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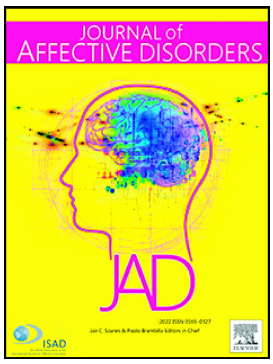

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Vortioxetine in patients with major depressive disorder and high levels of anxiety symptoms: an updated analysis of efficacy and tolerability

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ABSTRACT

Background: Patients with major depressive disorder (MDD) often experience comorbid anxiety symptoms. Vortioxetine has demonstrated efficacy in treating anxiety symptoms in patients with MDD; however, efficacy and tolerability have not been assessed across the entire approved dosage range.

Methods: The efficacy and tolerability of vortioxetine 5–20 mg/day were assessed in patients with MDD and high levels of anxiety symptoms (Hamilton Anxiety Rating Scale [HAM-A] total score ≥20) using pooled data from four randomized, fixed-dose, placebo-controlled studies (n=842). Data from a randomized, double-blind study of vortioxetine 10–20 mg/day versus agomelatine 25–50 mg/day in patients with an inadequate response to prior therapy (n=299) were analyzed separately. Mean changes from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS), HAM-A, and Sheehan Disability Scale (SDS) total scores were analyzed by vortioxetine dosage.

Results: The pooled analysis of fixed-dose studies demonstrated a clear dose–response relationship for vortioxetine 5–20 mg/day for improvements in MADRS, HAM-A, and SDS total scores. Vortioxetine 20 mg/day demonstrated significant effects versus placebo from week 4 onwards. In the post hoc analysis of the active-controlled study in patients with inadequate response to prior therapy, vortioxetine 10–20 mg/day was superior to agomelatine across all outcome measures from week 4 onwards. Up-titration of vortioxetine

to 20 mg/day was not associated with an increase in adverse events.

Limitations: Short-term trials.

Conclusions: Vortioxetine is efficacious and well tolerated in patients with MDD and high levels of anxiety symptoms, including those with an inadequate response to prior therapy. The greatest therapeutic benefits were observed with vortioxetine 20 mg/day.

Trial registration: NCT01140906, NCT01153009, NCT01163266, NCT01255787, NCT01488071.

Keywords: Major depressive disorder (MDD); generalized anxiety disorder (GAD); vortioxetine; depression; anxiety; dose response.

Abbreviations: CI, confidence interval; DFFS, Depression and Family Functioning Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; EQ-5D, EuroQol Five Dimensions; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; ICD, International Classification of Diseases; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; SDS, Sheehan Disability Scale; SE, standard error; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, serotonin reuptake inhibitor.

1. Introduction

Many patients with major depressive disorder (MDD) experience clinically significant anxiety symptoms (Fava et al., 2004; Gaspersz, 2018; Hasin et al., 2018; Kessler et al.; 2015); however, anxiety symptoms are not considered a core symptom of MDD according to Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria and patients with MDD may have anxiety symptoms without meeting the diagnostic criteria for any particular anxiety disorder. In recognition of the clinical relevance of anxiety symptoms in patients with MDD, DSM-5 included an 'anxious distress' specifier for such patients (American Psychiatric Association, 2013) and ICD-11 includes 'mixed depressive and anxiety disorder' (World Health Organization, 2019). Achieving response and remission appears to be more difficult in patients with MDD and concurrent anxiety symptoms than in those with either condition alone, and comorbidity is associated with greater symptom severity, increased functional impairment, reduced health-related quality of life, and poorer treatment outcomes, including a longer time to remission (Armbrecht et al., 2021; Buckman et al., 2018; Fava et al., 2008; Gaspersz et al., 2018; Penninx et al., 2011; Zhou et al., 2017).

Although MDD and specific anxiety disorders, such as generalized anxiety disorder (GAD), are frequently comorbid (Brown et al., 2001; McGrath et al., 2020; Saha et al., 2021; Simon, 2009; Zhou et al., 2017), randomized clinical trials in patients with MDD generally exclude

those with other mental health disorders, including anxiety disorders, and vice versa. This is largely driven by regulatory guidelines, which typically preclude assessment of efficacy for the treatment of two major psychiatric disorders in the same study. Evidence of antidepressant efficacy in patients with both MDD and anxiety is therefore often derived from post-hoc analyses in subgroups of patients considered to have high levels of anxiety symptoms based on relevant assessment scale scores (Bandelow et al., 2007; Fava et al., 2000; Nelson, 2010).

Vortioxetine is a multimodal antidepressant that has been shown to be efficacious and well tolerated in the treatment of depressive, cognitive, anxiety, and physical symptoms in patients with MDD (Baldwin et al., 2016a; Christensen et al., 2018; Gonda et al., 2019). In placebo-controlled studies, a dose–response relationship for vortioxetine in improving both depressive and anxiety symptoms has been demonstrated across the approved dosage range of 5–20 mg/day (Baldwin et al., 2016a; Christensen et al., 2021; Iovieno et al., 2021; Thase et al., 2016). An active-controlled, flexible-dose study has also demonstrated the anxiolytic effects of vortioxetine 10–20 mg/day versus agomelatine 25–50 mg/day in patients with MDD who had experienced an inadequate response to first-line treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin–noradrenaline reuptake inhibitor (SNRI) (Montgomery et al., 2014). In a recent open-label study, clinically meaningful and statistically significant improvements in symptoms of both depression and anxiety were seen in patients with MDD comorbid with GAD who were treated with vortioxetine 20 mg/day, together with broad improvements in overall functioning and health-related quality of life (Christensen et al., 2022).

A meta-analysis of short-term clinical trial data conducted in 2015 suggested that vortioxetine may be effective for the treatment of GAD—particularly severe GAD, defined as a baseline Hamilton Anxiety Rating Scale (HAM-A) score of ≥25 points (Pae et al., 2015). However, individual randomized controlled trials of vortioxetine in patients with GAD have yielded mixed results (Baldwin et al., 2012; Bidzan et al., 2012; Mahableshwarkar et al., 2014a, 2014b; Rothschild et al., 2012). Of note, vortioxetine has not yet been evaluated in randomized controlled trials in patients with a primary diagnosis of GAD alone at dosages greater than 10 mg/day. An updated analysis of the efficacy and safety of vortioxetine across the entire approved dosage range in patients with MDD and high levels of anxiety symptoms is therefore warranted, both in patients initiating treatment with vortioxetine and in those switching to vortioxetine because of inadequate response to another antidepressant.

This paper presents the results of a pooled analysis of data for patients with MDD and high levels of anxiety symptoms from the four pivotal fixed-dose studies of vortioxetine for the treatment of MDD that included a vortioxetine dosage of 20 mg/day and assessment of anxiety symptoms using the HAM-A. Results are also presented of a separate post-hoc

analysis in patients with MDD and high levels of anxiety symptoms participating in the randomized, double-blind study comparing the efficacy and tolerability of vortioxetine 10–20 mg/day versus agomelatine 25–50 mg/day following an inadequate response to first-line SSRI/SNRI monotherapy (Montgomery et al., 2014).

