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Research paper

Validation of the Oxford Depression Questionnaire: Sensitivity to change, minimal clinically important difference, and response threshold for the assessment of emotional blunting

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ABSTRACT

Background: The Oxford Depression Questionnaire (ODQ) is a patient-reported scale for assessing emotional blunting in patients with major depressive disorder (MDD). This analysis was undertaken to further validate the scale in patients experiencing emotional blunting while receiving antidepressant treatment.
Methods: Patients with MDD who experienced inadequate depressive-symptom resolution and emotional blunting on selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor monotherapy (adequate dose for ≥6 weeks) were switched to vortioxetine 10–20 mg/day. ODQ total scores were assessed excluding and including the "antidepressant-as-cause" domain (ODQ-20 and ODQ-26, respectively). Anchor- and distribution-based methods were used to determine the minimal clinically important difference in ODQ scores in terms of change from baseline to week 8 of antidepressant treatment.
Results: After 8 weeks of vortioxetine treatment, the mean change in ODQ-20 and ODQ-26 scores from baseline was −24.8 and −30.1 points, respectively. Greater mean changes from baseline in ODQ-20 and ODQ-26 scores were seen in patients reporting no emotional blunting vs those still experiencing emotional blunting after 8 weeks of vortioxetine treatment (ODQ-20: −27.0 vs −22.6 points; ODQ-26: –32.8 vs –27.5 points, respectively). In patients considered clinically minimally improved (Clinical Global Impression–Improvement score, 3) after 8 weeks of vortioxetine treatment, respective mean (standard deviation) change in ODQ-20 and ODQ-26 score from baseline was −15.5 (18.1) and –20.0 (20.5) points.
Limitations: Short study duration.
Conclusions: These results provide further validation of the clinical utility of the ODQ for assessing emotional blunting in patients with MDD. The suggested minimal clinically important difference for change in ODQ-20 and ODQ-26 scores is 16 and 20 points, respectively, after 8 weeks of antidepressant treatment.
Trial registration: ClinicalTrials.gov identifier: NCT03835715.

1. Introduction

Reduced emotional responsiveness is frequently observed in patients with major depressive disorder (MDD) (Goodwin et al., 2017; Opbroek et al., 2002; Price et al., 2009; Sandell and Bornäs, 2017). Patients experiencing emotional blunting report feeling a restricted range of emotions and an inability to experience expected emotional responses. Emotional blunting was first recognized in patients complaining of sexual dysfunction while taking a selective serotonin reuptake inhibitor (SSRI) for depression (Opbroek et al., 2002). Sexual dysfunction is a

Abbreviations: AC, antidepressant-as-cause; CGI-I, Clinical Global Impression–Improvement; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSST, Digit Symbol Substitution Test; MADRS, Montgomery–Åsberg Depression Rating Scale; MCID, minimal clinically important difference; MDD, major depressive disorder; 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.

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common and well-documented adverse effect associated with SSRIs in healthy volunteers and patients with depression (Montejo et al., 2011; Montejo et al., 2015; Rothmore, 2020). It has been widely assumed that emotional blunting is also an adverse effect associated with antidepressant therapy (Price et al., 2009) and in fact, in studies, up to 60% of patients with MDD treated with SSRIs or serotonin-noradrenaline reuptake inhibitors (SNRIs) report some degree of emotional blunting (Goodwin et al., 2017; Price et al., 2009; Read et al., 2014; Sansone and Sansone, 2010). Emotional blunting negatively affects health-related quality of life and daily functioning (Price et al., 2009), and is a common reason for patients with MDD to stop antidepressant treatment (Rosenblat et al., 2019). Recognition and management of emotional blunting is therefore an important contemporary challenge for clinicians who treat patients with MDD.

An alternative explanation for the phenomenon of emotional blunting is that it is a symptom of depressed mood and that its association with SSRIs and related drugs reflects their failure to produce full remission of symptoms, rather than it being solely a side effect of therapy *per se* (Goodwin et al., 2017). This appears to be a possibility because of the neurobiologic and phenotypic overlap between emotional blunting and other characteristics of MDD, particularly anhedonia (Cao et al., 2019a; Esperidião-Antonio et al., 2017; Loas et al., 1994; Pan et al., 2017; Sternat and Katzman, 2016). However, emotional blunting represents a clinical state of absence of both positive and negative emotions, while anhedonia is characterized by the absence of positive emotions alone (Sternat and Katzman, 2016). This may explain why SSRIs may show efficacy against symptoms of anhedonia during a major depressive episode (i.e. patients no longer experience the absence of positive emotions), but symptoms of emotional blunting may persist (e.g. patients still experience the inability to enjoy and engage in usually pleasurable activities and show impaired reactivity to life events). Emotional blunting and anhedonia have been implicated in disturbances of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways (Höflich et al., 2019; Pan et al., 2017; Sternat and Katzman, 2016). A simple prediction from this perspective is that an antidepressant with a broad mechanism of action that is effective against anhedonia might also reduce emotional blunting in patients with MDD.

