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REVIEW

Moving from serotonin to serotonin-norepinephrine enhancement with increasing venlafaxine dose: clinical implications and strategies for a successful outcome in major depressive disorder

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ABSTRACT

Introduction: Mental health disorders, especially depressive and anxiety disorders, are associated with substantial health-related burden. While the second-generation antidepressants are widely accepted as first-line pharmacological treatment for major depressive disorder (MDD), patient response to such treatment is variable, with more than half failing to achieve complete remission, and residual symptoms are frequently present.

Areas covered: Here, the pharmacodynamics of venlafaxine XR are reviewed in relation to its role as both a selective serotonin reuptake inhibitor (SSRI) and a serotonin-norepinephrine-reuptake inhibitor (SNRI), and we look at how these pharmacodynamic properties can be harnessed to guide clinical practice, asking the question 'is it possible to develop a symptom-cluster-based approach to the treatment of MDD with comorbid anxiety utilizing venlafaxine XR?.' Additionally, three illustrative clinical cases provide practical examples of the utility of venlafaxine-XR in real-world clinical practice. The place of venlafaxine XR in managing fatigue/low energy, a frequent residual symptom in MDD, is explored using pooled data from clinical trials of venlafaxine XR.

Expert opinion: Venlafaxine XR should be considered as a first-line treatment for MDD with or without comorbid anxiety, and there are clear pharmacodynamic signals supporting a symptom cluster-based treatment paradigm for venlafaxine XR.

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Venlafaxine; major depressive disorder; monoamines; symptom clusters; depression; anxiety

1. Introduction

Mental health disorders are associated with substantial health-related burden, with depressive and anxiety disorders the most disabling [1]. While global health has steadily improved over the past 30 years, there has been no reduction in the global prevalence of mental health disorders, despite evidence for interventions that reduce their impact [2,3]. Worldwide, the COVID-19 pandemic had significantly interrupted the continuity of care of chronic conditions, such as serious mental illness, as well as disrupting their detection and treatment [4,5]. The pandemic has created greater urgency and increased demand for improvements in the diagnosis and treatment of both anxiety and major depressive disorder (MDD) [6–10].

Complete remission of a depressive episode has long been considered the goal of treatment in MDD [11,12]. However, while complete remission is conceptualized as a return to normal functioning with minimal symptoms, it is defined in clinical trials by a cutoff or threshold on standardized scales (Hamilton Depression Rating Scale [HAM-D17] score of ≤ 7; Montgomery-Asberg Depression Rating Scale [MADRS] score of ≤ 10; Clinical Global Impressions Scale [CGI] score = 1), which do not require patients to be completely asymptomatic [13,14]. Importantly, many patients are left with residual symptoms, which frequently include loss of interest, fatigue and low energy, as well as anxiety, preventing complete functional recovery [13,15,16]. Relapse is more common in patients with residual symptoms following treatment of a MDD episode [13,17].

Tricyclic antidepressants (TCA) and mono-amine oxidase inhibitors (MAOI), termed first-generation antidepressants (FGA), were the mainstay of therapy prior to the 1980s. The second-generation antidepressants (SGA) were introduced from 1985 onwards and include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), like venlafaxine, and others including tetracyclics like mianserin and maprotiline [18]. The FGAs are plagued by multiple side effects which many find intolerable. TCAs exert anticholinergic effects including

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Article highlights

- Complete functional recovery should be the treatment goal in patients with major depressive disorder (MDD).
- Dopamine, norepinephrine, and serotonin play important roles in the pathophysiology of MDD.
- Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI), with dose-dependent action on serotonin, norepinephrine, and dopamine reuptake.
- Venlafaxine XR can be started at a lower dose to address depressed mood, psychomotor/agitation, feelings of worthlessness and suicidality, symptoms of serotonergic dysfunction.
- To address specific symptoms in MDD that require increased norepinephrine transmission, higher doses of venlafaxine XR are needed.
- Pooled clinical data demonstrate that venlafaxine XR is associated with significantly greater improvement in lassitude and energy than with placebo.

dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation, and MAOIs may result in hypertensive crisis if taken with certain foods containing excessive amounts of tyramine. The SGAs have increased the likelihood of a clinical response with a reduction in unwanted toxicity [19]. While the second-generation antidepressants are widely accepted as first-line pharmacological treatment for MDD [2], patient response to these agents is variable, with more than half failing to achieve complete remission, and residual symptoms frequently present [13,16,20–23]. This may be due to a number of factors, including the propensity for recurrence in patients with MDD [24], as well as the presence of comorbidities [25]. MDD frequently coexists with many general medical conditions and other psychiatric conditions such as generalized anxiety disorder [25,26]. In the Netherlands Study of Depression and Anxiety (NESDA), 67% of patients with a depressive disorder were also found to have a comorbid anxiety disorder diagnosis [27]. This comorbidity can give rise to both diagnostic and treatment challenges [28].

While the etiology of MDD is not completely understood, the monoamine hypothesis of depression, which suggests that a deficiency in certain neurotransmitters such as serotonin, dopamine, and norepinephrine is the primary cause of depression, is a widely recognized, although incomplete, model [29,30]. More specifically, while the monoamine hypothesis provides a valuable framework, it is increasingly acknowledged that the causal factors for depression are much more complex and multifaceted than simply a reduction in monoamine levels [31–33]. Despite its limitations, the monoamine hypothesis remains a crucial starting point for exploring the biological basis of depression. This hypothesized pathophysiology is supported by the mechanisms of action of antidepressant treatments, which act to elevate the levels of these neurotransmitters in the brain and thus alleviate depressive symptoms [31], with each of these neurotransmitters involved to various extents in each of these symptoms (Figure 1) [32,34].

Venlafaxine is an SNRI, approved for the treatment of MDD, generalized anxiety disorder (GAD), social anxiety disorder and panic disorder in adults [35]. Prolonged-release venlafaxine (venlafaxine XR) has been available as a treatment option for MDD in the US since 1997 [35], and it has been shown to be effective at doses of 75–375 mg/day, with possible dose-dependent effects [36–39].

For the treatment of MDD, the recommended starting dose of venlafaxine XR is 37.5-75 mg once daily [35]. Patients who do not respond to this initial dose may benefit from dose increases up to a maximum of 375 mg/day [35]. The efficacy of venlafaxine XR in MDD was established in three short-term placebo-controlled trials, with doses in the range 75 mg/day to 225 mg/day [35,40,41]. The long-term efficacy of venlafaxine XR in MDD was established in the PREVENT study, in which venlafaxine XR was associated with an estimated probability of recurrence at month 12 of 8% compared with 44.8% for placebo ($P < 0.001$), and with response or remission rates of 93% for venlafaxine XR and 63% for placebo ($P = 0.002$) [42]. An analysis that combined the two 12-month maintenance phases in the PREVENT study, comparing risk of recurrence over 24 months for venlafaxine XR vs placebo, showed a significantly greater cumulative probability of relapse for placebo

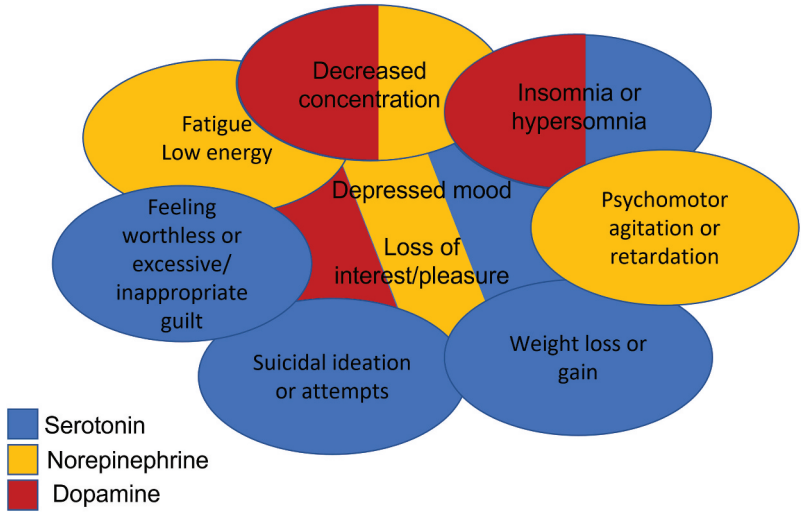

Figure 1. The nine symptoms of MDD from the DSM-5 broadly aligned with the predominant monoamine functions – a hypothesis [32,34].

