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ORIGINAL RESEARCH

Efficacy of Vortioxetine on Anhedonia: Results from a Pooled Analysis of Short-Term Studies in Patients with Major Depressive Disorder

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Purpose: Anhedonia is a core symptom of major depressive disorder (MDD), which has important functional consequences for the patient. This post hoc analysis investigated the relationship between anhedonia and functioning in patients with MDD treated with vortioxetine.

Patients and Methods: We conducted a pooled analysis of all 11 short-term, double-blind, randomized, placebo-controlled studies of vortioxetine (fixed dose, 5–20 mg/day) in patients with MDD which included Montgomery–Åsberg Depression Rating Scale (MADRS) and Sheehan Disability Scale (SDS) assessments. A short-term, randomized, active-controlled trial of flexible-dose treatment with vortioxetine (10–20 mg/day) versus agomelatine (25–50 mg/day) was also analyzed. Mean changes from baseline to study endpoint in MADRS total, MADRS anhedonia subscale, SDS total, and SDS social-functioning scores were analyzed by a mixed model for repeated measures. The relationship between treatment effects on anhedonia and functioning was investigated using path analysis.

Results: A total of 4988 patients with MDD were included in the placebo-controlled studies and 495 in the active-comparator study. Significant dose-dependent improvements in overall depressive symptoms, anhedonia, and measures of functioning were seen in vortioxetine-treated patients compared with those who received placebo or agomelatine. Results of the path analysis for the placebo-controlled studies suggested that the effect on functioning was mostly driven by the effect of treatment on MADRS anhedonia factors.

Conclusion: Vortioxetine showed significant short-term efficacy against anhedonia in this large population of patients with MDD. In the placebo-controlled studies, improvements in functioning associated with vortioxetine appeared to be mostly driven by the effect of treatment on MADRS anhedonia factors.

Keywords: anhedonia, functioning, major depressive disorder, vortioxetine

Introduction

Anhedonia – defined as loss of interest and lack of reactivity to pleasurable stimuli – is a multidimensional domain that includes motivational and consummatory aspects of reward anticipation, experience, and evaluation.[1,2] Anhedonia is a common symptom of major depressive disorder (MDD) and many other psychiatric disorders,[3] particularly schizophrenia,[4] and is a key diagnostic criterion for a major depressive episode.[3] It is reported in up to 75% of patients with MDD,[5,6] and is a common residual symptom in patients with MDD receiving antidepressant treatment.[7] Indeed, it has been suggested that experiencing a restricted range of

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emotions may be an adverse effect associated with some classes of antidepressants.[8] For example, up to 60% of patients with MDD treated with selective serotonin reuptake inhibitors (SSRIs) or serotonin-noradrenaline reuptake inhibitors (SNRIs) report some degree of emotional numbness or blunting.[8–11]

Presence of anhedonia has been shown to be significantly associated with MDD symptomatology, with higher rates of social withdrawal, social impairment, reactivity of mood, brooding about past events, and diurnal mood variation observed in patients reporting anhedonia compared with those who do not.[12] From the patient's perspective, anhedonia is also identified as having a major negative impact on self-reported psychosocial functioning.[13] Anhedonia appears to be a predictor of non-response to many antidepressants.[14–18] There is also evidence to suggest a complex relationship between anhedonia and suicidality in patients with MDD.[19–22]

There is currently no specific pharmacological approach recommended for the treatment of anhedonia in patients with MDD. The neurobiology of anhedonia implicates distinct neurochemical systems and brain regions and circuits, including disturbances of central dopaminergic mesolimbic and mesocortical reward circuit pathways that involve brain regions such as the ventral tegmental area, ventral striatum, nucleus accumbens, orbitofrontal cortex, anterior cingulate cortex, and prefrontal cortex.[23,24] Although there is evidence that serotonergic pathways have a role in the development of anhedonia in MDD,[24] disappointing treatment outcomes with SSRIs suggest that other neurotransmitters might play a more prominent role.[18] In particular, dopaminergic transmission has been shown to be key to the modulation of motivation and "reward processing" in humans.[25,26] However, there is also evidence for the involvement of glutaminergic and opioid systems,[24] and inflammatory cytokines may also play a role.[23]

