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Effect of venlafaxine on anhedonia and amotivation in patients with major depressive disorder

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Original Research

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Abstract

Objective. Serotonin norepinephrine reuptake inhibitors (SNRIs) have been postulated to afford benefits in alleviating anhedonia and amotivation. This post hoc pooled analysis evaluated the effect of venlafaxine XR, an SNRI, on these symptoms in patients with major depressive disorder (MDD).

Methods. Data was pooled from five short-term randomized, placebo-controlled studies of venlafaxine XR for the treatment of MDD, comprising 1087 (venlafaxine XR, n = 585; placebo, n = 502) adult subjects. The change from baseline score in the MADRS anhedonia factor (based on items 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel]) for anhedonia, and in motivational deficits (based on 3 items of HAM-D17: involvement in work and activities, psychomotor retardation, and energy level [ie, general somatic symptoms]) for amotivation, were measured through 8 weeks. Mixed model repeated measures (MMRMs) were used to analyze changes over time and ANCOVA to analyze the change from baseline at week 8 with LOCF employed to handle missing data.

Results. At the end of 8 weeks, the change from baseline was significantly greater in patients on venlafaxine XR in both anhedonia (mean, 95% CI: −2.73 [−3.63, −1.82], $p < 0.0001$) and amotivation scores (mean, 95% CI: −0.78 [−1.04, −0.52], $p < 0.0001$) than those on placebo. For both measures, the between-group separation from baseline was statistically significant starting from week 2 onwards, and it increased over time.

Conclusion. This analysis demonstrates that venlafaxine XR is effective in improving symptoms of anhedonia and motivational deficits in patients with MDD.

Introduction

Major depressive disorder (MDD) is a highly prevalent and often debilitating mental disorder associated with low mood, anhedonia, alterations in behavior and emotional processing,[1-3] and significant impairments in social and occupational functioning.[4,5]

Anhedonia and motivational deficits (amotivation) are core symptoms of MDD, present in the majority of patients. These two symptoms are principal indicators of functional impairment and non-recovery.[1,2] According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision criteria (DSM-5-TR), anhedonia and depressed mood are key diagnostic criteria for MDD.[1,2,6] Evidence indicates that disturbances in motivation (and cognition) are continuing deficits in MDD that mediate poor functional outcomes.[1,2,6,7]

Studies have reported that approximately 70% to 75% of patients with MDD experience clinically significant symptoms of anhedonia, making functional recovery a challenge in them.[2,8] Importantly, anhedonia has been associated with poorer disease prognosis and treatment response.[9] Therefore, in patients with MDD, appropriate recognition and evaluation of anhedonia may help in achieving better clinical outcomes.

The DSM-5-TR defines anhedonia as an impaired ability to pursue, experience, or anticipate pleasure in most activities, and it often clinically presents as a loss of desire for previously pleasant rewards or lack of pleasure after receiving rewards or both.[1,2,10,11] It is an affective component with melancholic features that involves both physical and psychic domains.[11,12] Neurobiologically, disturbances in the structure and function of components of the ventral striatum, including but not limited to the nucleus accumbens (NAc), have been implicated in anhedonia.[13,14] Individuals may present with not feeling enjoyment in activities that were previously considered pleasurable, such as hobbies, or family members may notice social withdrawal or neglect of pleasurable avocations and diminished levels of sexual desire.[1]

Amotivation refers to decreased interest and drive to initiate and maintain goal-oriented activities and involves reward salience as a key characteristic feature.[4,15] Amotivation is a multi-component symptom complex. As per the Research Domain Criteria (RdoC) of National Institute of Mental Health (NIMH), motivational processes involve analyzing reward responsiveness (liking) and expectation of the reward (wanting), evaluating the reward and the effort required in achieving it, and the corresponding decision making (action selection).[16] In MDD patients with amotivation, functioning of one or more of these components is affected.[16] Evidence suggests that multiple structures and networks are implicated in reward salience and motivation. These include the Nac, ventral tegmental area (VTA), central nucleus of amygdala, prefrontal cortex, caudate, putamen, and orbitofrontal cortex, and inhibition of amygdala is postulated to play a prominent role.[14,17,18]

Both anhedonia and motivational deficits are also residual symptoms seen in patients with MDD, which are often poorly recognized and under-treated, leading to cognitive and functional impairments, and poor treatment outcomes.[12,19,20] Anhedonia and amotivation have both been reported to be important risk factors for suicidal ideation and suicidal behavior.[21,22]