(47.3%; 95% confidence interval [CI] 36.4, 58.2) than for venlafaxine XR (28.5%; 95% CI 18.3, 38.7); $p = 0.005$ [42]. Venlafaxine XR is thus an established evidence-based treatment in MDD and can be considered a gold standard treatment option, frequently used as a reference treatment in clinical practice [11,43], and included in most clinical practice guidelines as a first-line treatment option in the management of MDD [44–46].

Here, we review the pharmacodynamics of venlafaxine XR in relation to its role as both an SSRI and an SNRI and look at how these pharmacodynamic properties can be harnessed to guide clinical practice. A summary of recommendations from the authors, who formed an expert scientific panel in Vienna, Austria, in November 2022 on the clinical utility of venlafaxine XR, is also provided.

2. Pharmacodynamics of venlafaxine

In-vitro studies have demonstrated that venlafaxine and its active metabolite, O-desmethylvenlafaxine, are potent and selective inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake [35]. Of note, in the rat brain, venlafaxine has a 30-fold higher affinity for serotonin receptors than for norepinephrine receptors [29,47].

There is evidence to suggest that venlafaxine has a dose-dependent effect on monoamine neurotransmitters [29,47,48]. The tyramine pressor response (intravenous injection of tyramine and assessing the associated increase in systolic blood pressure) has been utilized as a proxy for physiological norepinephrine transporter (NET) activity, providing consistent results in terms of the ability of various therapeutic reuptake inhibitors to block NET [49,50]. One study ($n = 46$) that employed this approach was designed to confirm serotonin blockade by venlafaxine at its minimal effective dose in depression of 75 mg/day (for 28 days), and investigate norepinephrine reuptake inhibitor action with higher doses (titration to 225 mg/day at day 5 then maintained at 375 mg/day from days 8 to 28) [48]. In this study, venlafaxine significantly reduced whole-blood serotonin levels, by more than 75%, in both the low- and high-dose groups, but the pressor response to tyramine was significantly attenuated only in the high-dose group. The researchers concluded that, at 75 mg/day, venlafaxine does not produce relevant binding to the NET, thus acting as an SSRI, with clinically relevant norepinephrine reuptake blockage occurring only at higher doses.

Further evidence of a dose-dependent action comes from a study showing inhibition of the NET in patients with MDD at venlafaxine doses of 225 and 300 mg/day, but not at lower doses (75 or 150 mg/day) [49]. Moreover, in a study in healthy volunteers, venlafaxine 375 mg/day, but not 75 mg/day, was shown to significantly blunt the pressor response to tyramine [51]. Evidence suggests that at a dosage of 75 mg/day, venlafaxine XR is sufficient for some patients, but that higher doses are associated with additional benefits – suggesting that a stepwise regimen may be useful in cases of nonresponse, increasing the dosage to upper limits before considering venlafaxine XR treatment to be ineffective [52].

Venlafaxine XR may also help to address residual symptoms, such as fatigue, decreased energy and lack of interest, which have been reported to be relieved by the use of an SNRI [53]. Moreover, when there is poor response with an SSRI, the use of an SNRI has been shown to improve outcomes in patients with depression. For example, switching patients with MDD to duloxetine after lack of response to fluoxetine has been shown to produce improvements in depression [54], with similar findings for patients who had failed to respond to or who were intolerant of SSRIs and then started receiving venlafaxine XR [55,56].