2. Methods

2.1. Studies

A pooled analysis was undertaken using data from the four 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies conducted by Takeda/Lundbeck that evaluated vortioxetine at dosages up to and including 20 mg/day in patients with MDD and included assessment of symptoms of depression and anxiety using the Montgomery-Åsberg Depression Rating Scale (MADRS) and HAM-A, respectively (NCT01140906, NCT01153009, NCT01163266, and NCT01255787) (Boulenger et al., 2014; Jacobsen et al., 2015; Mahableshwarkar et al., 2015; Nishimura et al., 2018). Key study inclusion criteria are summarized in **Table S1**. In all studies, patients had a primary diagnosis of MDD according to the DSM criteria at the time the study was undertaken and were experiencing a current major depressive episode (confirmed using the Mini International Neuropsychiatric Interview). Patients with any current DSM-defined psychiatric disorder other than MDD (including anxiety disorders) were excluded. Patients randomized to vortioxetine 5 or 10 mg/day initiated treatment at this dosage and remained on that dosage for the entire study period. Patients randomized to vortioxetine 15 or 20 mg/day received vortioxetine 10 mg/day for the first week of treatment, before up-titration to their randomized dosage for the remaining 7 weeks.

A separate post-hoc analysis was undertaken using data from a 12-week, randomized, double-blind, active-controlled study of flexible-dose vortioxetine (10–20 mg/day) versus agomelatine (25–50 mg/day) in patients with MDD who had an inadequate response to monotherapy with an SSRI or SNRI at an approved dosage for at least 6 weeks (NCT01488071) (Montgomery et al., 2014). Eligibility criteria are summarized in **Table S1**. Patients received vortioxetine 10 mg/day for the first week of treatment or agomelatine 25 mg/day for the first 2 weeks, after which the dosage was individually adjusted within the approved range based on the investigators' clinical judgment; after week 4, dosages were fixed.

All studies were approved by the relevant research ethics committees and conducted in accordance with Declaration of Helsinki and Good Clinical Practice guidelines. Patients provided written informed consent for participation.

2.2. Outcome assessments

Patients were assessed at baseline and at regular study visits. In all studies, depressive symptoms were assessed using the MADRS (Montgomery and Åsberg, 1979), anxiety

symptoms using the HAM-A (Hamilton, 1959), and psychosocial functioning using the Sheehan Disability Scale (SDS) (Sheehan et al., 1996; Sheehan and Sheehan, 2008), and treatment-emergent adverse events (TEAEs) were recorded. In the flexible-dose active-controlled study, functioning was also assessed using the Depression and Family Functioning Scale (DFFS) (DiBenedetti et al., 2012; Williams et al., 2016) and health-related quality of life was assessed using the EuroQol Five Dimensions (EQ-5D) questionnaire (EuroQoL Research Foundation, 2019).

The DFFS is a validated scale for assessment of the impact of depression on partner and family interactions and quality of relationships over the past 4 weeks (DiBenedetti et al., 2012; Williams et al., 2016). The patient version of the DFFS comprises 15 questions (**Table S2**). Responses are rated on a scale from 0 (none of the time) to 4 (all of the time), except for items 4, 8, and 12, which are reverse scored. The combined scores for items 1–11 form the DFFS partner and family interaction subscore and the combined scores for items 12–15 form the DFFS quality of relationship subscore. Total DFFS score ranges from 0 to 60; lower scores indicate better relationships and family functioning.

2.3. Data analysis

Only patients with a high level of anxiety symptoms, defined as baseline HAM-A total score of ≥20, were included in these analyses. Data for the pooled analysis of fixed-dose studies and the post hoc analysis of the flexible-dose active-controlled study were analyzed separately. For both analyses, the full analysis set included all randomized patients who received at least one dose of study medication and had at least one valid post-baseline efficacy assessment. For all efficacy outcomes, mean changes from baseline over time were analyzed by treatment arm using an individual patient data meta-analytical approach. A mixed model for repeated measures was used with terms including baseline values, study, visit, and treatment for the mean structure and using an unstructured covariance matrix.

The proportion of patients achieving MADRS and HAM-A response and remission was assessed using a logistic regression model with the relevant baseline score as a covariate (last observation carried forward in order to capture early response or remission in patients who did not complete the study). Response was defined as ≥50% decrease in MADRS or HAM-A total score from baseline, and remission as MADRS or HAM-A total score ≤10.

For both analyses, safety and tolerability data were assessed in all eligible patients who received at least one dose of study medication (all treated patients set). TEAEs occurring in ≥5% of patients in any study group were summarized using Medical Dictionary for Regulatory Affairs (version 14.1) preferred terms. For the pooled analysis of the fixed-dose studies, TEAEs are reported according to the randomized vortioxetine dosage based on time of onset: (i) over the entire 8-week treatment period; (ii) between day 1 and day 7 (i.e. when patients randomized to vortioxetine 15 or 20 mg/day were receiving the starting dose of

vortioxetine 10 mg/day); and (iii) from day 8 to day 56 (i.e. following dose up-titration to the randomized vortioxetine dosage of 15 or 20 mg/day until the end of the 8-week treatment period). For the flexible-dose active-controlled study, TEAEs were recorded according to treatment group over the entire 12-week treatment period. Information on treatment dosage was also recorded at all visits in the flexible-dose active-controlled study, and the final vortioxetine dosage is reported.

Analyses were performed using SAS statistical software (version 9.4); $p<0.05$ was considered statistically significant.

3. Results

3.1. Patients

The four fixed-dose studies included 1975 patients, 842 of whom (42.6%) had a HAM-A total score of ≥20 at baseline and were included in the safety analysis (261 in the placebo group and 60, 125, 140, and 256 in the vortioxetine 5, 10, 15, and 20 mg/day groups, respectively). In total, 830 patients were included in the full analysis set. Treatment groups were well matched in terms of sex, age, MADRS total score, HAM-A total score, and SDS total score at baseline (**Table 1**). Mean baseline MADRS total score was approximately 33 points and mean baseline HAM-A total score was approximately 25 points.

In the flexible-dose active-controlled study, 252 patients were treated with vortioxetine 10–20 mg/day and 241 with agomelatine 25–50 mg/day. In all, 157 (62.3%) patients in the vortioxetine group and 142 (58.9%) patients in the agomelatine group had a baseline HAM-A total score of ≥20. There were no differences in baseline demographic and clinical characteristics between the vortioxetine and agomelatine groups for the full analysis set (**Table 1**). At baseline, the mean MADRS total score was approximately 29 points and the mean HAM-A total score was approximately 25 points in each group.