Vortioxetine is a multimodal antidepressant, with a unique pharmacologic profile.[27–29] Vortioxetine acts as an inhibitor of the serotonin (5-HT) transporter as well as modulating the activity of multiple 5-HT receptor subtypes, thus directly and indirectly influencing the activity of several neurotransmitter systems relevant to the neurobiology of anhedonia including serotonergic, noradrenergic, dopaminergic, cholinergic, and histaminergic systems.[27–29] Preclinical findings (eg sucrose preference tests and hippocampal brain-derived neurotrophic factor levels) suggest that vortioxetine engages neurotransmitter systems relevant to reward, motivation, and pleasure.[30] Phenotypic and neurobiologic overlap exists between anhedonia and general cognitive processes.[31] For example, activation of the innate immunoinflammatory system in patients with MDD is highly associated with both impaired cognitive performance and measures of anhedonia.[32,33] The neurochemical and neurocircuit effects of vortioxetine, combined with its demonstrated pro-cognitive effects,[34] suggest it may also have beneficial effects on anhedonia in patients with MDD.

Significant improvement in anhedonia, as measured by both the Snaith–Hamilton Pleasure Scale (SHAPS) total score and the Montgomery–Åsberg Depression Rating Scale (MADRS) anhedonia subscale score, has been reported in patients with MDD treated with vortioxetine.[6] Of note, the observed improvement in anhedonia was found to be statistically significantly correlated with improvement in patient functioning. The present analysis was undertaken to replicate and extend these preliminary findings in a larger patient population.

Patients and Methods

Study Population

The analyses included all 11 short-term (6 or 8 weeks), double-blind, randomized, fixed-dose, placebo-controlled studies conducted by Takeda/Lundbeck that investigated the efficacy of vortioxetine (5–20 mg/day) for the treatment of MDD and which included MADRS and Sheehan Disability Scale (SDS) assessments. All studies were conducted in adult patients with a primary diagnosis of single-episode or recurrent MDD according to Diagnostic and Statistical Manual of Mental Disorders (4th Edition, Text Revision) criteria.[35] Additional eligibility criteria of individual studies are summarized in Table 1.

Data were also analyzed from a short-term (12-week), randomized, active-controlled trial of flexible-dose treatment with vortioxetine (10–20 mg/day) compared with agomelatine (25–50 mg/day) in patients with MDD who had an inadequate response to SSRI/SNRI monotherapy (NCT01488071).[47] This study was included as agomelatine was shown to be effective for the treatment of anhedonia (assessed by SHAPS total score) in patients with MDD in an 8-week, open-label trial.[48] Only patients with depressive symptoms considered nonresponsive or partially responsive to a single SSRI/SNRI treatment course of an adequate dose (approved) and duration (≥6 weeks) were eligible for this study. Other key eligibility criteria were duration of current major depressive episode <12 months, and MADRS total

