with MDD who experience emotional blunting is not fully understood. Vortioxetine's ability to improve general cognitive functions and mitigate anhedonia provides a basis for hypothesizing that the benefits observed in this study are mediated by modulation of cognitive control, as well as possibly by reward circuits (Cao et al., 2019a; Christensen et al., 2020). Also, vortioxetine has a lower serotonin transporter (SERT) occupancy than SSRIs (80% at 20 mg vs 95% with 20 mg escitalopram for instance) (Areberg et al., 2012; Meyer et al., 2004; Sanchez et al., 2015). Moreover, a downstream effect of vortioxetine on dopamine may contribute to a potential favorable effect on emotional blunting, and possibly be mediated by vortioxetine modulation on 5-HT neuronal connections of glutamate and GABA neurons to the prefrontal cortex and hippocampus (El Mansari et al., 2010; Komlósi et al., 2012; West and Weiss, 2011). Vortioxetine may enhance the output of glutamatergic pyramidal

Table 3
Partial correlations of improvements in emotional blunting, motivation and energy, and functional outcomes at week 8

	Correlation coefficient (*r*) with ODQ total score			
	N	MADRS unadjusted[a]	N	MADRS adjusted[b]
MEI total score	130	-0.775	130	-0.532
SDS total score	131	0.653	131	0.438
SDS work/school	90	0.700	90	0.513
SDS social life	131	0.674	131	0.434
SDS family life/home responsibilities	131	0.662	131	0.383

p<0.0001 for all coefficients.
MADRS=Montgomery-Åsberg Depression Rating Scale; MEI=Motivation and Energy Inventory; ODQ=Oxford Depression Questionnaire; SDS=Sheehan Disability Scale.
[a] Adjusted for site and baseline scores.
[b] Adjusted for site, baseline scores, and MADRS total score at baseline and change from baseline.

Table 4
Summary of TEAEs, TEAEs with an incidence of >2%, and TEAEs leading to discontinuation in the 8-week treatment period.

	No. of patients (%)
Patients treated (N)	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)
TEAEs leading to discontinuation	
Vomiting	4 (2.7)
Nausea	3 (2.0)
Diarrhea	2 (1.3)
Abdominal pain upper	1 (0.7)
Chromaturia	1 (0.7)
Dizziness	1 (0.7)
Feeling abnormal	1 (0.7)
Nightmare	1 (0.7)

TEAE=treatment-emergent adverse event.

neurons while reducing the output of GABAergic interneurons in the prefrontal cortex and hippocampus. These changes in neuronal activity may be due to blockade of the SERT and 5-HT_3 receptors, while stimulating 5-HT_{1A} receptors at nodes within neural networks where 5-HT neurons connect with glutamate and GABA neurons (Stahl, 2015).

The results of this study bring new information regarding the clinical value of vortioxetine. In clinical studies of patients with MDD, vortioxetine has shown significant and clinically relevant effects not only on depressive symptoms, but also on the physical and cognitive symptoms of depression (Christensen et al., 2018a; Kelliny et al., 2015; McIntyre et al., 2016). It has been demonstrated that treatment with vortioxetine can lead to improvement in overall functioning and health-related quality of life, both in the short and long term (Chokka et al., 2019; Christensen et al., 2018b; Florea et al., 2015; Florea et al., 2017; Jacobson et al., 2020). These benefits have also been demonstrated in studies of clinically important subpopulations of patients with MDD, including patients with a history of childhood trauma, patients with an insufficient response to SSRI or SNRI treatment, working patients with MDD, elderly patients, and patients with MDD who have a high level of anxiety symptoms (Baldwin et al., 2016b; Christensen et al., 2020; Katona et al., 2012; McIntyre et al., 2017; Montgomery et al., 2014).