Importantly, when selecting a treatment during the acute phase, it is essential to consider the efficacy, acceptability, tolerability, and safety. Moreover, since treatments prescribed for an acute depressive episode are typically continued into maintenance treatment, it is important to also assess the treatment's effectiveness and suitability for the maintenance phase [57,58]. For patients who will not receive maintenance treatment or have poor adherence during the treatment of acute episodes, it is essential to provide adequate psychoeducation about the risk of antidepressant discontinuation syndrome [59,60]. For instance, it is crucial to educate patients about the need to very gradually taper down medications such as venlafaxine once these medications are discontinued.

3. Symptom clusters in MDD

Several studies have been published looking at a symptom-cluster-based approach to the treatment of MDD [61–64]. Some symptoms of MDD are not adequately addressed by serotonergic antidepressants, such as loss of pleasure, loss of interest, fatigue and loss of energy, and for these symptoms, different classes of antidepressants may be more useful [64]. One study looked at a model that included MDD with 1 of 4 common symptoms clusters (anxiety, fatigue, insomnia or pain) and provided recommended drug classes, and drug classes to avoid, for each with the aim of equipping 'primary care doctors with a structured treatment strategy to deliver optimal patient-centered care in the battle against depression' [62]. In this work, researchers recommended SSRI treatment for MDD with anxiety, an SNRI or norepinephrine dopamine reuptake inhibitor for MDD with fatigue, a noradrenergic specific serotonergic antidepressant or a serotonin antagonist reuptake inhibitor for MDD with insomnia, and a tricyclic antidepressant or SNRI for MDD with pain. The 2020 clinical practice guidelines for mood disorders by The Royal Australian and New Zealand College of Psychiatrists [45] and the 2016 clinical guidelines for MDD from the Canadian Network for Mood and Axiety Treatments (CANMAT) [44] provide examples of a cluster-based approach, outlining a pharmacological treatment strategy that considers symptom clusters or clinical profiles, which is described in detail in Table 1. Importantly, there is clinical evidence to support such an approach, for example, in a case series pilot study, utilizing four symptom clusters (anxiety/irritability cluster, fatigue/anhedonia cluster, insomnia cluster, and chronic pain cluster), it was shown that symptom-cluster-matching antidepressant treatment was an effective approach [63]. In addition, using rating scales in depression to identify symptom clusters, researchers utilized data from 4706 patients and identified three symptom clusters, broadly described as mood/emotional symptoms,

Table 1. A symptom cluster approach to pharmacological treatment of MDD as recommended by Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Royal Australian and New Zealand College of Psychiatrists [44,45].

Symptom	Choice of antidepressant
Anxious distress	Use an AD with efficacy in GAD – SSRIs, SNRIs, bupropion
Fatigue	Bupropion, SSRIs
Melancholia (anhedonia, empty mood, psychomotor agitation/ retardation)	No specific ADs have demonstrated superiority. TCAs and SNRIs have been studied
Atypical symptoms (hypersomnia, increased appetite, leaden paralysis)	No specific ADs have demonstrated superiority. Older studies found MAOIs superior to TCAs
Sleep disturbance-related symptoms	Agomelatine, mirtazapine, quetiapine, trazodone
Cognitive difficulties (learning, memory, decision-making)	Duloxetine, vortioxetine, bupropion, SSRIs, moclobemide
Somatic symptoms	
Pain	Duloxetine, TCAs, SNRIs
Anergia	Duloxetine

AD, antidepressant; GAD, generalized anxiety disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressants; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder.
Adapted from Kennedy et al. 2016 and Malhi et al. 2020.

insomnia symptoms and atypical symptoms (including psychomotor symptoms or suicidal ideation) and demonstrated that different antidepressants had different efficacy in these clusters [61].