Table 1 Key Inclusion Criteria for the Placebo-Controlled Trials

Study	Treatment Arm	N	Age Range (Years)	Duration of Current MDE	MADRS Total Score
NCT00635219 (11984A)[36]	Placebo Vortioxetine 5 mg/day Vortioxetine 10 mg/day	145 155 151	18–75	≥3 months	≥26
NCT01140906 (13267A)[37]	Placebo Vortioxetine 15 mg/day Vortioxetine 10 mg/day	158 149 152	18–75	≥3 months	≥26
NCT00672958 (303)[38]	Placebo Vortioxetine 5 mg/day	286 292	18–75	≥3 months	≥30
NCT00672620 (304)[39]	Placebo Vortioxetine 5 mg/day	149 153	18–75	≥3 months	≥22
NCT00735709 (305)[40]	Placebo Vortioxetine 5 mg/day Vortioxetine 10 mg/day	139 139 139	18–75	≥3 months	≥26
NCT01153009 (315)[41]	Placebo Vortioxetine 15 mg/day Vortioxetine 20 mg/day	153 145 147	18–75	≥3 months	≥26
NCT01163266 (316)[42]	Placebo Vortioxetine 10 mg/day Vortioxetine 20 mg/day	155 155 148	18–75	≥3 months	≥26
NCT01179516 (317)[43]	Placebo Vortioxetine 10 mg/day Vortioxetine 15 mg/day	149 143 142	18–75	≥3 months	≥26
NCT01255787 (CCT-002)[44]	Placebo Vortioxetine 5 mg/day Vortioxetine 10 mg/day Vortioxetine 20 mg/day	150 144 147 149	20–64	≥3 months	≥26
NCT01355081 (CCT-003)[45]	Placebo Vortioxetine 15 mg/day Vortioxetine 20 mg/day	124 119 122	20–75	≥3 months	≥26
NCT02389816 (CCT-004)[46]	Placebo Vortioxetine 10 mg/day Vortioxetine 20 mg/day	161 165 163	20–75	≥3 months	≥26

Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depressive episode.

score ≥22 and MADRS item 1 (apparent sadness) score ≥3 at screening and baseline visits. Following a screening period of 4–10 days, eligible patients were switched from their previous treatment for 12 weeks of double-blind treatment with either vortioxetine or agomelatine. During the first 4 weeks of the study, vortioxetine and agomelatine doses were individually adjusted according to the investigator's clinical judgment. After week 4, doses were fixed.

All studies included in this analysis were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by the necessary research ethics committees. Patients provided written informed consent for participation. Further ethical approval was not required for this pooled analysis, as it used data from studies that have already been published.

Outcome Measures

Overall depression severity was assessed by the MADRS total score.[49] Anhedonia was assessed by means of the MADRS 5-item anhedonia subscale score, which was based on the following MADRS items: 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel).[6] Functional impairment was assessed using the SDS.[50,51] This brief self-report measure assesses three functional domains (work/school, social life/leisure, and family life/home responsibility) over the previous 7 days. Patients rate the severity of impairment for each domain on a scale of 0–10, with higher scores indicating greater impairment. Scores from the individual domains are combined to generate the SDS total score, which ranges from 0 (unimpaired) to 30 (highly impaired). For all these scales, higher scores indicate greater impairment.

Statistical Analysis

The population analyzed was the full analysis set comprising all treated patients with at least one valid post-baseline efficacy assessment. For all studies, mean changes from baseline to study endpoint in MADRS total score, MADRS anhedonia subscale score, SDS total score, and SDS social-functioning score were analyzed by a mixed model for repeated measures, with freely varying mean and covariance structure and adjusting for baseline levels and site. A standard, aggregated-data, random-effects statistical meta-analysis methodology was applied based on the estimates obtained in the individual placebo-controlled studies. For the placebo-controlled studies, data were analyzed by vortioxetine dose (5, 10, 15, or 20 mg).

The relationship between potential effects on anhedonia and functioning was investigated further using a path analysis approach. The direct effect of vortioxetine on functioning was separated from the total effect by adjusting for the change in anhedonia in an analysis of covariance model. The direct effect was expressed as a percentage of the originally obtained total effect (ie 100 × direct effect/total effect).

Nominal significance levels were set at $P < 0.05$, although the individual studies involved separate multiplicity adjustments and test strategies. Analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study Population

Patient demographics and clinical characteristics at baseline for the included studies are shown in Table 2. In the placebo-controlled studies, 3219 patients were treated with vortioxetine and 1769 received placebo. In the active-comparator study, 253 patients received vortioxetine and 242 received agomelatine. Demographic and treatment characteristics were generally similar across treatment groups.