Both pharmacological and non-pharmacological treatment approaches have been evaluated for treating anhedonia.[23,24]

Selective serotonin reuptake inhibitors (SSRIs) are frequently used as first-line agents in the management of MDD.[25,26] They have been shown to have a more pronounced role in reducing the negative affect compared to their role in improving the positive affect or ability of pleasure (ie, improving reward processing and motivation).[12,26-28] Additionally, they have also been shown to worsen apathy and emotional blunting.[29] For instance, studies have reported that escitalopram is less effective than agomelatine or cognitive behavioral therapy in treating anhedonia. Sertraline and fluoxetine, which interact with the dopaminergic system, are reported to be somewhat effective in improving anhedonia.[24] Overall, SSRIs may be of limited clinical utility in the management of anhedonia and amotivation.[12,26-28]

A few studies on serotonin-norepinephrine reuptake inhibitors (SNRIs) have reported that they may have a role in improving these symptoms in patients with MDD.[12,28,30,31] Other antidepressants that have been reported to be beneficial in improving anhedonia are bupropion, either alone or in combination with dextromethorphan, agomelatine, and vortioxetine.[24] Ketamine, with a faster onset of action, may have a rapid anti-anhedonic effect.[24]

Other classes of drugs which have been evaluated include stimulants such as methylphenidate. An RCT reported its beneficial effect on anhedonia when concomitantly used with an antidepressant. Preliminary studies on psilocybin have demonstrated its effect on anhedonia control.[24]

Non-pharmacological approaches such as transcranial magnetic stimulation and cognitive-behavioral therapy, particularly behavioral activation, have been reported to be beneficial for anhedonia. While cognitive-behavioral therapy affects the negative thought patterns responsible for the development of anhedonia, behavioral activation focuses on improving reward salience.[24]

Although studies have focused on treatment approaches for anhedonia and amotivation in patients with MDD,[32-34] evidence is limited due to the paucity of data and heterogeneity of study designs. Moreover, only a few of these studies have evaluated the outcomes of anhedonia and amotivation in patients with MDD. Given this scenario, there is a need for robust studies that evaluate the efficacy of various antidepressants on these important symptomatic domains.[23]

Venlafaxine, an SNRI, has been available in the United States since 1993[35] and its extended-release (XR) formulation has been approved for the treatment of MDD since 1997.[36] Venlafaxine has been reported to have an action on serotonin, norepinephrine, and dopamine in a dose-dependent manner. Therefore, venlafaxine may have an effect on symptoms mediated by norepinephrine and dopamine, such as anhedonia, amotivation, and low energy.[23,24,37-39] However, there is limited information about the effect of venlafaxine on motivational deficits.

This study aimed to conduct a post hoc pooled analysis of clinical trials of venlafaxine XR to assess its effect on the symptoms of anhedonia and amotivation.

Methods

The data set selected for our pooled analysis was based on the meta-analysis by Thase et al., which evaluated the efficacy of venlafaxine XR (75–225 mg/day) in adult patients with MDD, utilizing HAM-D17 and MADRS as efficacy measures.[40] The patient-level data required for our study that made use of derived measures from HAM-D17 and MADRS for evaluating amotivation and anhedonia was available in this data set, and thus, it was deemed a good fit.

Data set

Thase et al's study considered the following criteria for the selection and inclusion of the studies: all studies should be phase II, III, or IV clinical trials of venlafaxine XR conducted in Europe or United States of America (USA) and sponsored; should be double-blind, placebo-controlled, short-duration studies with fixed- or flexible-dose of venlafaxine XR (75–225 mg/day); and studies that had compared only venlafaxine XR and placebo groups.[40] Studies conducted in regions other than Europe and the USA were not considered because of study population differences.[40]

In all, 215 venlafaxine studies retrieved from company-sponsored clinical studies list were screened. Studies were excluded if they were venlafaxine immediate release (IR) studies (n = 46), were non-randomized controlled trials (epidemiologic, observational, non-drug, non-interventional or non-comparative studies; n = 42), were phase I pharmacokinetics studies (n = 42), were non-MDD studies (n = 38), or not double-blind, or not placebo-controlled (n = 20).[40] A total of five short-term (up to 12 weeks) clinical studies that met the selection criteria were considered for the assessment (Table 1).[40]

Of these five studies, four had flexible doses and one had two fixed-dose arms of venlafaxine XR.[40] Patients were randomized to receive at least one dose of the treatment (venlafaxine XR or placebo). For data analysis and assessment of treatment outcomes, data up to and including week 8 have been used.[40]

Outcome measures

Anhedonia

Anhedonia was measured with the Montgomery–Åsberg Depression Rating Scale (MADRS) 5-item anhedonia sub-scale.[40-42]

Primary outcome measures were changes from baseline scores in the MADRS anhedonia factor (based on items 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel]).[2] Only four of the five studies measured the MADRS scale (Silverstone et al's study did not measure[43]). Higher scores on this measure reflect greater severity.