Emotional blunting was first measured with the Laukes Emotional Intensity Scale (described in Opbroek et al., 2002) and subsequently with the Bell–Shipman Apathy/Emotional Blunting Questionnaire (Bell et al., 2006), but neither of these scales has been adequately validated in patients with MDD (Price et al., 2012). The Oxford Depression Questionnaire (ODQ; previously called the Oxford Questionnaire on the Emotional Side-effects of Antidepressants) is a novel patient-reported scale for assessing symptoms of emotional blunting in patients with MDD (Price et al., 2012). It was developed after in-depth qualitative patient interviews and was validated in a diverse population of patients receiving antidepressant medication (Price et al., 2012). The key domains of emotional blunting are: "not caring", a general reduction of emotional experience, emotional detachment from others, and an absence of positive experience. These domains overlap with clinical descriptions of depression, but they are not necessarily well captured by existing scales. In keeping with this, a review of the phenomenology of depressed mood concluded that volition/motivation and depersonalization/derealization (absence of feeling) are not represented in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria for depression (Kendler, 2016).

The Montgomery–Åsberg Depression Rating Scale (MADRS) includes "lassitude" and "inability to feel" among the 10 items rated by a trained observer; these factors are potentially self-rated by the ODQ. The MADRS is widely used as a primary outcome measure and to assess recovery and remission in treatment trials in mood disorders. However, if the MADRS does not adequately measure emotional blunting, low scores may exaggerate the completeness of the clinical response, which may at least in part explain why the complaint of emotional blunting appears to be so common in patients with MDD despite the quantified response of other symptoms of depression to treatment.

Vortioxetine is a multimodal antidepressant that acts as an inhibitor of the serotonin transporter, as well as modulating the activity of multiple serotonin receptor subtypes (Gonda, et al., 2019; Sanchez et al., 2015). Vortioxetine both directly and indirectly influences the activity of a number of different neurotransmitters, including the serotonergic, noradrenergic, dopaminergic, cholinergic, and histaminergic systems (Gonda et al., 2019; Sanchez et al., 2015). However, vortioxetine appears to have lower serotonin transporter occupancy than SSRIs or SNRIs (50–80% across the therapeutic dose range of 5–20 mg compared with approximately 80% at the minimum therapeutic doses of citalopram, fluoxetine, sertraline, paroxetine, or extended-release venlafaxine) (Meyer et al., 2004; Sanchez et al., 2015).

Vortioxetine has been shown to have significant effects on symptoms of anhedonia in patients with MDD (Cao et al., 2019b; McIntyre et al., 2021; Subramaniapillai et al., 2019). The 8-week, single-arm COMPLETE study was undertaken to evaluate the effectiveness of vortioxetine in alleviating emotional blunting, as assessed by the ODQ, in patients with MDD who had inadequate depressive-symptom resolution and emotional blunting on SSRI/SNRI monotherapy (Fagiolini et al., 2021). Vortioxetine 10–20 mg/day showed significant short-term efficacy in this population, as evidenced by improvements in emotional blunting, depressive symptoms, motivation and energy, cognitive performance, and overall functioning. After 8 weeks of vortioxetine treatment, almost half of all patients achieved remission of their core depressive symptoms (defined as MADRS score $\leq$10) and half reported an absence of emotional blunting (Fagiolini et al., 2021). Improvement in emotional blunting was found to be strongly and positively correlated with functional outcome, even after adjusting for depressive symptoms. Mediation analysis confirmed that approximately two-thirds of the improvement in functioning was directly related to the effect of treatment on emotional blunting.

COMPLETE is the first study to include longitudinal analysis of ODQ data as a primary pre-specified endpoint (Fagiolini et al., 2021). The current analysis was undertaken to further validate the ODQ in the COMPLETE study population, including a detailed analysis of how the ODQ correlates with other outcome assessments at baseline and with treatment response. The minimal clinically important difference (MCID) in change in the ODQ total score from baseline after 8 weeks of antidepressant treatment, and the response threshold for assessment of emotional blunting with the ODQ were also evaluated.

2. Methods

2.1. Study design

COMPLETE was an international, multicenter, single-arm, open-label study conducted at 23 sites in France, Spain, Italy, and Lithuania between February 2019 and February 2020 (NCT03835715). Outpatients aged 18–65 years with a primary diagnosis of MDD according to DSM-5 criteria who had a partial response to SSRI/SNRI monotherapy at an adequate dose for $\geq$6 weeks of treatment and were experiencing emotional blunting were switched to 8 weeks of treatment with vortioxetine (10 mg/day for the first week, followed by 10–20 mg/day). Partial response to SSRI/SNRI therapy was defined as a clinically inadequate response based on the investigators' clinical judgment of the type and severity of symptoms. Key inclusion criteria were: duration of current depressive episode <12 months; MADRS total score >21 and <29 (indicative of moderate to severe depression); and response of "*Yes*" to the following standardized screening question on emotional blunting: *"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?"* In addition, patients were required to have an ODQ total score $\geq$50.

Patients with an inadequate response to two or more previous antidepressant treatment courses of adequate dosage and duration, and those with a current primary psychiatric diagnosis other than MDD, a history of substance abuse within the previous 6 months, or considered at risk of suicide were excluded. The COMPLETE study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the local ethics committee at each study site. Patients provided written informed consent for participation.