Placebo-Controlled Studies

Significant dose-dependent improvements in overall depressive symptoms, anhedonia, and measures of functioning were seen in vortioxetine-treated patients compared with those who received placebo. The mean difference in change from baseline versus placebo for MADRS total score was −1.71 for vortioxetine 5 mg ($P = 0.006$), −2.49 for vortioxetine 10 mg ($P < 0.001$), −2.60 for vortioxetine 15 mg ($P = 0.105$), and −3.79 for vortioxetine 20 mg ($P < 0.001$) (Figure 1A). The mean difference versus placebo for the MADRS anhedonia subscale score was −0.97 for vortioxetine 5 mg ($P = 0.009$), −1.37 for vortioxetine 10 mg ($P < 0.001$), −1.68 for vortioxetine 15 mg ($P = 0.086$), and −2.24 for vortioxetine 20 mg ($P < 0.001$) (Figure 1B). The mean difference versus placebo for SDS total score was −0.68 for vortioxetine 5 mg ($P = 0.104$), −1.49 for vortioxetine 10 mg ($P < 0.001$), −0.91 for vortioxetine 15 mg ($P = 0.452$), and −1.73 for vortioxetine 20 mg ($P < 0.001$) (Figure 1C). The mean difference versus placebo for SDS social-functioning score was −0.26 for vortioxetine 5 mg ($P = 0.056$), −0.53 for vortioxetine 10 mg ($P < 0.001$), −0.21 for vortioxetine 15 mg ($P = 0.602$), and −0.68 for vortioxetine 20 mg ($P = 0.002$) (Figure 1D).

Results of the path analysis for the placebo-controlled studies showed that the effect of vortioxetine on functioning was almost entirely driven by the effect of treatment on anhedonia (Figure 2).

Comparison with Agomelatine

Statistically significant differences between vortioxetine (flexible dose 10–20 mg/day) and agomelatine were seen for change from baseline in MADRS total score, MADRS anhedonia subscale score, SDS total score, and SDS social-functioning score from week 4 onwards (Table 3). At week 12, the mean difference for vortioxetine versus agomelatine was −2.03 for MADRS total score

Table 2 Demographics and Baseline Clinical Characteristics

	Placebo-Controlled Studies (N=11)					Active-Comparator Study	
	Placebo	Vortioxetine 5 mg/day	Vortioxetine 10 mg/day	Vortioxetine 15 mg/day	Vortioxetine 20 mg/day	Vortioxetine 10–20 mg/day	Agomelatine 25–50 mg/day
No. of patients	1769	1002	1022	436	759	253	242
Sex, % female	61.5	62.4	61.0	68.8	63.1	77.1	72.3
Age, years	43 ± 12	43 ± 13	44 ± 12	45 ± 14	43 ± 13	47 ± 12	46 ± 12
MADRS total score	31.9 ± 4.1	32.2 ± 4.2	32.1 ± 4.3	32.5 ± 4.1	31.6 ± 3.9	29.1 ± 4.4	28.7 ± 4.0
MADRS anhedonia score	19.0 ± 2.5	19.1 ± 2.5	18.9 ± 2.5	19.3 ± 2.3	18.8 ± 2.3	17.3 ± 2.4	17.1 ± 2.3
SDS total score	18.3 ± 6.3	18.5 ± 6.5	17.9 ± 6.4	20.2 ± 5.6	18.2 ± 5.9	19.2 ± 5.3	19.3 ± 5.3
SDS social-functioning score	6.5 ± 2.3	6.4 ± 2.4	6.3 ± 2.3	7.1 ± 2.1	6.3 ± 2.2	6.4 ± 2.1	6.5 ± 2.0

Note: All values are mean ± standard deviation unless otherwise indicated.
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale.

($P = 0.005$), −1.02 for MADRS anhedonia subscale score ($P = 0.027$), −1.75 for SDS total score ($P = 0.021$), and −0.55 for SDS social-functioning score ($P = 0.015$).

The path analysis for this study estimated the direct effect of treatment to account for 64% of the total effect on functioning (Figure 3).

Discussion

Results of this analysis show that vortioxetine is effective for the treatment of anhedonia in patients with MDD. This finding is in keeping with the results of other meta- and network analyses showing vortioxetine to be efficacious in reducing overall depressive symptom severity in patients with MDD.[52–55] Significant dose-dependent effects were seen on measures of anhedonia and functioning compared with placebo over the range of 5–20 mg/day, with higher doses (10, 15, and 20 mg) shown to be associated with greater clinical response. Compared with agomelatine, which has previously been shown to be effective for the treatment of anhedonia in patients with MDD,[48] vortioxetine 10–20 mg also demonstrated a superior effect on anhedonia and functioning.