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Table 1. Venlafaxine XR Clinical Studies Considered for the Pooled Analysis[a] Based on the Meta-analysis by Thase et al

Trial	Phase	Study population (N)[b]	Treatment arms	Dosing	Study period (weeks)	Study design
Cunningham et al[62]	III	293	Placebo Venlafaxine XR 75 mg/day or 150 mg/day Venlafaxine IR 75 mg/day or 150 mg/day	Venlafaxine XR, twice daily (morning and evening) Placebo, once daily (evening)	12	Flexible–dose, DB, PBO controlled study in adult out–patients with major depression.
Thase et al[60]	III	197	Placebo Venlafaxine XR 75 mg/day to 225 mg/day	Once daily (morning)	8	Flexible–dose, DB, PBO controlled study in adult out–patients with major depression.
Rudolph et al[63]	II	301	Placebo Venlafaxine XR 75 mg/day to 225 mg/day Fluoxetine 20 mg/day to 60 mg/day	Once daily (morning)	8	Flexible–dose, DB, PBO controlled study in adult out–patients with major depression.
Silverstone et al[43]	III	368	Placebo Venlafaxine XR 75 mg/day to 225 mg/day Fluoxetine 20 mg/day to 60 mg/day	Once daily (morning)	12	Flexible–dose, DB, PBO controlled study in adult out–patients with major depression and anxiety.
Salinas et al[64]	III	329	Placebo Venlafaxine XR 75 mg/day and 150 mg/day Paroxetine 20 mg/day	Once daily (morning)	8	Fixed–dose, DB, PBO controlled study in adult out–patients with major depression and anxiety.

[a]Studies considered in this pooled analysis were based on the clinical trials evaluated in the meta-analysis of venlafaxine XR by Thase et al (reproduced and modified from Thase et al[40]).
[b]Total number of patients in the safety population (randomized patients who received at least one dose of study medication).
DB, double-blind; IR, immediate release; PBO, placebo; XR, extended release.

Amotivation

Amotivation was evaluated using three items from the HAM-D17 (based on items 7 [involvement in work and activities], 8 [psychomotor retardation], and 13 [general somatic symptoms]).[4,41,44] The primary outcome evaluated was to measure the changes from baseline in the HAM-D17 amotivation score. Available evidence suggests these three items of HAM-D17 have greatest face validity in their relationship to motivational deficits and correlate strongly with more detailed assessments of amotivation.[4,45] Higher scores on this measure reflect greater severity.

For both anhedonia and amotivation, the primary time point of evaluation was week 8. In this post hoc pooled analysis, the safety outcome measures were discontinuations due to adverse events (AEs) and rate of discontinuations.

The derived measures to quantify anhedonia and amotivation (MADRS 5-item anhedonia sub-scale and the three-item HAM-D17, respectively) have been used in other interventional studies with antidepressants, post hoc analyses, and meta-analyses. Similar derived measures were adopted in this analysis.[2,19,46]

Statistical analyses

All efficacy analyses were based on the full analyses set (FAS), which contained all subjects who received at least one dose of the treatment according to randomization. A mixed-effects model for repeated measures (MMRMs) was used to analyze the continuous efficacy variables over time (baseline and weeks 1, 2, 3, 4, 6, and 8) with terms for study, visit, treatment group, interaction between visit and treatment group, and baseline score as a covariate.

Analysis of covariance (ANCOVA) model was also used for analyzing the change from baseline at week 8, with terms for study, treatment group, and baseline score, using the last observation-carried-forward (LOCF) approach to deal with missing post-baseline scores.

For the safety analyses, all patients who took at least one dose of double-blind treatment were included. Discontinuations due to AEs and rate of discontinuations were summarized by treatment group.

Results

The full analysis set of this post hoc pooled analysis involved 1087 subjects (Supplementary Table 1).