2.2. Outcome measures

Outcomes were assessed at baseline and at weeks 1, 4, and 8. Emotional blunting was assessed using the ODQ (Price et al., 2012). The full questionnaire comprises 26 items over three sections covering four dimensions of emotional blunting: not caring, emotional detachment, positive reduction, and general reduction. Section 1 (comprising 12 items, three from each of the four dimensions) evaluates the patient's experience of emotional blunting during the past week. Section 2 (eight items, two from each dimension) compares the current experience of emotional blunting with the patient's recollection of their normal emotional state before their depression. Section 3 (six items) is only completed by respondents currently prescribed antidepressants for their depression, and assesses the patient's perception of a potential link between their current antidepressant and their experience of emotional blunting, and whether this has affected adherence to treatment (antidepressant-as-cause [AC] domain). Each item is rated on a 5-point Likert scale ranging from 1 (disagree) to 5 (agree); higher scores (4 or 5 on each item) indicate greater emotional blunting. The ODQ score excluding the AC domain (ODQ-20) ranges from 20 to 100, while that including the AC domain (ODQ-26) ranges from 26 to 130. In the COMPLETE study, patients completed the ODQ-26 (Fagiolini et al., 2021). Patients were asked to respond again to the standardized screening question on emotional blunting at the end of the 8-week study period.

Depressive symptoms were evaluated using the MADRS (Montgomery and Åsberg, 1979). The MADRS is a 10-item, clinician-administered scale evaluating: (1) apparent sadness, (2) reported sadness, (3) inner tension, (4) reduced sleep, (5) reduced appetite, (6) concentration difficulties, (7) lassitude, (8) inability to feel, (9) pessimistic thoughts, and (10) suicidal thoughts. The MADRS total score ranges from 0 to 60, with higher scores indicating more severe symptoms. MADRS anhedonia items were also assessed, specifically the 5-item MADRS anhedonia subscale score (i.e. the sum of MADRS items 1, 2, 6, 7, and 8, as described by Cao et al., 2019b) and the combined score for MADRS items 7 and 8.

Overall severity and improvement/worsening of depression were also assessed using the Clinical Global Impression–Improvement (CGI-I) scale (Busner and Targum, 2007; Guy, 1976). The CGI-I score ranges from 1 (very much improved) to 7 (very much worse), with a CGI-I score of 4 indicating no change. Other outcomes assessed were motivation and energy (using the Motivation and Energy Inventory [MEI]) (Fehnel et al., 2016), cognitive performance (using the Digit Symbol Substitution Test [DSST]) (Wechsler, 1997), and overall functioning (using the Sheehan Disability Scale [SDS]) (Sheehan et al., 1996).

2.3. Statistical analysis

The population for analysis comprised all randomized patients who received at least one dose of study medication and had assessment data at week 8. Correlations between the ODQ and other assessment scores at baseline and after 8 weeks of vortioxetine treatment were assessed using Pearson's correlation coefficient (r). The distribution of ODQ scores at baseline and of the change in ODQ scores from baseline to week 8 were also assessed. ODQ scores were assessed including and excluding the AC domain, and also according to response (yes/no) to the screening question on experience of emotional blunting at week 8.

Anchor- and distribution-based methods were used to determine the MCIDs and response thresholds for ODQ-26 and ODQ-20 scores after 8 weeks of treatment with vortioxetine. The MCID is defined as the minimal amount of change that appears to be important to the patient (Wright et al., 2012). For the anchor-based method, patients with a CGI-I score of 3 were considered to show minimal clinical improvement, while those with a CGI-I score of 2 were considered responders. The MCID for the ODQ was therefore considered to be the mean change in ODQ score from baseline in patients with a CGI-I score of 3 after 8 weeks of vortioxetine treatment. For the distribution-based approach, the MCID was considered to be a change equivalent to half of the standard deviation (SD) of the mean ODQ score at baseline.

Correlations were also assessed between the four dimensions of the ODQ (not caring, emotional detachment, positive reduction, and general reduction) and the MADRS anhedonia items (i.e. the MADRS anhedonia subscale score and the combined score for MADRS items 7 and 8).

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). Reported p-values <0.05 were considered significant.

3. Results

Demographics and baseline characteristics of the 150 patients enrolled in the COMPLETE study have been reported in detail previously (Fagiolini et al., 2021). The mean (SD) age of the study population was 47.1 (12.0) years, and 70.0% were women. The mean (SD) duration of the current depressive episode was 22.3 (12.3) weeks (range 3–56 weeks), and most patients (82.0%) were switched to vortioxetine from an SSRI (most commonly escitalopram 42.0% of those switching from an SSRI]).

A total of 131 patients (87.3%) were eligible for inclusion in this analysis (i.e. received at least one dose of study medication and had assessment data at week 8). At week 8, 51.4% of patients were receiving vortioxetine 20 mg. After 8 weeks of vortioxetine treatment, 66 patients (50.4%) reported that they were no longer experiencing emotional blunting in response to the standardized screening question.