The therapeutic dose range for vortioxetine is 5–20 mg/day; the recommended starting dose is 10 mg once daily, which can be adjusted based on clinical response.[56] Results of this analysis confirm the dose–response relationship for vortioxetine on both the MADRS total and MADRS anhedonia subscale scores, as well as on measures of patient functioning. In line with the World Federation of Societies of Biological Psychiatry guidelines,[57] it is important to assess clinical response to antidepressant therapy early in the course of treatment (ie about 2 weeks after treatment initiation) to allow for any necessary dose adjustment to optimize response.[58]

For the placebo-controlled studies, path analysis suggested that the effect of vortioxetine on functioning was mostly driven by the improvement in MADRS anhedonia factors. This suggests a potential mediation effect for anhedonia on other outcomes in patients with MDD. However, for the active-comparator study, results of the path analysis implied some direct effect of factors other than anhedonia. It is important to note that there was no worsening of anhedonia and no suggestion of emotional blunting in vortioxetine-treated patients. In contrast, worsening of anhedonia and emotional blunting have been reported in patients with MDD treated with other antidepressants.[8–11]

The relationship between depressive symptoms and functioning in MDD is complex. Early in the disease course, the correlation between presence, type, and severity of symptoms and functioning appears to be more consistent and can be replicated. However, in treated patients with depression, the relationship between depressive symptoms and functioning appears less consistent, suggesting that particular types or domains of depressive symptoms or other unmeasured factors are more relevant to and explain functioning.[59,60] Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed individual symptoms of depression to have differential effects in terms of functional impairment in outpatients with depression receiving their first antidepressant treatment, with variance ranging from