4. Efficacy of venlafaxine in patients with MDD with low energy

The place of venlafaxine in managing fatigue, or low energy, a commonly observed residual symptom in MDD [13,15,16] was explored by members of the expert panel using pooled data from clinical trials of venlafaxine XR in the treatment of MDD. This data included information from short-term, double-blind, placebo-controlled Wyeth/Pfizer-sponsored studies of venlafaxine XR at doses of 75–225 mg/day for the treatment of MDD, which were used in a pooled analysis to explore the efficacy of venlafaxine in MDD [65]. Researchers looked at measures of fatigue/energy from the efficacy assessments that were used in the trials that were included in this pooled analysis, specifically HAM-D (sum of work and activities, and retardation) and MADRS (lassitude) scoring systems. Using a mixed model for repeated measures (MMRM), with data from four placebo-controlled venlafaxine XR studies, venlafaxine XR was found to be associated with a significantly greater improvement from baseline than placebo in lassitude score as early as week 3 ($p = 0.0307$), and in energy (sum of work and activities, and retardation from HAM-D) score from week 2 ($P = 0.0049$), with these differences increasing over time until the end of the study at week 8 (both $p < 0.001$). On ANCOVA analysis of change at week 8, after controlling for study, treatment and baseline scores, the least squares mean (LSM) differences between venlafaxine XR and placebo were −0.52 (95% CI −0.72, −0.32; $P < 0.0001$) for lassitude and −0.52 (95% CI −0.71, −0.33; $p < 0.0001$) for energy (Figure 2).

5. Conclusions

Venlafaxine XR can be considered as a single agent that is able to act as both an SSRI and an SNRI, depending on the dose used. At low doses, venlafaxine can be considered to primarily act as an SSRI and may therefore be effective for those symptoms more likely to benefit from increased serotonin transmission, and once these symptoms are controlled, the dose of venlafaxine can be increased, if necessary, to further enhance serotonin transmission and increase norepinephrine, to achieve complete symptom remission and functional recovery. In our experience, when a patient presents with concomitant depression and anxiety, it is generally more effective to prioritize the treatment of anxiety first (for instance, by enhancing serotonin transmission). Once the anxiety symptoms are better managed, we can then focus on empowering norepinephrine transmission to address the depressive symptoms, such as reduced energy, which may benefit from increased norepinephrine. We have frequently observed that anxiety symptoms may worsen if norepinephrine transmission is increased too soon and too quickly. On the other hand, we have seen that a more gradual and slightly delayed increase in norepinephrine transmission, once anxiety has improved, is often beneficial for treating depressive symptoms that have not responded to increased serotonin transmission and that can benefit from an increase in norepinephrine. A symptom cluster approach to the treatment of MDD presenting with low interest and energy has the potential to improve the response rates to first-line venlafaxine XR treatment.

6. Clinical practice

Is it possible to develop a symptom-cluster-based approach to the treatment of MDD with comorbid anxiety utilizing venlafaxine XR?

6.1. Case 1 - low-dose venlafaxine XR

A 28-year-old woman presented with an episode of depression that started about 3 months prior. No trigger factors were identified. She reported feeling down, extremely sad, anxious, tense, and irritable, crying easily, overreacting to minor things, and not thinking enough before reacting. She was not sleeping well and never felt rested. She was no longer wearing makeup, struggling to make even minor decisions, such as what to do, what to eat, and whom to call. She was experiencing difficulty thinking or concentrating; she was unable to follow a conversation or remember what she had just read, and rarely watched TV because she was unable to pay enough attention. She reported feeling tense and anxious and