3.1. Distribution of ODQ scores and correlation with other measures

At baseline, mean ODQ-20 score was 73.4 (SD 12.8, range 42–98) and mean ODQ-26 score was 89.1 (SD 15.3, range 50–121). ODQ scores at baseline were normally distributed, with no apparent outliers (**Fig. 1**). A scatter-plot matrix of ODQ score distributions and correlations between outcome scores at baseline is shown in **Fig. S1**. At baseline, mean ODQ-20 score was moderately correlated with MEI total score (r=–0.47; p<0.0001) (**Table 1**). Weaker correlations were observed between mean ODQ-20 score and MADRS total score (r=0.28; p=0.0015) and SDS total score (r=0.33; p<0.0001). No statistically significant correlation was seen between ODQ-20 and DSST scores at baseline (r=–0.16; p=0.0714). Similar patterns of moderate to weak correlations were seen between ODQ-26 score and the other clinical assessments at baseline (**Table 1**).

After 8 weeks of vortioxetine treatment, mean change in ODQ-20 score from baseline was −24.8 (SD 18.2, range −72 to 17). The corresponding mean change in ODQ-26 score was −30.1 (SD 21.5, range −86 to 17). Correlations between change in ODQ-20 and ODQ-26 scores and other outcome scores after 8 weeks of vortioxetine treatment showed a similar pattern to that seen for baseline scores, but correlations were generally stronger for all outcomes except DSST (**Table 1**). The effects of treatment with vortioxetine on ODQ, MADRS, MEI, and SDS scores were significantly correlated and supported a global improvement in objectively and subjectively rated symptoms (**Fig. S2**).

The distribution of change in ODQ scores from baseline to week 8 is shown in **Fig. 2**; improvement was observed in most patients. Greater change in ODQ scores was seen in patients who responded "No" to the screening question on emotional blunting after 8 weeks of vortioxetine treatment than in those who responded "Yes" at this time (i.e. still

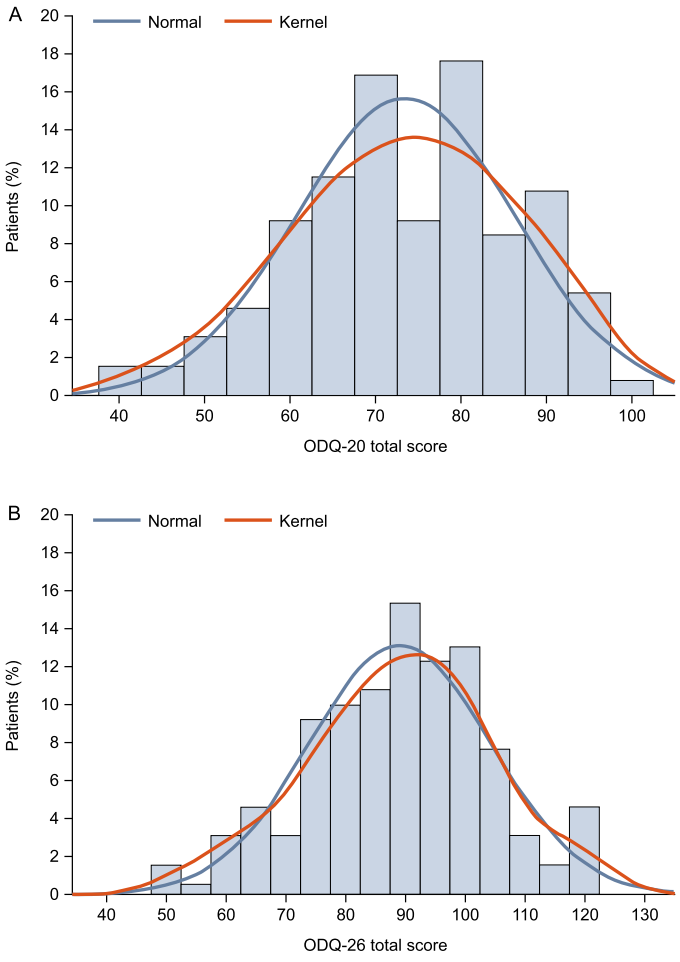

Fig. 1. Distribution of ODQ scores at baseline: (A) ODQ-20 and (B) ODQ-26. 'Kernel' refers to kernel smoothing, which is a statistical technique to smooth a distribution to give a good representation of the data. ODQ = Oxford Depression Questionnaire; ODQ-20 = ODQ total score excluding the antidepressant-as-cause domain; ODQ-26 = ODQ total score including the antidepressant-as-cause domain.

reported emotional blunting) (Fig. 3); however, improvement was seen in both groups of patients. Changes in ODQ-20 score were normally distributed, with a mean change of −27.0 (SD 19.1, range −72 to 11) in patients who responded "No" and −22.6 (SD 17.2, range −54 to 17) in those who responded "Yes." Corresponding mean changes from baseline in ODQ-26 score were −32.8 (SD 23.2, range −86 to 15) and −27.5 (SD 19.4, range −64 to 17).