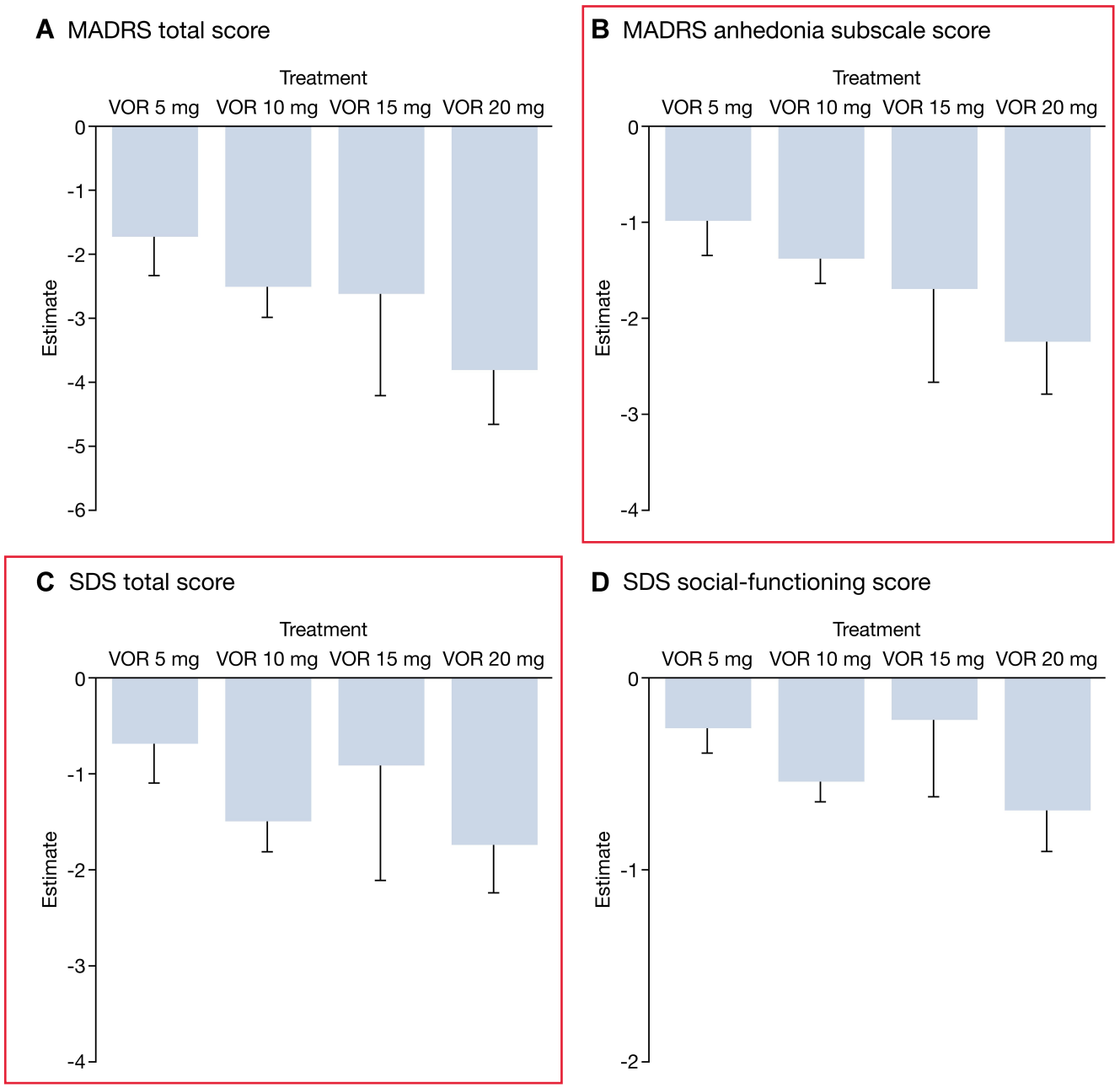

Figure 1 Mean difference in change from baseline for vortioxetine versus placebo for (**A**) MADRS total score, (**B**) MADRS anhedonia subscale score, (**C**) SDS total score, and (**D**) SDS social-functioning score (full analysis set; mixed-model repeated-measures analysis).
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale; VOR, vortioxetine.

20.7% for sad mood and 16.5% for concentration, to 0.7% for hypersomnia.[59] In patients with remitted MDD in STAR*D, principal-component analysis showed that relapse was more likely in patients with decreased self-rated quality of life and functioning at baseline than those without.[61] The observation that certain symptoms or domains associated with depression are more relevant than others to functioning appears to be substantiated by the results of the current study, in which improvement in anhedonia appeared to mediate treatment effects on functioning in patients with MDD.

Anhedonia encompasses multiple discrete and overlapping phenotypic dimensions as well as neurobiological substrates;[2] for example, it may include aspects of reward valuation, reward response, and reward learning. Both reward valuation and response overlap with the typology "anticipatory" as well as "consummatory hedonism".[62] Reward learning involves aspects of reward salience and

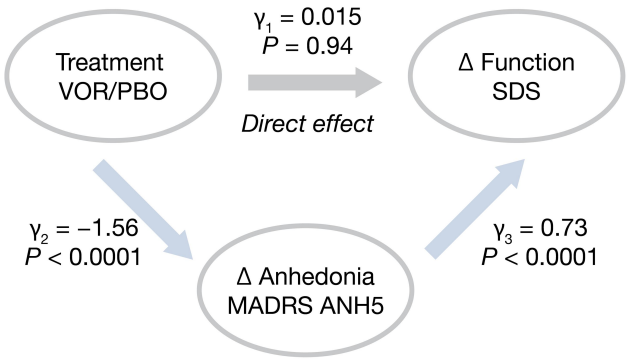

Figure 2 Path analysis to estimate direct effects of treatment with vortioxetine on functioning: placebo-controlled studies.
Notes: Indirect effect = −1.56*0.73 = −1.14; total effect = −1.14 + (0.015) = −1.13 ≈ −1.14; percent direct effect = 0.15/−1.14 ≈0%.
Abbreviations: ANH5, 5-item anhedonia subscale; MADRS, Montgomery–Åsberg Depression Rating Scale; PBO, placebo; SDS, Sheehan Disability Scale; VOR, vortioxetine; γ, estimates of effects and associations obtained from the analysis of covariance models.