Anhedonia

For anhedonia, the analysis set comprised 839 subjects (venlafaxine XR, n = 456; placebo, n = 383). Compared with placebo, at the end of 8 weeks, venlafaxine XR was associated with a significantly higher change from baseline in the least square (LS) mean (SE) anhedonia scores (LS mean, [95% CI]: venlafaxine XR, −9.06 [−9.68, −8.44] and placebo, −6.33 [−6.99, −5.68]; Supplementary Table 1 and Figure 1A). The difference in the LS means (analyzed by ANCOVA) between the treatment groups measured at week 8 was also statistically significant (95% CI: −2.73 [−3.63, −1.82], p < 0.0001) (Supplementary Table 1).

This between-group separation in change from baseline of the anhedonia score (analyzed by MMRM analysis) was statistically significant starting from week 2 ($p < 0.005$) and increased over time (week 4 to week 8: $p < 0.0001$) (Supplementary Table 1 and Figure 1B).

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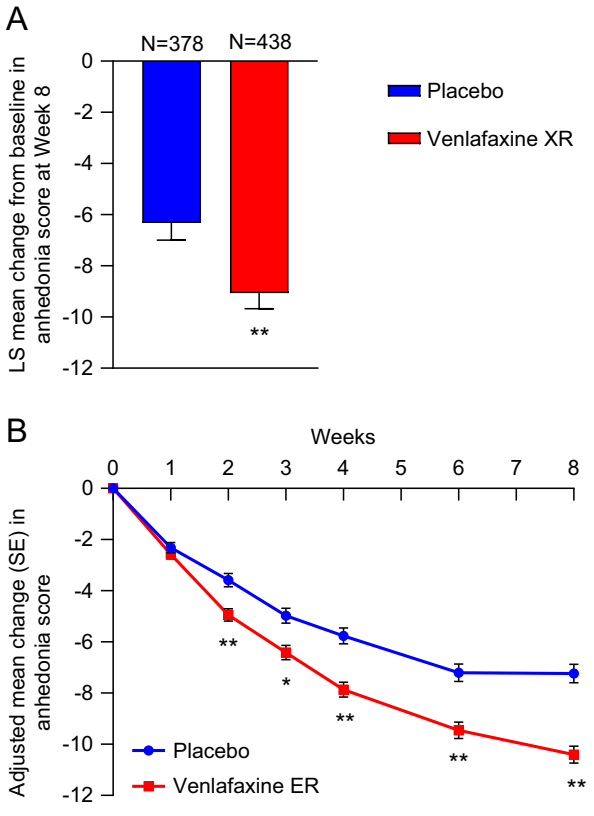

Figure 1. Mean change from baseline MADRS anhedonia sub-scale score—ANCOVA and MMRM analyses. A) Least square mean (95% CI) change from baseline MADRS anhedonia sub-scale score in the treatment groups at the end of 8 weeks (ANCOVA); $^{**}p < 0.0001$. B) Adjusted mean (SE) change from baseline MADRS anhedonia factor sub-scale score (MMRM analysis); $^{*}p < 0.005$; $^{**}p < 0.0001$. CI, confidence interval; XR, extended release; LSM, least square mean; MADRS, Montgomery–Åsberg Depression Rating Scale; ANCOVA, analysis of covariance; MMRM, mixed-effects model for repeated measures; SE, standard error.