3.2. MCID and response threshold

In patients considered minimally improved (i.e. CGI-I score of 3) after 8 weeks of treatment with vortioxetine, the mean change in ODQ-20 score from baseline was −15.5 points (SD 18.1) (Table 2). The corresponding mean percent change in ODQ-20 score from baseline was −28.2% (SD 33.8%). Using the distribution-based method (i.e. a value

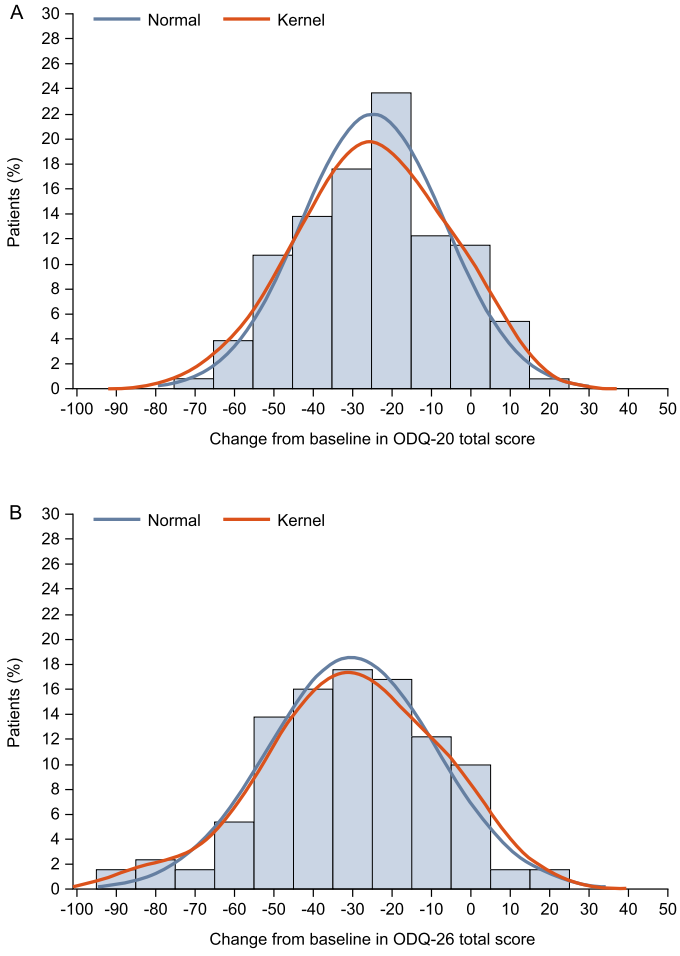

Fig. 2. Distribution of change from baseline in ODQ scores at week 8: (A) ODQ-20 and (B) ODQ-26. 'Kernel' refers to kernel smoothing, which is a statistical technique to smooth a distribution to give a good representation of the data. ODQ = Oxford Depression Questionnaire; ODQ-20 = ODQ total score excluding the antidepressant-as-cause domain; ODQ-26 = ODQ total score including the antidepressant-as-cause domain.

Table 1
Pearson correlation coefficients (*r*) between ODQ score excluding and including the AC domain and other outcome assessment scores at baseline, and between changes in scores after 8 weeks of vortioxetine treatment.

Outcome measure	Baseline				Week 8			
	ODQ-20		ODQ-26		Δ ODQ-20[a]		Δ ODQ-26[a]	
	r	p-value	*r*	p-value	*r*	p-value	*r*	p-value
ODQ-20	1	–	0.92	<0.0001	1	–	0.96	<0.0001
ODQ-26	0.92	<0.0001	1	–	0.96	<0.0001	1	–
MADRS	0.28	0.0015	0.27	0.0015	0.53	<0.0001	0.53	<0.0001
MEI	–0.47	<0.0001	–0.45	<0.0001	–0.71	<0.0001	–0.74	<0.0001
DSST	–0.16	0.0714	–0.13	0.1415	–0.14	0.1226	–0.18	0.0459
SDS	0.33	<0.0001	0.31	0.0003	0.53	<0.0001	0.56	<0.0001

[a] Correlation between change in outcome measures at week 8.

DSST = Digit Symbol Substitution Test; MADRS = Montgomery–Åsberg Depression Rating Scale; MEI = Motivation and Energy Inventory; ODQ = Oxford Depression Questionnaire; ODQ-20 = ODQ score excluding the antidepressant-as-cause domain; ODQ-26 = ODQ score including the antidepressant-as-cause domain; SDS = Sheehan Disability Scale.