is also considered to be abnormal in many individuals with MDD. When evaluating neurochemical systems as a "unit of analysis", dopaminergic functioning is more closely linked to reward valuation, with opioid and cannabinoidergic systems implicated in reward response. Hierarchically, neural circuits/networks subserving cognitive emotional processing are also implicated in all aspects of reward phenomenology.[63]

A number of neurobiological mechanisms may account for the observed beneficial effects of vortioxetine on anhedonia. These include its well-documented effects on 5-HT_3 receptors,[27–29] as well as indirect downstream effects on dopamine[64,65] and glutamate neurotransmission.[66] Disturbed dopaminergic transmission has been shown to have a higher correlation with anhedonia severity than with other symptoms of depression,[67] and it has been hypothesized that the pro-cognitive effects of vortioxetine may be mediated via 5-HT_3 heteroreceptors on GABAergic interneurons, thereby increasing glutamatergic activation.[66] Glutamate targeting appears to be a promising approach for the treatment of anhedonia in MDD.[68] Indeed, the reported beneficial effects of ketamine on anhedonia appear to be mediated through localized effects on glutamate in the nucleus accumbens.[69,70] The potential antidepressant effects of lumateperone, an atypical antipsychotic recently approved in the USA for the treatment of schizophrenia in adults and in development for bipolar disorder and MDD, also appear to be mediated by glutaminergic mechanisms, albeit indirectly through dopamine D1 receptors.[71]

In patients with remitted depression and healthy controls, vortioxetine has also been shown to have direct effects on the efficiency of neural circuits supporting cognitive function, for example, in the hippocampus and dorsolateral prefrontal cortex.[72] These upstream circuit effects may at least in part account for the observed improvement in anhedonia in vortioxetine-treated patients. Vortioxetine may additionally have beneficial effects on inflammatory systems.[73] Inflammation is known to amplify anhedonia, and drugs that affect inflammation appear to have anti-anhedonic properties.[33,74]

The observed differences between vortioxetine and agomelatine in this analysis may at least in part be due to differences in their mechanism of action. Agomelatine is a melatoninergic MT_1 and MT_2 receptor agonist (modulating circadian rhythms) and a selective 5-HT_{2C} receptor antagonist (increasing serotonin and dopamine levels in the frontal cortex).[75] Studies investigating the effects of agomelatine on anhedonia have only utilized the SHAPS scale, which mostly measures consummatory pleasure.[48,76,77] In contrast,

Table 3 Analysis of Difference in Change from Baseline in MADRS Total Score, MADRS Anhedonia Subscale Score, SDS Total Score, and SDS Social-Functioning Score for Vortioxetine 10–20 mg/day versus Agomelatine 25–50 mg/day (Full Analysis Set; Mixed-Model Repeated-Measures Analysis)

Timepoint (Week)	MADRS Total Score		MADRS Anhedonia Subscale Score		SDS Total Score		SDS Social-Functioning Score	
	Diff (SE)	*P*	Diff (SE)	*P*	Diff (SE)	*P*	Diff (SE)	*P*
1	−0.56 (0.34)	0.098	−0.22 (0.20)	0.286				
2	−0.15 (0.47)	0.758	0.01 (0.28)	0.980				
3	−0.86 (0.56)	0.126	−0.28 (0.34)	0.410				
4	−1.99 (0.63)	0.002	−1.13 (0.39)	0.005	−2.50 (0.67)	< 0.001	−0.62 (0.21)	0.003
8	−2.16 (0.69)	0.002	−1.05 (0.42)	0.014	−2.22 (0.72)	0.002	−0.66 (0.23)	0.004
12	−2.03 (0.72)	0.005	−1.02 (0.46)	0.027	−1.75 (0.75)	0.021	−0.55 (0.22)	0.015

Abbreviations: Diff, difference (vortioxetine – agomelatine); MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale; SE, standard error.