3.2. Efficacy: fixed-dose studies

In the pooled analysis of fixed-dose studies in patients with MDD and high levels of anxiety at baseline, a dose–response relationship for vortioxetine was seen for change from baseline in MADRS, HAM-A, and SDS total scores at all time points assessed (**Fig. 1**). Statistically significant differences in mean change in MADRS total score from baseline versus placebo were seen from week 4 onwards in patients treated with vortioxetine 15 or 20 mg/day, and from week 6 in those who received vortioxetine 10 mg/day (**Fig. 1A**). The mean (95% confidence interval [CI]) difference in change from baseline versus placebo for MADRS total score at week 8 was −2.6 (−4.9, −0.4) for vortioxetine 10 mg ($p=0.0234$), and −4.4 (−6.2, −2.6) for vortioxetine 20 mg ($p<0.0001$) (**Table 2**). At week 8, the proportion of patients achieving a MADRS response was 32.8% in the placebo group, 41.1% in the vortioxetine 10 mg/day group, and 46.8% in the vortioxetine 20 mg/day group (**Table S3**). Respective rates of MADRS remission were 18.4%, 23.4%, and 27.0%. Differences for

vortioxetine 20 mg/day versus placebo were statistically significant (p=0.0013 for response and p=0.0195 for remission).

Statistically significant differences in mean change in HAM-A total score from baseline versus placebo were seen from week 4 onwards for vortioxetine 20 mg/day and at weeks 4 and 6 for vortioxetine 15 mg/day (**Fig. 1B**). At week 8, the mean (95% CI) difference in change from baseline in HAM-A total score versus placebo was significant only for the vortioxetine 20 mg/day group (−2.3 [−3.7, −1.0]; p=0.0007) (**Table 2**). Statistically significant differences in mean change in HAM-A psychic anxiety score from baseline versus placebo were seen from week 4 onwards for vortioxetine 15 and 20 mg/day (**Fig. S1A**). For HAM-A somatic score, a statistically significant difference in mean change from baseline versus placebo was seen at week 6 only in the vortioxetine 20 mg/day group (**Fig. S1B**). The proportion of patients who achieved a HAM-A response after 8 weeks of treatment was 37.4% in the placebo group, 39.5% in the vortioxetine 10 mg/day group, and 46.4% (p=0.0428 vs placebo) in the vortioxetine 20 mg/day group (**Table S3**). Respective rates of HAM-A remission were 29.5%, 34.7%, and 39.1% (p=0.0206 for vortioxetine 20 mg/day vs placebo).

The mean change from baseline in SDS total score was statistically significant versus placebo at week 6 for vortioxetine 10 and 15 mg/day, and at weeks 6 and 8 for vortioxetine 20 mg/day (**Fig. 1C**). The mean (95% CI) difference in change from baseline in SDS total score at week 8 versus placebo was significant only for the vortioxetine 20 mg/day group (−2.1 [−3.7, −0.4]; p=0.0158) (**Table 2**).

3.3. Efficacy: flexible-dose active-controlled study

In the flexible-dose study in patients with high levels of anxiety at baseline, significantly greater improvements were seen at weeks 8 and 12 in patients treated with vortioxetine 10–20 mg/day than in those who received agomelatine 25–50 mg/day across all outcome measures (**Fig. 2**). The mean (95% CI) difference in change in MADRS total score from baseline between the two groups at week 8 was −2.4 (−4.2, −0.7) points (p=0.0074), and the difference between the two groups was further increased at week 12 (−2.8 [−4.7, −0.9] points; p=0.0043). At week 12, the proportion of patients who had achieved a MADRS response was 70.5% in the vortioxetine group versus 55.3% in the agomelatine group (p=0.0058). The respective proportions of patients achieving MADRS remission were 53.2% and 38.3% (p=0.0051).

At week 8, the mean (95% CI) difference in change in HAM-A total score from baseline between the two groups was −2.4 (−3.9, −0.8) points (p=0.0032), and this difference was maintained at week 12 (−2.4 [−4.0, −0.8] points; p=0.0036). Mean changes from baseline in HAM-A psychic anxiety and somatic scores were significantly greater in the vortioxetine group than in the agomelatine group at weeks 8 and 12 (at both time points, p<0.01 for

psychic anxiety scores and p<0.05 for somatic scores) (**Fig. S2**). The proportion of patients who achieved a HAM-A response after 12 weeks of treatment was 68.6% in the vortioxetine group versus 54.7% in the agomelatine group (p=0.0147). Respective rates of HAM-A remission were 58.8% and 44.6% (p=0.0141).

Mean changes from baseline in SDS total score (**Fig. 2C**) and all SDS domain scores (**Fig. S3**) at weeks 4, 8, and 12 were statistically significantly greater in the vortioxetine group than in the agomelatine group (all differences, p≤0.0056). The mean (95% CI) difference in change in SDS total score from baseline between the two groups was −3.2 (−5.0, −1.5) points at week 8 (p=0.0004) and −3.0 (−4.8, −1.2) points at week 12 (p=0.0014). DFFS scores also improved in both groups, with vortioxetine showing statistical superiority over agomelatine at weeks 8 and 12 (**Fig. 2D**). The mean (95% CI) difference in change in DFFS total score from baseline between the two groups at week 8 was −3.6 (−6.1, −1.1) points (p=0.0050), and this difference was sustained at week 12 (−3.5 [−6.2, −0.9] points; p=0.0083). Mean change from baseline in the DFFS partner and family interaction subscore was also statistically significantly greater in the vortioxetine group than in the agomelatine group at weeks 8 and 12 (p=0.0012 and p=0.0083, respectively). Mean changes in individual DFFS item scores from baseline to weeks 8 and 12 are shown in **Fig. 3**. Statistically significant differences for vortioxetine versus agomelatine were seen for items 1, 2, 3, 7, 10, 11, and 15 at week 8, and for items 1, 2, 3, 8, 10, 14, and 15 at week 12.

Improvement in health-related quality of life was seen in both groups; however, mean change in the EQ-5D summary index score from baseline at weeks 4, 8, and 12 was significantly greater in the vortioxetine group than in the agomelatine group (all differences, p<0.05). The mean (95% CI) difference in change in EQ-5D score from baseline between the two groups was 0.05 (0.00, 0.10) points at week 8 (p=0.0372) and 0.07 (0.01, 0.12) points at week 12 (p=0.0135).

3.4. Safety and tolerability: fixed-dose studies

In the pooled analysis of fixed-dose studies, the proportion of patients reporting at least one TEAE during the 8-week, double-blind treatment period was 62.5% in the placebo group, 68.0% in the vortioxetine 10 mg/day group, and 71.1% in the vortioxetine 20 mg/day group (**Table 3**). Irrespective of dose, nausea and headache were the most commonly reported TEAEs in vortioxetine-treated patients. The proportion of patients who withdrew from treatment due to TEAEs was 2.3% in the placebo group, 5.6% in the vortioxetine 10 mg/day group, and 8.6% in the vortioxetine 20 mg/day group. The incidence of serious adverse events (SAEs) was low (≤1.7% across treatment groups), and no individual SAE was reported by more than a single patient in any group.

During the first week of treatment (i.e., before vortioxetine dose up-titration in the 15 and 20 mg/day groups), the proportion of patients reporting at least one TEAE was 33.7% in the

placebo group, 49.6% in the vortioxetine 10 mg/day group, and 49.2% in the vortioxetine 20 mg/day group (**Table 3**). The most common TEAEs during the first week of treatment were nausea and headache in all groups. From day 8 onwards (i.e. following vortioxetine dose up-titration), the proportion of patients reporting at least one TEAE was 46.7% in the placebo group, 59.2% in the vortioxetine 10 mg/day group, and 52.0% in the vortioxetine 20 mg/day group (**Table 3**). Nausea, headache, and nasopharyngitis were the most common TEAEs from day 8 onwards. The incidence of nausea between days 8 and 56 was 3.1% in the placebo group, 9.6% in the vortioxetine 10 mg/day group, and 9.8% in the vortioxetine 20 mg/day group.