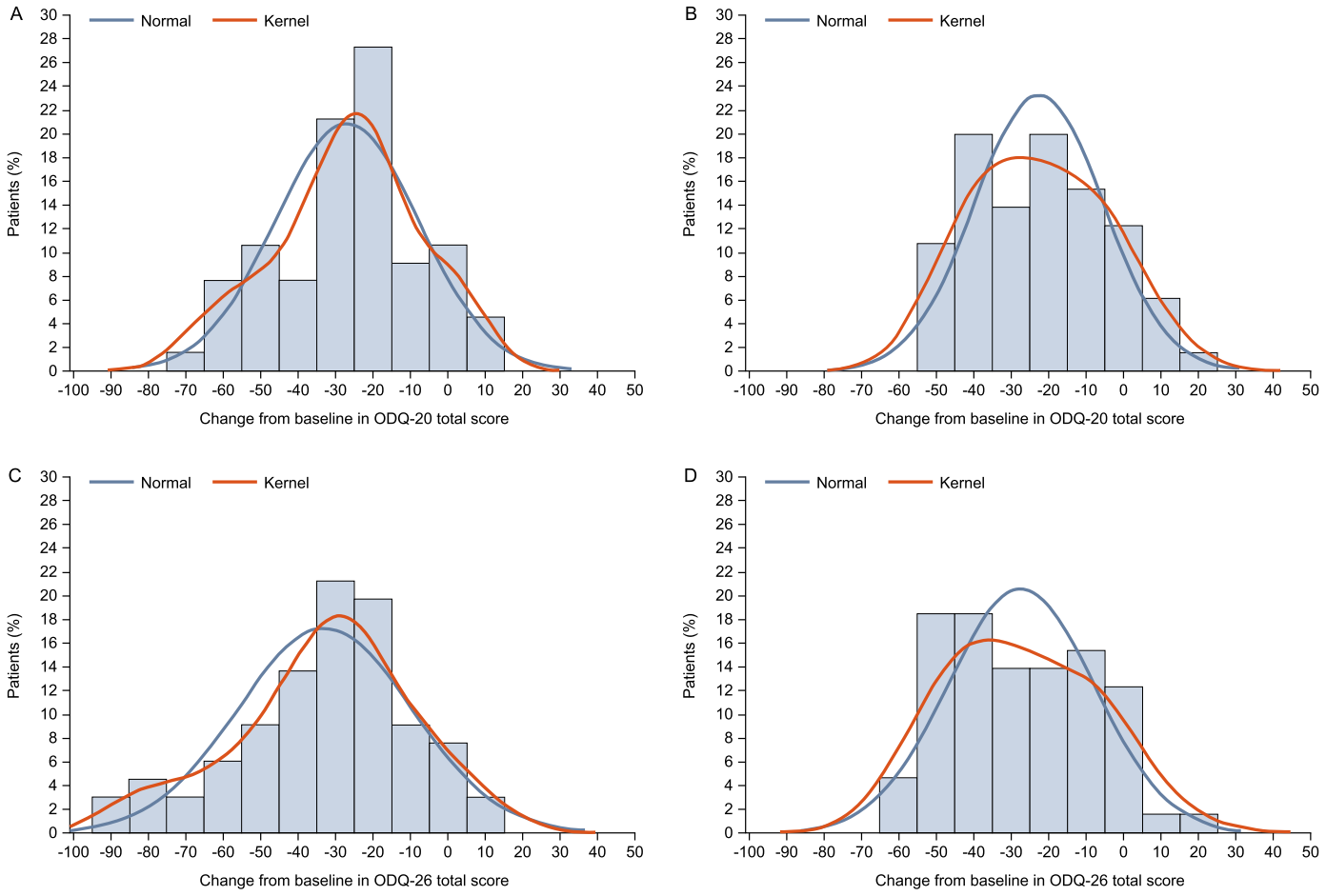

Fig. 3. Distribution of change in ODQ scores from baseline at week 8 according to response to the screening question on emotional blunting: (A) ODQ-20 in patients responding "No"; (B) ODQ-20 in patients responding "Yes"; (C) ODQ-26 in patients responding "No"; (D) ODQ-26 in patients responding "Yes". 'Kernel' refers to kernel smoothing, which is a statistical technique to smooth a distribution to give a good representation of the data. ODQ = Oxford Depression Questionnaire; ODQ-20 = ODQ total score excluding the antidepressant-as-cause domain; ODQ-26 = ODQ total score including the antidepressant-as-cause domain.

Table 2
Change from baseline in ODQ and MADRS scores at week 8 according to CGI-I response level.

	CGI-I score at week 8				
Outcome measure	1 (n=42)	2 (n=54)	3 (n=23)	4 (n=11)	6 (n=1)
ODQ-20					
Mean (SD) change from baseline	–34.1 (18.5)	–25.5 (14.4)	–15.5 (18.1)	–6.1 (12.1)	–14.0
Percent (SD) change from baseline	–62.7 (29.3)	–46.1 (26.0)	–28.2 (33.8)	–9.1 (20.7)	–21.5
ODQ-26					
Mean (SD) change from baseline	–42.2 (23.1)	–29.3 (16.5)	–20.0 (20.5)	–11.5 (12.5)	–10.0
Percent (SD) change from baseline	–63.2 (31.9)	–46.3 (27.0)	–31.5 (30.5)	–16.8 (15.0)	–13.5
MADRS					
Mean (SD) change from baseline	–20.3 (2.9)	–13.9 (3.6)	–8.7 (3.6)	–1.2 (6.0)	12.0
Percent (SD) change from baseline	–79.0 (9.4)	–54.5 (13.4)	–35.9 (14.7)	–4.3 (23.2)	44.4

CGI-I = Clinical Global Impression–Improvement; MADRS = Montgomery–Åsberg Depression Rating Scale; ODQ = Oxford Depression Questionnaire; ODQ-20 = ODQ score excluding the antidepressant-as-cause domain; ODQ-26 = ODQ score including the antidepressant-as-cause domain; SD = standard deviation. CGI-I score: 1, very much improved since the initiation of treatment; 2, much improved; 3, minimally improved; 4, no change from baseline; 5, minimally worse; 6, much worse; 7, very much worse.

equivalent to half of the SD for ODQ-20 score at baseline), the MCID for the ODQ-20 score was −12.8 points. In patients defined as responders (i.e. patients with a CGI-I score of 2 after 8 weeks of treatment with vortioxetine), mean change in ODQ-20 at week 8 was −25.5 points (SD 14.4) or −46.1% (SD 26.0%).