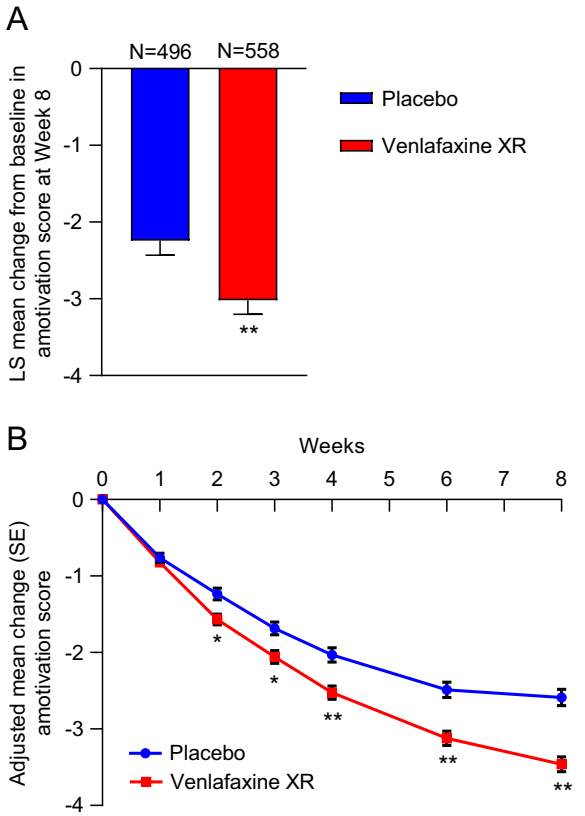

Figure 2. Mean change from baseline HAM-D17 amotivation measure score - ANCOVA and MMRM analyses. A) Least square mean (95% CI) change from baseline HAM-D17 amotivation measure score in the treatment groups at the end of 8 weeks (ANCOVA); $^{**}p < 0.0001$. B) Adjusted mean (SE) change from baseline HAM-D17 motivation measure score (MMRM analysis); $^{*}p < 0.005$, $^{**}p < 0.0001$. CI, confidence interval; XR, extended release; LSM, least square mean; HAM-D17, Hamilton Rating Scale for Depression; ANCOVA, analysis of covariance; MMRM, mixed-effects model for repeated measures; SE, standard error.

Amotivation

For amotivation, the analysis set comprised of1087 subjects (venlafaxine XR, n = 585; placebo, n = 502). Compared with placebo, at the end of 8 weeks, venlafaxine XR was associated with a significantly higher change from baseline in the LS mean (SE) amotivation scores (LS mean, [95% CI]: venlafaxine XR, −3.02 [−3.20, −2.84] and placebo, −2.24 [−2.43, −2.06]; Supplementary Table 1 and Figure 2A). The difference in the LS means (analyzed by ANCOVA) between the treatment groups at week 8 was also statistically significant (95% CI: −0.78 [−1.04, −0.52], $p < 0.0001$) (Supplementary Table 1).

This between-group separation in change from baseline of the amotivation scores (analyzed by MMRM analysis) was statistically significant starting from week 2 ($p < 0.005$) and increased over time (week 6 to week 8: $p < 0.0001$) (Supplementary Table 1 and Figure 2B).

Association between baseline values and efficacy outcomes

Anhedonia

The relationship between the baseline severity of anhedonia sub-scale score and the change from baseline at week 8 was explored. Results showed that at week 8 (LOCF), for those with more severe anhedonia or higher baseline anhedonia score, the magnitude of change from baseline was greater. This difference was more prominent in the venlafaxine XR arm compared to that in the placebo arm (Figure 3A).

Similarly, for those with less severe anhedonia or lesser baseline anhedonia score, the magnitude of change from baseline was small across both arms (Figure 3A).

Amotivation

A similar analysis was performed for the amotivation score as well (the range of amotivation scale is smaller than the range of anhedonia scale). Results showed that at week 8 (LOCF), for those with more severe motivational deficits or higher baseline amotivation scores, the magnitude of change from baseline was greater. This difference was more prominent in the venlafaxine XR arm compared to that in placebo arm (Figure 3B).

Similarly, for those with less severe motivational deficits or lesser baseline amotivation score, the magnitude of change from baseline was small for both venlafaxine XR and placebo (Figure 3B).

Safety profile

In the five studies included, patients discontinuing from the study were 26.7% (n = 156/585) and 34.9% (n = 175/502) in the

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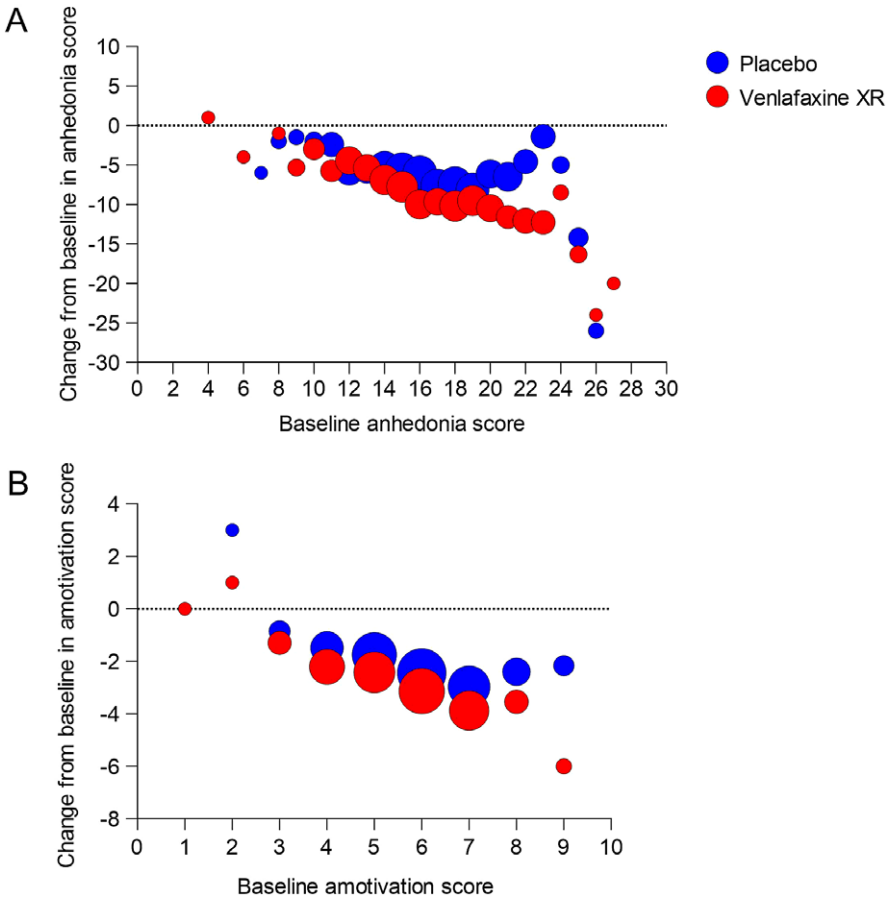