3.5. Safety and tolerability: flexible-dose active-controlled study

In the flexible-dose active-controlled study, the proportion of patients reporting at least one TEAE over the 12-week treatment period was 56.7% in the vortioxetine 10–20 mg/day group and 52.1% in the agomelatine group (**Table S4**). Nausea, headache, and dizziness were the most frequently reported TEAEs in both groups. The proportion of patients who withdrew from treatment due to TEAEs was 6.4% in the vortioxetine group and 8.5% in the agomelatine group. The only TEAEs leading to treatment withdrawal in more than a single patient in either group were vomiting (two patients in the vortioxetine group) and dizziness (two patients in the agomelatine group). SAEs were reported by one patient in the vortioxetine group and three patients in the agomelatine group; no individual SAE was reported by more than a single patient in either group.

3.6. Vortioxetine dosing: flexible-dose active-controlled study

Of the 156 patients with HAM-A total score ≥20 receiving vortioxetine in the flexible-dose active-controlled study (full analysis set), 99 (66.5%) received vortioxetine 20 mg/day and 57 (36.5%) received vortioxetine 10 mg/day as their final dose.

4. Discussion

Patients with MDD experiencing high levels of anxiety symptoms are difficult to treat, and typically achieve poorer treatment outcomes than those with MDD alone (Armbrecht et al., 2021; Buckman et al., 2018; Fava et al., 2008; Pennix et al., 2011; Zhou et al., 2017). However, data are lacking concerning the efficacy and tolerability of antidepressants in this population. Assessment of treatment effectiveness in patients with MDD and anxiety is clinically relevant, given the high rate of comorbidity of these two conditions (Montgomery, 2019; Saha et al., 2021).

Results of the pooled analysis of the pivotal fixed-dose studies demonstrate a clear dose–response relationship for vortioxetine in patients with MDD and high levels of anxiety symptoms (i.e., baseline HAM-A total score ≥20 points). The greatest effects were observed at a vortioxetine dosage of 20 mg/day in terms of reduction in symptoms of depression and anxiety, rates of symptomatic response and remission, and improvement in overall

functioning. For anxiety symptoms, dose-dependent improvements were seen in both HAM-A psychic anxiety and HAM-A somatic scores. Our findings are in keeping with the results of previous analyses showing vortioxetine to have broad dose-dependent efficacy across the spectrum of symptoms experienced by patients with MDD, including depressive, anxiety, cognitive, and physical symptoms, and functional impairment (Baldwin et al., 2016a; Christensen et al., 2018, 2021; Florea et al., 2017; Iovieno et al., 2021; McIntyre et al., 2021; Thase et al., 2016). In the present analysis, the observed dose–response relationship for vortioxetine appeared most pronounced for symptoms of anxiety, as assessed by mean change in HAM-A total score. While statistically significant improvements in symptoms of depression, as assessed by mean change in MADRS total score, were seen for vortioxetine 10 mg/day at weeks 6 and 8, no significant differences were seen in terms of mean change in HAM-A total score from baseline at any time point in the vortioxetine 10 mg/day group. In contrast, statistically significant improvement in anxiety symptoms was seen in the vortioxetine 20 mg/day group versus placebo from week 4 onwards.

In the post-hoc analysis of the flexible-dose, active controlled study in patients with MDD and high levels of anxiety symptoms who had experienced an inadequate response to monotherapy with either an SSRI or SNRI (Montgomery et al., 2014), vortioxetine 10–20 mg/day was found to be superior to agomelatine 25–50 mg/day across all outcome measures from week 4 onwards. The difference in mean change from baseline in MADRS total score between the two treatment groups at week 12 was 2.8 points; a reduction in MADRS total score of ≥2 points versus placebo and a difference of ≥1 point between active treatments is considered to be clinically significant (Duru and Fantino, 2008; Montgomery and Möller, 2009). Vortioxetine-treated patients were also significantly more likely to achieve response and remission from symptoms of depression and anxiety than those who received agomelatine.

Statistically superior improvements in overall and family functioning, as assessed by the SDS and DFFS, respectively, were also seen for vortioxetine versus agomelatine, with the difference in total scores between the two groups at weeks 8 and 12 approaching the threshold for clinical relevance of 4 points on both scales (Sheehan and Sheehan 2008; Williams et al. 2016). The beneficial effects of vortioxetine on functioning were evident across all SDS domains and most DFFS items, in line with the results of a previous analysis undertaken for the overall patient population in this study (François et al., 2017). The improvements in family functioning assessed using the DFFS are particularly noteworthy, as this scale provides data on outcomes that are not routinely assessed in clinical studies in patients with MDD and/or anxiety. Vortioxetine was also statistically superior to agomelatine in terms of improvements in health-related quality of life, as assessed using the EQ-5D.

The observed dose-dependent beneficial effects of vortioxetine on both depressive and

anxiety symptoms are most likely related to its multimodal mechanism of action (Sanchez et al., 2015). Indeed, it has been suggested that inhibition of the serotonin (5-HT) transporter (SERT) alone is insufficient for clinical response against anxiety symptoms (Hjorth et al., 2021). As well as acting as a SERT inhibitor, vortioxetine also modulates the activity of several 5-HT receptor subtypes (Sanchez et al., 2015). The effects of vortioxetine on 5-HT_{1A}, 5-HT_3, and 5-HT_7 receptors, in particular, are considered responsible for its anxiolytic activity. Interestingly, the affinity of vortioxetine varies between serotonin receptor types, with 5-HT_{1A}, 5-HT_3, and 5-HT_7 receptors occupied at higher dosages than other 5-HT receptors (Bang-Andersen et al., 2011). It is also noteworthy that SERT occupancy ranges from approximately 50% to >80% over the approved vortioxetine dosage range of 5–20 mg/day (Areberg et al., 2012).

The significantly greater improvements seen for some individual items on the DFFS with vortioxetine versus agomelatine are likely related to improvements in symptoms such as anhedonia, low motivation, and anergia. For example, improvements in social functioning relating to spending and/or enjoying time with others may be linked to reduced anhedonia, while improvements in the item relating to household chores may be due to increased energy and motivation. Due to its multimodal mechanism of action, vortioxetine directly or indirectly modulates the activity of several neurotransmitter systems, including the serotoninergic, dopaminergic, and noradrenergic systems (Sanchez et al., 2015). Disturbances of dopaminergic systems have been implicated in the neurobiology of anhedonia, as well as in motivation and reward processing (Dunlop and Nemeroff, 2007), while noradrenergic system disturbances have been implicated in the regulation of motivation and energy in depression (Moret and Briley, 2011). The observed improvements in family functioning items in vortioxetine-treated patients in this analysis could therefore be hypothesized to reflect improvements in anhedonia, motivation, and energy arising from modulation of these neurotransmitter systems.