Similar findings were seen for ODQ-26 score (Table 2). In patients considered minimally improved after 8 weeks of treatment with vortioxetine, the mean change in ODQ-26 score from baseline was −20.0 points (SD 20.5), with a corresponding mean percent change in ODQ-26 score from baseline of −31.5% (SD 30.5%). The MCID based on the distribution of the ODQ-26 score was estimated to be 7.7 points. In responders, mean change in ODQ-26 score at week 8 was −29.3 (SD 16.5). The corresponding percent change in ODQ-26 score was −46.3% (SD 27.0%).

3.3. Correlation of ODQ domains with MADRS anhedonia items

Correlations between the four dimensions of the ODQ and MADRS anhedonia items at baseline are shown in **Fig. S3** and **Table S1.** At baseline, the "not caring" dimension showed greater correlation with the MADRS anhedonia subscale score than the other ODQ dimensions; however, *r* values for all correlations were only of moderate magnitude (all ≤0.31). Stronger correlations were seen between changes in ODQ dimension scores and MADRS anhedonia subscale score after 8 weeks of vortioxetine treatment (**Fig. S4** and **Table S2**). Similar patterns of correlations were seen between ODQ dimension scores and the combined score for MADRS items 7 and 8 at baseline and at 8 weeks.

4. Discussion

The ODQ was developed specifically to evaluate symptoms of emotional blunting in patients with MDD (Price et al., 2012). Results of this analysis of data from the COMPLETE study demonstrate that the ODQ captures aspects and symptoms of MDD that are not adequately covered by other scales commonly used to assess depression severity. Low correlation was observed between ODQ total scores and MADRS total score at baseline, with low correlations also observed between ODQ scores and the MADRS items that specifically assess symptoms of anhedonia, namely, "inability to feel" and "lassitude". Highest correlation was seen between ODQ scores and MEI total score at baseline, confirming some overlap with this motivational measure. We believe that the low correlation between the ODQ total score and MADRS total score may be due to the fact that patients with emotional blunting likely under-report symptoms of depression and disability, given that they are detached from, and numbed to, most emotions and feelings (including emotional blunting itself). Improvement was seen across all the different scales in response to therapy. Significant correlation was seen between mean changes in ODQ scores and other assessment scores after 8 weeks of vortioxetine treatment, suggesting that the ODQ is sensitive to changes in the clinical state.

Both anchor- and distribution-based methods were used to determine the MCID in ODQ total score. The CGI-I scale was used as the anchor for establishing MCID because it provides a broader multidimensional assessment of depressive-symptom severity and impact on patient functioning than the MADRS. Using the more widely accepted anchor-based method, the MCID was estimated to be 16 points on the ODQ-20 and 20 points on the ODQ-26; corresponding percent changes in ODQ scores were 28% and 46%. The lower MCIDs estimated by the distribution-based method (13 and 8 points, respectively) are most likely an underestimate due to the strict study inclusion criteria for disease severity, which would be expected to reduce the SD in ODQ score at baseline. From a clinical perspective, our results indicate that a reduction of approximately 30% in symptoms of emotional blunting can be considered clinically meaningful after 8 weeks of antidepressant treatment.

During an acute depressive episode, most emotions (i.e. reactions to external stimuli) are intensely negative; consequently, emotional blunting may not be perceived to be as bothersome during this disease phase as during maintenance treatment of depression, when negative emotions are typically less intense. In non-depressed individuals, both positive and negative emotions can be a stimulus or trigger to continue or change behavior. For example, the happiness generated by experiencing positive emotions reinforces the behaviors that generated those emotions. Conversely, the sadness experienced when facing negative emotions typically prompts actions that may change the unpleasant situation. In contrast, patients with MDD experiencing emotional blunting live with the unpleasant sensation of being emotionally numbed, and are deprived of such positive and negative behavioral reinforcements.

During development of the ODQ, it was unclear whether patients would be able to distinguish between emotional blunting attributable to depression *per se* and a putative drug side effect. However, the dimensions described as "not caring" and "positive reduction" seemed closer to the depressive experience than "emotional detachment" and a "general reduction in emotions" in the initial cross-sectional validation of the scale (Price et al., 2012). In the present analysis, the "not caring" and "positive reduction" dimensions showed greater correlation at baseline with the MADRS anhedonia subscale score than did the other ODQ dimensions. Narrowing the MADRS anhedonia-associated items to two of the five items in the subscale – "lassitude" and "inability to feel" – did not change the magnitude of the correlations with the ODQ dimensions to any great extent.