Figure 3. Effect of baseline anhedonia sub-scale score and baseline amotivation score (derived score from HAM-D17) on change from baseline. Bubble size/area and number of data points are proportional to each other, which contributed to each mean. A) Effect of baseline anhedonia sub-scale score on change from baseline at week 8 (LOCF). MADRS anhedonia factor sub-scale scores are based on the following items: 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties], 7 (lassitude), and 8 (inability to feel). B) Effect of baseline amotivation score (derived score from HAM-D17) on change from baseline at week 8 (LOCF). The three items of HAM-D17 with greatest validity to amotivation are involvement in work and activities; psychomotor retardation; and energy level (ie, general somatic symptoms). ER: extended release; MADRS: Montgomery–Åsberg Depression Rating Scale; LOCF: last observation carried forward; HAM-D17_{17}: 17-item Hamilton Rating Scale for Depression.

venlafaxine XR and placebo arms, respectively. Treatment discontinuation due to AEs was 9.4% (n = 55/585) and 3.6% (n = 18/502) in the venlafaxine XR and placebo arms, respectively.

The most common treatment-emergent AEs (≥10%) in the venlafaxine XR arm compared to that in the placebo arm included nausea (33.8% vs 15.9%), headache (32.8% vs 36.9%), dizziness (25.0% vs 10.6%), abnormal ejaculation/orgasm (17.4% vs 1.6%; in males only), sweating (16.6% vs 4.6%), dry mouth (16.1% vs 9.4%), somnolence (14.4% vs 7.0%), constipation (13.5% vs 8.4%), nervousness (12.0% vs 5.6%) and diarrhea (11.3% vs 10.8).

Discussion

This post hoc pooled analysis of venlafaxine XR clinical studies evaluated its utility in reducing the symptoms of anhedonia and amotivation in patients with MDD. Anhedonia and amotivation are core symptoms of MDD and also common residual symptoms. They are often difficult to treat, less responsive to many antidepressants, and are a frequent reason for non-remission as well as ongoing functional challenges.

Association between anhedonia and amotivation

Anhedonia and amotivation are conceptually distinct from one another. Anhedonia refers more restrictively to the inability to experience pleasure.[4,47] Amotivation, although it overlaps with anhedonia in the aspect of reward salience, is different as it involves other aspects related to cognition and contextual factors (Table 2).

The current study is one of the first studies assessing the impact of venlafaxine XR on anhedonia and amotivation in patients with MDD. In this analysis, statistically significant change from baseline in the MADRS anhedonia sub-scale score and in amotivation measure derived from HAM-D17 with venlafaxine XR was observed at week 2 and at all subsequent assessments compared with placebo.

An assessment of the effect of baseline severity of anhedonia or motivational deficits on efficacy outcomes in patients treated with venlafaxine XR or placebo showed an association between the severity of baseline score and the probability of achieving improvement. The magnitude of change from baseline in the anhedonia or amotivation scores was prominent in patients with severe disease or higher baseline scores.