The observed improvements in symptoms of depression and anxiety in both the pooled analysis of fixed-dose studies in patients with MDD and high levels of baseline anxiety symptoms and in the post-hoc analysis of the flexible-dose active-controlled study in patients with MDD and high levels of anxiety symptoms switching to vortioxetine due to an inadequate response to prior therapy are consistent with those seen in the recent open-label, 8-week RECONNECT study in patients with MDD and comorbid GAD receiving vortioxetine as a first-line treatment for their current major depressive episode or switching to vortioxetine due to an inadequate response to another antidepressant (Christensen et al., 2022). In RECONNECT, the vortioxetine starting dosage was 10 mg/day, with forced up-titration to 20 mg/day after 1 week.

The tolerability profile of vortioxetine is well established and has been well described in

previous analyses (e.g., Baldwin et al., 2016b). Safety is also continuously monitored in patients receiving vortioxetine through post-approval pharmacovigilance, with estimates from the end of 2021 indicating that more than 1 million patients are treated with vortioxetine on a daily basis (IQVIA, data on file). In the pooled analysis of fixed-dose studies, vortioxetine was found to be well tolerated across the approved dosage range, with no increase in the incidence of TEAEs seen in patients in whom the vortioxetine dosage was increased from 10 to 20 mg/day after the first week of treatment. Nausea, headache, and nasopharyngitis were the most common TEAEs reported from the time of vortioxetine dose up-titration, the incidences of which were low and similar between vortioxetine dosage groups. The proportion of patients who discontinued treatment due to TEAEs was low across all dosage groups, and no unexpected safety concerns were identified. In the post-hoc analysis of the flexible-dose active-controlled study, the incidence of TEAEs was low and broadly similar in both treatment groups; however, fewer vortioxetine-treated patients than agomelatine-treated patients withdrew due to TEAEs.

Our findings confirm that vortioxetine dosage can be increased without compromising tolerability in patients with MDD and high levels of anxiety. In the flexible-dose active-controlled study (Montgomery et al., 2014), two-thirds (66.5%) of patients were receiving vortioxetine 20 mg/day as their final dosage. This is consistent with the results of a recent pooled analysis of data from flexible-dose studies of vortioxetine in patients with MDD, which found that 64.3% of patients were receiving vortioxetine 20 mg/day at study end or treatment discontinuation (Christensen et al., 2021). These findings suggest that when clinicians have the opportunity to increase vortioxetine dosage to 20 mg/day based on assessment of efficacy and tolerability, this occurs in most patients. The optimal dosage of an antidepressant should balance efficacy, tolerability, and acceptability. Our findings indicate that, in patients with MDD and high levels of anxiety symptoms who tolerate the starting dose of vortioxetine 10 mg/day, vortioxetine 20 mg/day should be considered the optimal target dosage.

A potential limitation of this research is the relatively short duration of follow-up (i.e., 8–12 weeks) in the included studies, as MDD and anxiety are conditions that generally require long-term treatment. It is also important to note that patients were not categorized according to their level of anxiety symptoms at baseline before randomization in any of the included studies. For the pooled analysis of fixed-dose studies, results for the vortioxetine 5 mg/day group should be interpreted with caution as this dosage was used in only one study (NCT01255787 [Nishimura et al., 2018]), and data for all outcomes are not available for this dosage at all time points. However, using the individual patient data meta-analytical approach, data for this small group of patients were compared with pooled data for the placebo group across all four studies included in this analysis, providing an adequate sample

size and basis for comparison.

In summary, our findings confirm the efficacy and tolerability of vortioxetine for treating symptoms of depression and anxiety in patients with MDD and high levels of anxiety, including those who had experienced an inadequate response to first-line treatment with an SSRI or SNRI. Our findings also confirm a clear dose–response relationship for efficacy across the approved vortioxetine dosage range of 5–20 mg/day in this patient population. In the pivotal fixed-dose studies, the greatest therapeutic benefits were observed for all outcomes at a vortioxetine dosage of 20 mg/day. In patients with an inadequate response to first-line treatment, vortioxetine was also associated with improvements in both overall and family functioning, as well as health-related quality of life. Treatment with vortioxetine was well tolerated, and up-titration of vortioxetine dosage from 10 to 20 mg/day after 1 week of treatment was not associated with an increase in TEAEs.

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Figure legends

Figure 1. Mean change from baseline in (**A**) MADRS total score, (**B**) HAM-A total score, and (**C**) SDS total score at weeks 2, 4, 6, and 8 in patients with major depressive disorder and high levels of anxiety treated with vortioxetine 5–20 mg/day (full analysis set; MMRM analysis of four fixed-dose, placebo-controlled studies). Note: data are not available for HAM-A total score and SDS total score for the vortioxetine 5 mg/day group at all time points.
HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; SDS, Sheehan Disability Scale; VOR, vortioxetine
*p<0.05, **p<0.01, ***p<0.001 versus placebo

Figure 2. Mean change from baseline in (**A**) MADRS total score, (**B**) HAM-A total score, (**C**) SDS total score, and (**D**) DFFS total score up to week 12 in patients with major depressive disorder and high levels of anxiety treated with vortioxetine 10–20 mg/day or agomelatine 25–50 mg/day (full analysis set; MMRM analysis of flexible-dose, active comparator study)
DFFS, Depression and Family Functioning Scale; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; SDS, Sheehan Disability Scale
*p<0.05, **p<0.01, ***p<0.001 versus agomelatine

Figure 3. Mean change from baseline in DFFS item scores in patients with major depressive disorder and high levels of anxiety treated with vortioxetine 10–20 mg/day or agomelatine 25–50 mg/day at (**A**) week 8 and (**B**) week 12 (full analysis set; MMRM analysis of flexible-dose, active-controlled study)
DFFS, Depression and Family Functioning Scale; MMRM, mixed model for repeated measures

*p<0.05, **p<0.01 versus agomelatine

Table 1. Summary of demographics and baseline characteristics for patients with major depressive disorder and high levels of anxiety symptoms (HAM-A total score ≥20) included in the pooled analysis of fixed-dose studies and the post-hoc analysis of the flexible-dose, active comparator study (full analysis set)

Treatment group	Patients, n	Female, %	Age, years	MADRS total score	HAM-A total score	SDS total score
Fixed-dose studies (pooled)						
Placebo	256	71.5	45.3±11.9	33.0±3.9	24.4±4.3	20.5±5.6
Vortioxetine 5 mg/day	60	73.3	45.2±12.1	32.2±3.9	25.2±4.1	18.5±6.1
Vortioxetine 10 mg/day	124	74.2	44.3±11.5	33.4±4.7	24.4±3.9	19.9±6.0
Vortioxetine 15 mg/day	138	73.2	44.2±13.8	33.0±3.9	24.9±4.5	21.8±5.2
Vortioxetine 20 mg/day	252	73.4	45.4±12.8	33.1±4.0	24.6±4.3	20.5±5.0
Flexible-dose study (REVIVE)						
Vortioxetine 10–20 mg/day	156	77.6	47.0±11.9	29.9±4.5	25.3±4.5	19.1±5.4
Agomelatine 25–50 mg/day	141	73.0	45.6±11.7	29.4±4.1	25.4±4.5	20.1±5.3

Abbreviations: HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale.