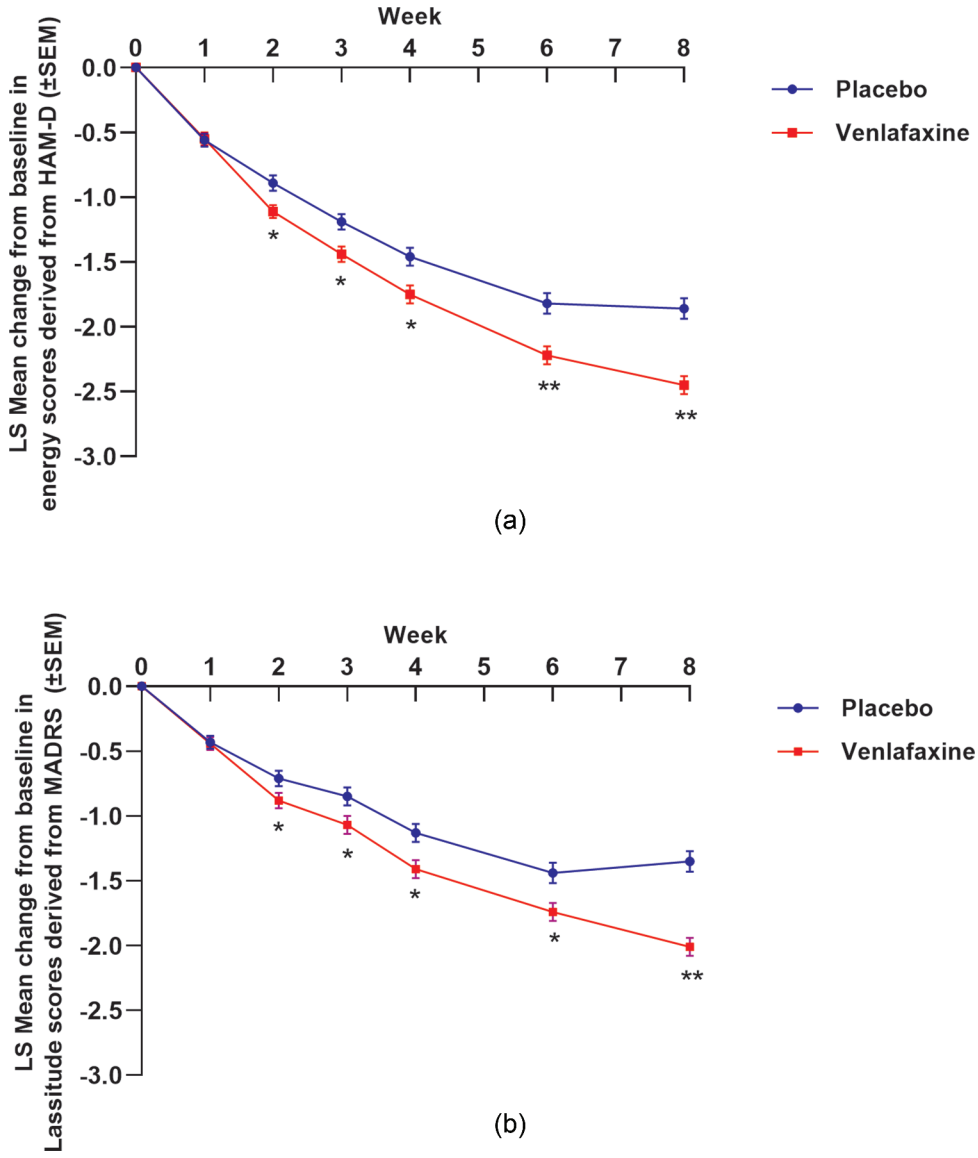

Figure 2. Mixed model repeated measures (MMRM) analysis of change from baseline for venlafaxine versus placebo in energy (a) and lassitude (b) (*p<0.05, **p<0.001).

experiencing panic attacks at night, that contributed to her insomnia.

She was prescribed venlafaxine XR 37.5 mg a day, to be increased to 75 mg a day after one week, along with alprazolam 0.25 mg at night, to be increased to 0.25 mg twice a day after two days. After 10 days on venlafaxine XR 75 mg and alprazolam 0.50 mg a day, she reported feeling somewhat better, but still tense, sad, and worried. She was no longer experiencing insomnia, and was less tired, but still did not feel her usual self. After a further week on venlafaxine XR 75 mg and alprazolam 0.50 mg, she reported continued, but marginal, improvement, and still felt depressed and anxious. Venlafaxine XR was increased to 150 mg a day and alprazolam to 0.75 mg a day (0.25 mg three times a day). After two more weeks, she reported feeling well, back to her best, able to think straight and that she was no longer anxious, worried, or sad, and was able to concentrate and make decisions; she felt happy and normal. Alprazolam was gradually tapered off and the patient remained completely stable on venlafaxine XR 150 mg/day.