This is not unexpected; although there is some overlap between emotional blunting and anhedonia, these symptoms are not identical. Emotional blunting presents as emotional indifference, 'numbing' or 'flattening' of emotions, and reduced responsiveness to emotionally significant positive or negative stimuli (Goodwin et al., 2017). In contrast, anhedonia manifests as the inability to anticipate and experience pleasure and is not associated with a lack of emotional responsiveness (Franken et al., 2007; Ho and Summers, 2013; Watson et al., 2020). Indeed, patients with anhedonia are able to experience negative emotions, the perception of which is typically heightened rather than blunted.

The different phenomenology of emotional blunting and anhedonia is most likely due to subtle differences in underlying neurobiologic mechanisms. Although the precise etiopathogenesis has not been determined, it has been hypothesized that emotional blunting is a consequence of reduced dopaminergic or noradrenergic activity in the prefrontal cortex (Nutt et al., 2007; Sansone and Sansone, 2010). By broadly enhancing serotonergic transmission, SSRIs induce activation of gamma-aminobutyric (GABA) interneurons, resulting in dampening of both noradrenergic and dopaminergic inputs (Blier, 2014). While there is evidence that serotonergic pathways may play a role in the development of anhedonia in MDD (Höflich et al., 2019), dopaminergic transmission appears key to the modulation of motivation and 'reward processing' in humans (Belujon and Grace, 2017). Accordingly, anhedonia in patients with MDD has been shown to be associated with disturbances in central dopaminergic mesolimbic and mesocortical reward circuit pathways (Pan et al., 2017). Vortioxetine, with a lower serotonin transporter occupancy than SSRIs (Meyer et al., 2004; Sanchez et al., 2015), has been shown to have favorable effects on both anhedonia and emotional blunting in patients with MDD (Cao et al., 2019b; McIntyre et al., 2021; Subramaniapillai et al., 2019; Fagiolini et al., 2021), possibly due to downstream effects on dopaminergic neurotransmission (Sanchez et al., 2015).

Our results provide further validation of the ODQ for assessing the patient experience in MDD. The scale shows some overlap and so correlates with constructs such as motivation and anhedonia in other commonly used scales, yet only to a moderate extent. The scale therefore clearly measures different aspects of depressive symptoms compared with the MADRS and other outcome scales commonly used for the evaluation of therapeutic interventions in MDD. It has the advantage of being able to assess the full spectrum of symptoms of emotional blunting from the patient's perspective, i.e. absence of both positive and negative emotions. For example, patients may report: *"All my emotions, both 'pleasant' and 'unpleasant', are toned down,"* or *"I don't fully enjoy things that should give me pleasure, such as beautiful places or things or music,"* or *"Unpleasant emotions, such as sadness, disappointment, and upset, feel toned down or different in some way."* With regard to the impact of emotional blunting, patients may report that *"Day to day life just doesn't have the same emotional impact on me that it did before my illness/problem"*.

The development of the ODQ from qualitative interviewing (Price et al., 2009) meets the recognized need to supplement investigator-assessed outcomes for measuring recovery from mental health conditions in a way that is meaningful to patients. A scale derived from lived experience, such as the ODQ, may be more meaningful to patients and facilitate the general move toward increased patient involvement in treatment decisions (Andresen et al., 2010; Guo et al., 2015; IsHak et al., 2014; Oliveira-Maia et al., 2016; Slade and Longden, 2015). Given the increased recognition that full functional recovery from MDD should be the ultimate treatment goal to prevent relapse, and the central role of emotional blunting in preventing relapse, it is important to have valid and easy-to-use scales for assessing the prevalence of these specific symptoms.

The main limitation of this analysis is the short study duration, and further evaluation of the utility of the ODQ in longer-term studies may be of interest.

In summary, the ODQ measures emotional blunting and captures aspects of the patient experience of symptoms of MDD that are not well measured by other symptom scales, such as the MADRS, or functional

scales, such as the SDS, as reflected by the weak correlation between the ODQ and these scales at baseline; the ODQ would appear to share more of the properties of the MEI. We suggest that MCIDs of 16 points for the ODQ-20 and 20 points for the ODQ-26 are appropriate. The ODQ may have particular value in estimating the completeness of recovery and remission in patients being treated for MDD.

Contributors

H. Loft performed the statistical analysis. All authors – M.C. Christensen, A. Fagiolini, I. Florea, H. Loft, A. Cuomo, and G.M. Goodwin – materially participated in the research, and contributed to the interpretation of the results of the analyses and the preparation of this article and approved the final article.

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Declaration of Competing Interest

A. Fagiolini was the principal investigator for the COMPLETE study, and has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Aspen, Boehringer Ingelheim, Daiichi Sankyo Brasil Farmacêutica, DOC Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, and Vifor Pharma. M.C. Christensen, I. Florea, and H. Loft are employees of H. Lundbeck A/S. A. Cuomo has been a consultant and/or a speaker for Angelini, Pfizer, Otsuka, GSK, Lundbeck, Janssen, and Recordati. G.M. Goodwin is a National Institute for Health Research (NIHR) Emeritus Senior Investigator, holds shares in P1vital and P1vital products, and has served as consultant, advisor, or CME speaker in the last 3 years for Beckley Psytech, Clerkenwell Health, COMPASS Pathways, EVA pharma, Janssen, Lundbeck, Medscape, Novartis, P1vital, Sage, and Servier. The views expressed are those of the author(s) and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health.

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Supplementary materials

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