All values are mean ± standard deviation unless otherwise indicated

Table 2. Meta-analysis of difference in change from baseline to week 8 in MADRS total score, HAM-A total, psychic anxiety, and somatic scores, and SDS total score versus placebo in patients with high levels of anxiety symptoms at baseline in the fixed-dose vortioxetine studies (full analysis set, MMRM)

Outcome	Treatment and dosage	N[a]	Mean (SE) change from	Difference vs PBO	SE	95% CI	p value[b]

	(mg/day)		baseline					
MADRS total score	PBO	256	−12.5	(0.65)	–	–	–	–
	VOR 5 mg	60	−14.4	(1.36)	−1.8	1.51	−4.8, 1.1	0.224 0
	VOR 10 mg	124	−15.2	(0.85)	−2.6	1.16	−4.9, −0.4	**0.023 4**
	VOR 15 mg	138	−16.1	(0.92)	−3.6	1.12	−5.8, −1.4	**0.001 5**
	VOR 20 mg	252	−16.9	(0.67)	−4.4	0.93	−6.2, −2.6	**<0.00 01**
HAM-A total score	PBO	254	−9.7	(0.48)	–	–	–	–
	VOR 5 mg	60	−9.9	(1.06)	−0.2	1.16	−2.5, 2.1	0.864 7
	VOR 10 mg	124	−10.5	(0.72)	−0.8	1.21	−2.5, 0.9	0.365 6
	VOR 15 mg	138	−11.2	(0.69)	−1.5	0.84	−3.1, 0.2	0.082 2
	VOR 20 mg	248	−12.0	(0.49)	−2.3	0.69	−3.7, −1.0	**0.000 7**
HAM-A psychic anxiety score	PBO	254	−5.7	(0.30)	–	–	–	–
	VOR 5 mg	60	−6.0	(0.66)	−0.3	0.72	−1.8, 1.1	0. 6382
	VOR 10 mg	124	−6.5	(0.45)	−0.9	0.54	−1.9, 0.2	0.115 1
	VOR 15 mg	248	−7.5	(0.31)	−1.8	0.43	−2.6, −0.5	**0.003 0**
	VOR 20 mg						−2.7, −1.0	**<0.00 01**
HAM-A somatic anxiety score	PBO	254	−4.1	(0.22)	–	–	–	–
	VOR 5 mg	60	−3.8	(0.49)	0.2	0.54	−0.8, 1.3	0.688 9
	VOR 10 mg	124	−4.0	(0.34)	0.1	0.40	−0.7, 0.9	0.861 9
	VOR 15 mg	138	−4.0	(0.33)	0.1	0.39	−0.7, 0.8	0.879 6
	VOR 20 mg	248	−4.6	(0.23)	−0.6	0.32	−1.2, 0.1	0.085 9
SDS total	PBO	168	−6.9	(0.60)	–	–	–	–

score	VOR 5 mg	39	−6.6	(1.38)	0.3	1.49	−2.6, 3.2	0.8500
	VOR 10 mg	84	−8.1	(0.92)	−1.3	1.09	−3.4, 0.9	0.2527
	VOR 15 mg	84	−8.6	(0.93)	−1.7	1.10	−3.9, 0.4	0.1181
	VOR 20 mg	163	−8.9	(0.60)	−2.1	0.85	−3.7, −0.4	**0.0158**

Abbreviations: CI confidence intervals; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; PBO, placebo; SDS, Sheehan Disability Scale; SE, standard error; VOR, vortioxetine.

[a] Number of randomized patients who received at least one dose of study medication and who had at least one post-baseline efficacy assessment (full analysis set).

[b] Bold indicates significant p values.

Table 3. TEAEs by Medical Dictionary for Regulatory Affairs (version 14.1) preferred terms with incidence ≥5% in at least one treatment group in patients with major depressive disorder and high levels of anxiety (HAM-A total score ≥20) in short-term, randomized, placebo-controlled, fixed-dose studies of vortioxetine. TEAEs are shown for the overall 8-week treatment period, with onset before day 8 (i.e., before vortioxetine dose up-titration, when all patients in the vortioxetine 15 and 20 mg/day groups received vortioxetine 10 mg/day), and from day 8 onwards (i.e. following vortioxetine dose up-titration from 10 to 20 mg/day).

Time of onset	**TEAE**	**Placebo (n=261)**	**VOR 5 mg/day (n=60)**	**VOR 10 mg/day (n=125)**	**VOR 15 mg/day (n=140)**	**VOR 20 mg/day (n=256)**
Overall	Any TEAE	163 (62.5)	38 (63.3)	85 (68.0)	97 (69.3)	182 (71.1)
	Any TEAE leading to withdrawal	6 (2.3)	0	7 (5.6)	8 (5.7)	22 (8.6)
	Any SAE	1 (0.4)	1 (1.7)	2 (1.6)	1 (0.7)	3 (1.2)
Days 1–7	Any TEAE	88 (33.7)	18 (30.0)	62 (49.6)	59 (42.1)	126 (49.2)
	Nausea	19 (7.3)	5 (8.3)	30 (24.0)	30 (21.4)	55 (21.5)
	Headache	21 (8.0)	2 (3.3)	7 (5.6)	10 (7.1)	15 (5.9)
	Dizziness	5 (1.9)	1 (1.7)	4 (3.2)	3 (2.1)	14 (5.5)
	Diarrhea	4 (1.5)	0	7 (5.6)	7 (5.0)	10 (3.9)

	Fatigue	7 (2.7)	3 (5.0)	0	1 (0.7)	4 (1.6)
Days 8–56[a]	Any TEAE	122 (46.7)	31 (51.7)	74 (59.2)	83 (59.3)	133 (52.0)
	Nausea	8 (3.1)	6 (10.0)	12 (9.6)	19 (13.6)	25 (9.8)
	Headache	20 (7.7)	4 (6.7)	10 (8.0)	18 (12.9)	19 (7.4)
	Nasopharyngitis	11 (4.2)	6 (10.0)	8 (6.4)	5 (3.6)	13 (5.1)
	Dizziness	6 (2.3)	3 (5.0)	6 (4.8)	6 (4.3)	11 (4.3)
	Dry mouth	9 (3.4)	1 (1.7)	3 (2.4)	7 (5.0)	11 (4.3)
	Constipation	5 (1.9)	3 (5.0)	5 (4.0)	5 (3.6)	9 (3.5)
	Diarrhea	9 (3.4)	3 (5.0)	11 (8.8)	6 (4.3)	3 (1.2)
	Somnolence	4 (1.5)	3 (5.0)	1 (0.8)	3 (2.1)	3 (1.2)
	Hyperhidrosis	4 (1.5)	3 (5.0)	3 (2.4)	4 (2.9)	2 (0.8)

Abbreviations: HAM-A, Hamilton Anxiety Rating Scale; SAE: serious adverse event; TEAE, treatment-emergent adverse event; VOR, vortioxetine

All values are n (%)

[a] Day 56, end of the 8-week treatment period

Author statements

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

Role of the funding source

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CONFLICT OF INTEREST STATEMENT

M. Adair, M.C. Christensen, H. Loft, and I. Florea are employees of H. Lundbeck A/S. A. Fagiolini has been a consultant and/or speaker and/or has received research grants from Allergan, Angelini, Apsen, Boehringer Ingelheim, Daiichi Sankyo Brasil Farmacêutica, DOC Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, and Vifor Pharma.