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Table 2. Anhedonia and Amotivation as Clinical Constructs

	Anhedonia	Amotivation
Understanding the difference	• Reduced pleasure in routine activities • Not enjoying activities that were previously considered pleasurable[1]	• Reduced drive to perform activities • Feeling of the objective not being worthy enough of the computed effort and action plan[65]
The commonality–Reward salience	• Loss of desire for previously pleasant rewards or lack of pleasure after receiving rewards or both[12]	• Inability to determine whether the reward is essentially equal to the efforts applied • Inability to initiate goal–directed behavior • Inability to control the environment that influences reward salience[11,20,23]
Influence on cognitive control	• Poor disease control, functional recovery, and treatment or clinical outcomes • Influences functional outcomes and quality of life in MDD patients • Impaired physical functioning[11,20,23]	• Poor clinical outcomes • Impaired cognitive functioning[11,20,23]

The baseline severity by treatment interaction was not significant. Comparison between the treatment groups for the degree of improvement, based on baseline severity score, showed that the improvement was greater with venlafaxine XR compared with placebo, although the baseline severity score by treatment interaction was not statistically significant (Figure 3).

The methods adopted in our analysis have been validated in previously published studies.[2,4,19,46] In the study by Fervaha et al, three items of HAM-D (involvement in work and activities, psychomotor retardation, and general somatic symptoms) were selectively used for the evaluation of motivational deficits. They reported that these three items of HAM-D correlated strongly not only with symptoms of motivational deficits, but also with other rating scales that exclusively assess amotivation.[4]

These derived measures can be positioned as a potential way of assessing anhedonia and motivational deficits in a clinical setting. They may also be useful in implementing measurement-based care (MBC). MBC has been reported to offer the advantages of improved outcomes, better monitoring and control of symptoms, improvement in overall functioning and quality of life, enhancing collaborative care and aiding communication and relationship between patients and care providers. It may enhance the accuracy of decision making and clinical judgment and may provide more opportunities for treatment individualization.[48] Due to the ease of use of derived measures for patient care, MBC could be applied in a larger population. Additionally, they may also aid in evaluating the functional recovery in patients with MDD.

Venlafaxine is an SNRI that blocks both serotonin and norepinephrine transporters. Studies have reported that at low doses, venlafaxine increases serotonergic neurotransmission, and at high doses, it brings out changes in different forms of plasticity in discrete brain areas and also increases the tone of 5-HT and NE concurrently.[49] In the US, venlafaxine has been prescribed for MDD for more than two decades.[35,36,40]

Studies performed in patients with severe depression have reported that venlafaxine may be an effective treatment option. It may have a quick onset of action and a better dose-response curve. These studies have demonstrated its efficacy, safety, and tolerability in treating patients with severe depression.[50]

A pooled post hoc analysis of eight short-term, placebo-controlled clinical trials of venlafaxine XR (75–375 mg/day) showed that for low and high psychic anxiety subgroups, the likelihood of achieving response or remission was significantly higher for patients treated with venlafaxine XR than for placebo, based on change from baseline in HAM-D17 item 11 score.[51]

Fagiolini et al, in a pooled data analysis of the clinical trials of venlafaxine XR, reported on its ability to alleviate symptoms of anergia in patients with MDD. Data showed that venlafaxine XR significantly improved lassitude and energy compared with placebo. The authors suggested that venlafaxine XR may be considered as a first-line agent for the treatment of anergia, as it demonstrates both SSRI and SNRI activity. Also, they suggested that treatment of MDD by the symptom cluster approach may improve treatment outcomes.[23,39] The efficacy of venlafaxine in MDD with comorbid anxiety has been established by Lyndon et al.[51]

Trivedi et al evaluated the role and importance of risk factors in guiding long-term therapy. This study showed that in patients with recurrent MDD, the treatment outcomes improved, and relapse or recurrence decreased when patients were treated with venlafaxine XR for 2 years compared to 1-year therapy.[52,53]

A study by Kang et al, which compared the efficacy of mirtazapine versus venlafaxine in MDD patients with somatic symptoms, showed that both treatment groups had similar improvements in depressive symptoms. Comparison between the two groups showed no significant differences in mean change of the Symptom Check List-90-Revised (SCL-90-R) somatization sub-scores. This study concluded that the overall efficacy of mirtazapine and venlafaxine are similar in treating the overall symptoms of MDD. Both these drugs may be of benefit for treating the somatic symptoms in MDD patients.[54]

Network meta-analyses involving head-to-head trials showed that venlafaxine had a better response compared to fluoxetine, duloxetine, paroxetine, and sertraline.[52,55,56] An SLR and network meta-analysis by Cipriani A et al. on the efficacy and acceptability of 21 antidepressants for acute treatment of patients with MDD showed that in head-to-head comparisons, the efficacy of agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine was greater compared to other antidepressants. Fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs. When comparing the antidepressants for tolerability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were tolerable and had less dropouts, whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropouts.[57]