The therapeutic dose range for vortioxetine is 5-20 mg/day, with a starting and recommended dose of 10 mg/day (European Medicines Agency, 2020). Based on clinical response the dose can be increased up to 20 mg/day or decreased to 5 mg/day. Higher doses of vortioxetine have been shown to provide greater clinical response (European Medicines Agency, 2020). Of clinical interest, we observed that 50% of patients were receiving 20 mg/day at the end of this study. All patients started at 10 mg/day, and after 1 week of treatment the dose could be increased to 20 mg/day. This observation is consistent with a previous study investigating the effect of vortioxetine (10-20 mg/day) versus agomelatine (25-50 mg/day) in patients with MDD with inadequate response to SSRI or SNRI monotherapy, showing superiority of vortioxetine to agomelatine on depressive symptom resolution (Montgomery et al., 2014). All patients started at 10 mg/day at baseline and could have their dose increased to 20 mg/day at week 1 if they did not completely respond to 10 mg/day. Of note, 64.7% of the patients in the vortioxetine group received the higher dose (20 mg/day) at the end of the study. In an 8-week comparative study of vortioxetine 10 and 20 mg/day (flexible dose) versus duloxetine 60 mg/day, approximately 60% of all patients treated with vortioxetine were receiving 20 mg/day at the end of the study (Mahableshwarkar et al., 2015).

This study confirmed the benign safety and tolerability profile of vortioxetine demonstrated in previous studies (Baldwin et al., 2016a). In addition, this is the first study to use a dedicated scale (the DESS) to evaluate the tolerability of vortioxetine in patients who were switched to the drug after experiencing a partial response to an SSRI/SNRI. The DESS scores showed no clinically relevant changes in terms of signs and symptoms after the switch, 1 week after baseline.

This study has some limitations. First, the absence of a prospective phase to study the incidence of emotional blunting during SSRI or SNRI treatment before switching to vortioxetine makes it difficult to establish if the effect observed on emotional blunting was due to the previous antidepressant or due to depression. However, we did investigate the effect on emotional blunting while adjusting for the effect on depressive symptoms and still observed a significant effect. Furthermore, according to the study's inclusion criteria all study subjects had to have been treated at an adequate dose of commonly prescribed antidepressants for at least 6 weeks before being switched to vortioxetine, and all patients experienced emotional blunting to a substantial degree. Moreover, correlation analysis indicated only moderate correlation between change from baseline in ODQ total score and MADRS total score (r=0.529; $p<0.0001$). Second, it would be of scientific interest to prospectively evaluate the effect of vortioxetine versus an active comparator in this substantial group of MDD patients with emotional blunting and partial response to SSRI/SNRI treatment.

This is the first study to specifically evaluate the effectiveness of vortioxetine on emotional blunting. The ability of vortioxetine to significantly reduce symptoms of emotional blunting and completely eradicate these symptoms in nearly half of the patients with MDD with a partial response to SSRI and SNRI treatment suggests a double benefit of improving depressive symptoms and emotional blunting with a switch to vortioxetine in this patient population. Further studies to evaluate if a switch to vortioxetine improves emotional blunting in formerly depressed patients, who are currently stable on other antidepressants but are experiencing emotional blunting could be of clinical interest.

5. Conclusion

In this study, patients with MDD with partial response and emotional blunting after treatment with an SSRI or SNRI at an adequate dose for at least 6 weeks, showed large and significant clinical improvements when switched to treatment with vortioxetine 10-20 mg/day. At week 8, 50% reported an absence of emotional blunting and nearly half of the patients were in remission for their core depressive symptoms. Significant improvements were seen on all other study endpoints assessing motivation and energy, depressive symptoms, overall functioning, and cognitive symptoms. Improvement in emotional blunting was associated with better functional outcomes independently of improved depressive symptoms. Vortioxetine was well tolerated with no new safety signals.

Contributors

All authors – Andrea Fagiolini, Ioana Florea, Henrik Loft and Michael Cronquist Christensen – materially participated in the research and the preparation of this article.

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Disclosures

M.C. Christensen, I. Florea and H. Loft are employees of H. Lundbeck A/S.

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Supplementary materials

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