Highlights

- Patients with major depressive disorder often experience comorbid anxiety symptoms
- Vortioxetine was assessed in patients with MDD and high levels of anxiety symptoms
- Vortioxetine 20 mg/day had the greatest effects on depressive and anxiety symptoms
- Dose-dependent effects were also observed on overall patient functioning
- Dosage increase to 20 mg/day after 1 week did not compromise tolerability

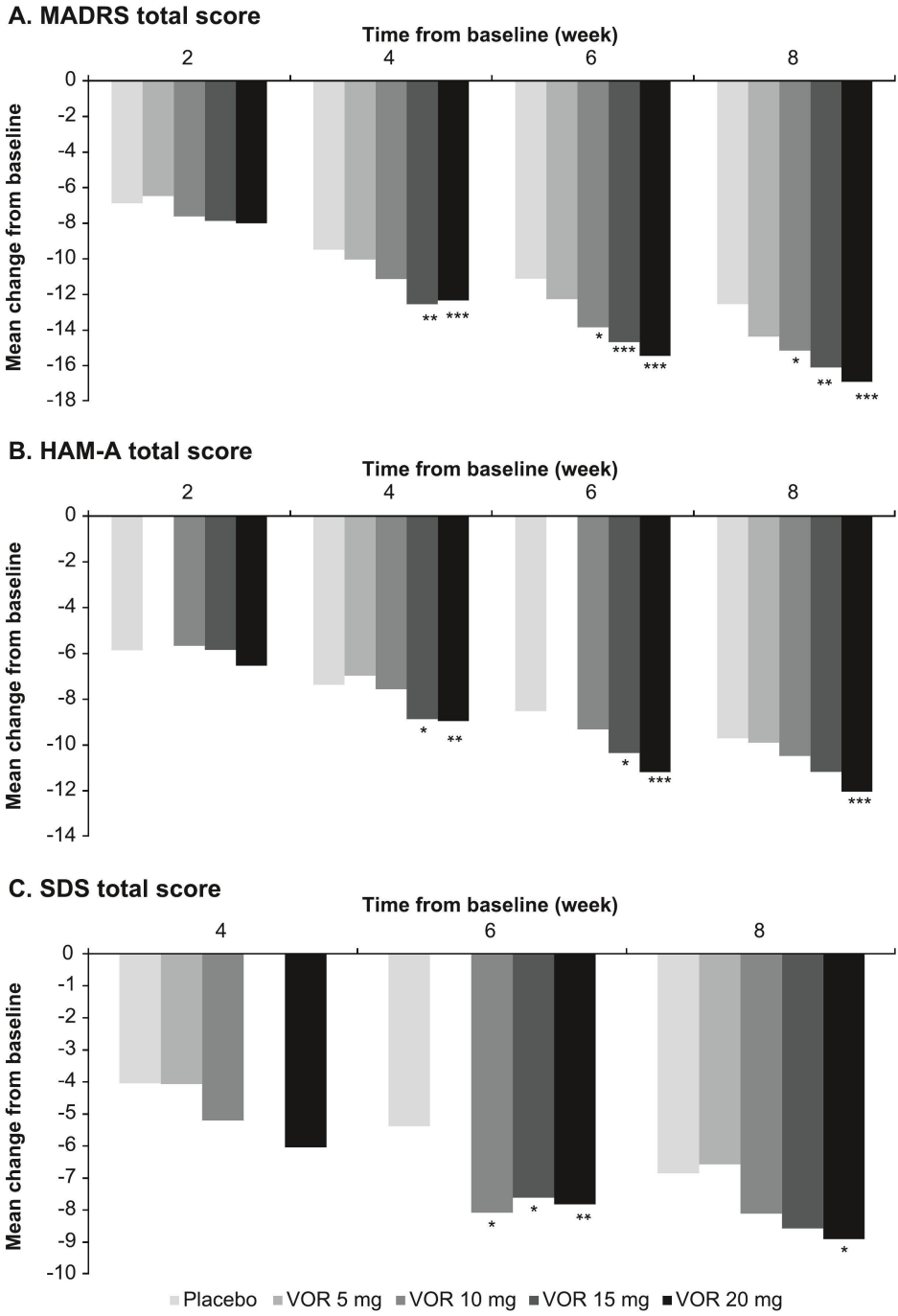
A. MADRS total score
Time from baseline (week)
2
4
6
8
Mean change from baseline
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
B. HAM-A total score
Time from baseline (week)
Mean change from baseline
C. SDS total score
Time from baseline (week)
Mean change from baseline
Placebo
VOR 5 mg
VOR 10 mg
VOR 15 mg
VOR 20 mg

Figure 1

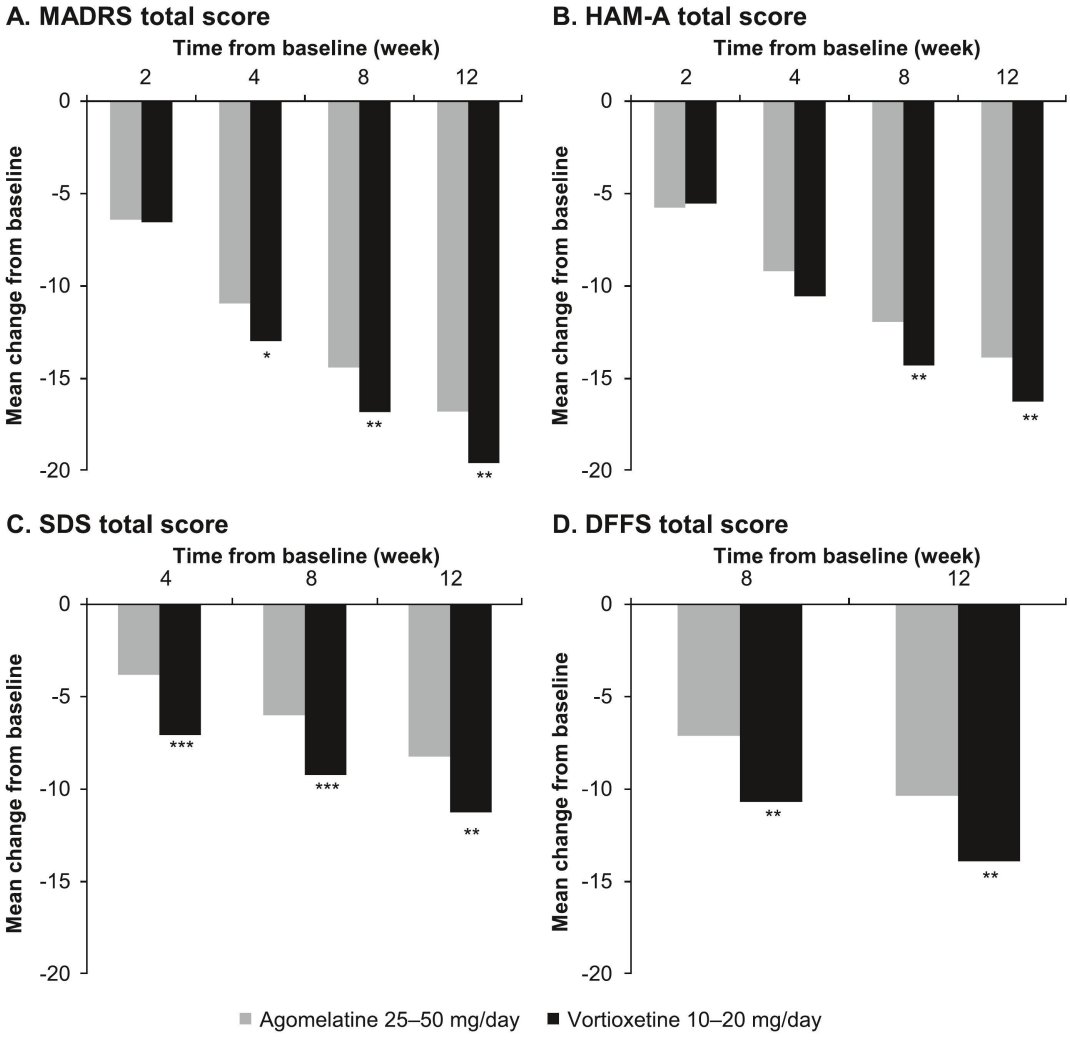
A. MADRS total score
Time from baseline (week)
2
4
8
12
0
-5
-10
-15
-20
Mean change from baseline
*
**
**
B. HAM-A total score
Time from baseline (week)
2
4
8
12
0
-5
-10
-15
-20
Mean change from baseline
**
**
C. SDS total score
Time from baseline (week)
4
8
12
0
-5
-10
-15
-20
Mean change from baseline
***
***
**
D. DFFS total score
Time from baseline (week)
8
12
0
-5
-10
-15
-20
Mean change from baseline
**
**
Agomelatine 25–50 mg/day
Vortioxetine 10–20 mg/day