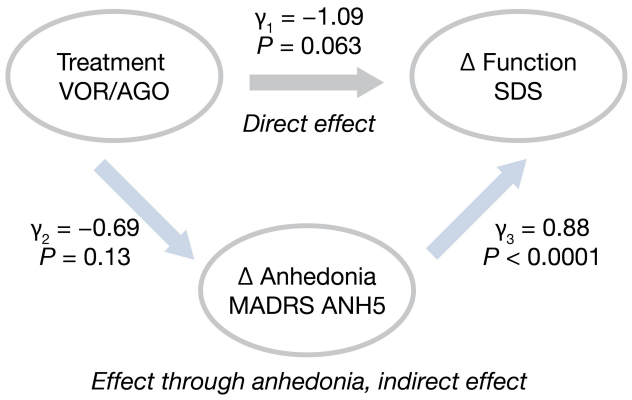

Figure 3 Path analysis to estimate direct effects of treatment with vortioxetine on functioning: active-comparator study.
Notes: Indirect effect = –0.69*0.88 = –0.61; total effect = –0.61 + (–1.09) = –1.70; percent direct effect = –1.09/1.70 = 64%.
Abbreviations: AGO, agomelatine; ANH5, 5-item anhedonia subscale; MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale; VOR, vortioxetine; γ, estimates of effects and associations obtained from the analysis of covariance models.

vortioxetine has been shown to have effects on two different measures of anhedonia (the SHAPS scale and the MADRS anhedonia subscale), with improvements in anhedonia in vortioxetine-treated patients shown to directly mediate the association between improvements in overall depressive symptom severity and functioning.[6] Vortioxetine has also been separately studied on two disparate aspects of anhedonia in patients with MDD: anticipation (assessed by the Effort Expenditure Reward Task [EEfRT]),[78] and consummatory pleasure.[6] To our knowledge, similar mediation analyses and motivational/effort tests have not been undertaken for agomelatine.

This analysis has some limitations. First, this was a post hoc analysis, and evaluating the effect of vortioxetine on anhedonia was not the primary aim of the placebo-controlled studies included. Second, only short-term studies were available for inclusion, precluding assessment of long-term treatment effects. Nevertheless, the acute effect of antidepressant treatment on anhedonia is still a relevant outcome for practicing psychiatrists.[79] Third, only the MADRS anhedonia subscale was used as a measure of anhedonia in this analysis and it may also have been of scientific interest to investigate effects on anhedonia using scales specifically developed for this symptom (such as the SHAPS, the Fawcett–Clark Pleasure Capacity Scale, or the Chapman Scales for Physical and Social Anhedonia).[80–82] However, unlike the MADRS, these scales are not routinely used in randomized controlled trials of antidepressant therapy. Finally, the general limitation of randomized controlled trials in MDD apply to our findings, particularly that study participants may not be fully representative of patients with MDD in routine practice settings. Clinical presentation of MDD is known to be highly heterogeneous and its differential diagnosis may be influenced by multiple factors that alter over time.[83] In particular, many patients with MDD have other psychiatric illnesses;[84] however, patients with psychiatric comorbidities were excluded from the studies included in this pooled analysis. Nevertheless, our results replicate earlier findings showing a significant effect of vortioxetine on anhedonia in an open-label study,[6] and extend these to a much larger patient population derived from randomized controlled clinical trials versus placebo and an active comparator (agomelatine).

Conclusion

Vortioxetine showed significant short-term efficacy against anhedonia in this large population of patients with MDD. Improvements in functioning conferred by vortioxetine appeared to be mostly driven by the effect of treatment on MADRS anhedonia factors.

Abbreviations

EEfRT, Effort Expenditure Reward Task; 5-HT, serotonin; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, Major depressive disorder; SDS, Sheehan Disability Scale; SHAPS, Snaith–Hamilton Pleasure Scale; SNRI, Serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

Data Sharing Statement

The majority of data accessed from the trials are freely available; the corresponding author may be contacted for further data sharing.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the

version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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