Another network meta-analysis compared the efficacy and tolerability of 20 different antidepressants in the maintenance

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treatment of MDD. Compared with placebo, SSRIs such as citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, SNRIs such as desvenlafaxine, venlafaxine and duloxetine, and other antidepressants such as mirtazapine, tianeptine, amitriptyline, nefazodone, vortioxetine and reboxetine had a lower 6-month relapse rate. The all-cause discontinuation was lower with paroxetine, sertraline, venlafaxine, desvenlafaxine, and vortioxetine than placebo. However, the discontinuation rate due to adverse events was higher with sertraline. Higher incidence of nausea/vomiting was seen with desvenlafaxine, sertraline, and vortioxetine when compared with placebo, while venlafaxine had a lower incidence of dizziness. Overall, paroxetine, venlafaxine, desvenlafaxine, and vortioxetine had a fair balance of efficacy, acceptability, and tolerability in adults with stable MDD.[58]

When potential drug-drug interactions between newer antidepressants and atypical antipsychotics are considered, it is reported that antidepressants such as citalopram, desvenlafaxine, escitalopram, mirtazapine, and venlafaxine have low potential for drug-drug interaction with paliperidone alone, compared to other antidepressants such as agomelatine, bupropion, vortioxetine, fluoxetine, paroxetine and so forth with other antipsychotics.[52]

Venlafaxine seems to have a favorable drug-drug interaction profile. It has been reported to be an insignificant to weak inhibitor of the isoenzymes CYP2C9, CYP2D6, CYP1A2, or CYP3A3/4.[59]

A study by Wang et al showed that in patients with depression, there exists a correlation between residual symptoms and social functioning. Patients with residual symptoms were reported to have more severe impairment of social functioning and cognitive dysfunction, with resultant decrease in quality of life. The residual symptoms included depressed feeling, low mood, lack of attention, diminished interest, reduced energy, and anxiety. Therefore, while making a choice of an antidepressant, it is important to consider its efficacy in addressing these residual symptoms to improve social and cognitive functioning and to attain functional recovery and patient satisfaction.[60,61]

Conclusion

This post hoc pooled analysis demonstrates that venlafaxine XR is effective in treating anhedonia and amotivation in patients with MDD. This was demonstrated by significant improvement in the derived measures with venlafaxine XR compared to placebo. Future studies should seek to compare antidepressants on these measures.

Limitations

The limitations of this analysis should be considered in the discussion of results. Although this was a post hoc analysis of data from clinical trials which were not designed to assess the symptoms of anhedonia or amotivation, validated derived measures were used for their measurement, and the results obtained were statistically significant. Due to its post hoc character, no statistical correction for multiple comparisons has been applied.

Another limitation of this analysis is the heterogeneity of the five pooled trials. These studies had enrolled different populations based on inclusion criteria, different study designs, use of fixed versus flexible dosing, dosages evaluated, and duration of the trials. However, basic statistical assumptions like residual and QQ plots were checked, and first-order interaction terms, including the study by treatment interaction, were added to the MMRM model and did not reveal any concern. We recognize the limitations of the LOCF approach while dealing with missing data, as it might introduce methodological bias. Hence, the results of the MMRM model have to be considered as well, because, in general, MMRM models are less prone to bias.

This study included short-term clinical trials, with the studies being conducted for 8 to 12 weeks. It might limit the generalizability of the findings for long-term effects of venlafaxine XR on anhedonia and amotivation.

Another limitation that needs to be considered is the absence of a control treatment group. Therefore, a comparison with another antidepressant cannot be made. While it is not the intent of this analysis, it can be explored in future studies.

While analyzing derived measures could be considered a limitation, we believe that these validated measures are important for clinicians in assessing anhedonia and motivational deficits.

The current study does not assess the impact of the dose of venlafaxine XR on its efficacy in anhedonia and amotivation, and this could be an interesting subject for future studies.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000245.

Data availability statement. Data and materials are not available to be shared publicly.

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Author contribution. All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work. The collective thoughts of all authors have been represented through the paper. All authors have provided their critical review, feedback, additions, further references, and guidance.

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Ethical statement. Primary data from research on human or animal subjects were not used in the analyses for this paper. Secondary, deidentified and anonymized data from previously conducted clinical trials were utilized in this paper. Hence, ethics approval has been deemed not required. Not all studies have been previously published.

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