Figure 2

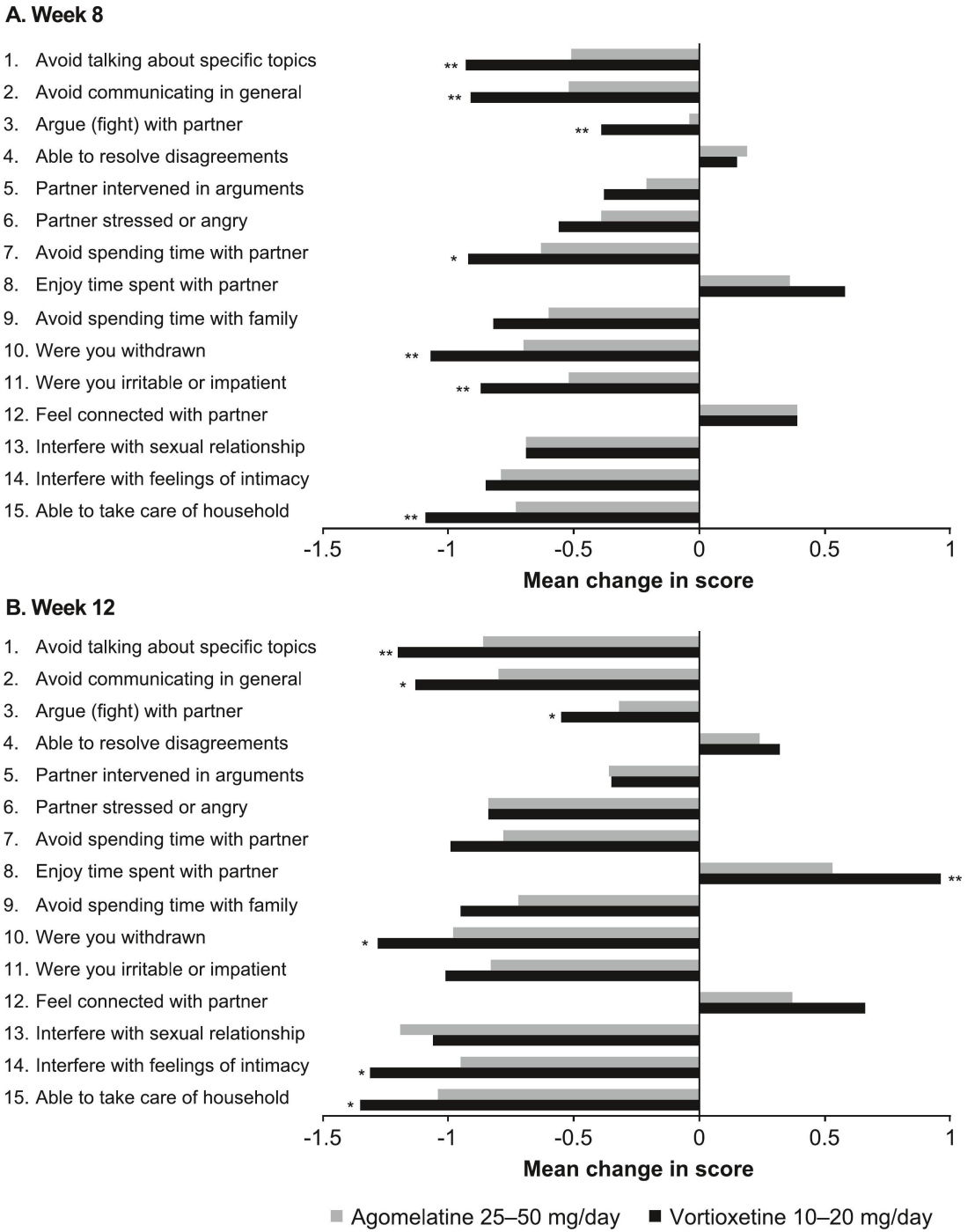
A. Week 8
1. Avoid talking about specific topics
2. Avoid communicating in general
3. Argue (fight) with partner
4. Able to resolve disagreements
5. Partner intervened in arguments
6. Partner stressed or angry
7. Avoid spending time with partner
8. Enjoy time spent with partner
9. Avoid spending time with family
10. Were you withdrawn
11. Were you irritable or impatient
12. Feel connected with partner
13. Interfere with sexual relationship
14. Interfere with feelings of intimacy
15. Able to take care of household
-1.5
-1
-0.5
0
0.5
1
Mean change in score
B. Week 12
1. Avoid talking about specific topics
2. Avoid communicating in general
3. Argue (fight) with partner
4. Able to resolve disagreements
5. Partner intervened in arguments
6. Partner stressed or angry
7. Avoid spending time with partner
8. Enjoy time spent with partner
9. Avoid spending time with family
10. Were you withdrawn
11. Were you irritable or impatient
12. Feel connected with partner
13. Interfere with sexual relationship
14. Interfere with feelings of intimacy
15. Able to take care of household
-1.5
-1
-0.5
0
0.5
1
Mean change in score
Agomelatine 25–50 mg/day
Vortioxetine 10–20 mg/day

Figure 3