6.1.1. Expert comment

In this case, venlafaxine XR (an SNRI) at 150 mg a day appeared to have been effective in reducing her symptoms of depression, anxiety, irritability, and impulsivity. Additional short-term use of alprazolam (a benzodiazepine) effectively treated her severe, disabling anxiety with panic attacks.

6.2. Case 2 – high-dose venlafaxine

A 42-year-old female presented following a referral from her gynecologist who suspected depression on the basis of complaints of a decrease in libido, lack of energy and tiredness, vague complaints of pain in the spine and joints, and feeling of discouragement in various life situations, without any

apparent reason. The patient stated, 'everything is getting boring.' There were no notable findings on laboratory examination. The patient had no history suggestive of mania, and no use of alcohol or other substances. Physical examination revealed good general condition. She had a family history of depression, with both her mother and a maternal aunt having had a history of depressive episodes, and an alcoholic maternal uncle, but not of bipolar disorder. Psychological examination revealed depressed mood and anhedonia, cognitive deficit, increased irritability, along with physical symptoms such as vague pain, intermediate insomnia and very low energy. She did not complain of any psychotic symptoms.

She was initially prescribed citalopram 40 mg/day. This was subsequently decreased to 20 mg/day, and discontinued after 5 days, at which time venlafaxine XR 75 mg/day was initiated, and increased to 150 mg/day after one week. After two weeks, she reported a mild improvement, but that it was not sufficient. Venlafaxine XR was increased to 225 mg/day and, one week later, she reported having improved quite a lot, but was still unable to do things due to feeling constantly tired and slowed down. Venlafaxine XR was increased further, to 300 mg/day and, after another 2 weeks, she returned with a smile on her face and was neatly dressed. She felt like her energy and life were back. She was able to think straight again, no longer feeling like she was walking in water or driving a car with the brakes on. She said 'I can walk, run, think, and get things organized. My mood is back where it should be, and I would like to go back to work and get back to my best life.'

6.2.1. Expert comment

Venlafaxine XR was chosen for its dual action as an SNRI, due to the clinical picture of major depression, with both depressive mood and anhedonia, associated with low energy, insomnia, somatic symptoms, and cognitive impairment. SNRIs may be better suited for such patients than SSRIs, as they have a fast onset of action, as well as a low likelihood of adverse effects on weight and sexual function, which enhances adherence to treatment. In this case, venlafaxine XR was prescribed, with the dose gradually increased until it reached 300 mg/day. This treatment appeared to be effective in reducing symptoms of fatigue, slowed thinking, psychomotor retardation, and difficulty with daily activities,

6.3. Case 3 – sequential treatment

A 42-year-old woman sought treatment from her family physician for feelings of sadness, crying spells, anxiety, muscle tension, poor concentration, and insomnia, which had gradually worsened over the 6 months following the unexpected death of her father. Her medical history included hypothyroidism (on replacement therapy) and morbid obesity with a body mass index (BMI) of 65.

Buspirone 10 mg three times daily was prescribed, which was switched to paroxetine 20 mg once a day within 6 weeks, due to lack of response. Paroxetine helped her symptoms considerably within 3 weeks but caused fatigue and weight gain (BMI = 67), and she was referred for psychiatric review. She reported constant worry about daily events, low and irritable mood, non-refreshing sleep, muscle tension, low energy, and a progressive sense of helplessness and frustration. She was constantly tense and restless, with difficulty concentrating and making decisions, and mild, frequent headaches and stomach pain. She had lost interest in her usual activities, including church and family functions. She was diagnosed with a major depressive episode and generalized anxiety disorder (see Table 2; visit 1).

Her treatment was then switched from paroxetine to venlafaxine XR 75 mg/day, and a recommendation to gradually increase her level of physical activity. Her symptoms improved partially after two weeks (visit 2; Table 2), with no side effects and most importantly no weight gain or fatigue, so the dose of venlafaxine XR was increased to 150 mg/day. Four weeks later, she had considerable improvement in depressive and especially anxiety symptoms, with decreased worrying, muscle tension, restlessness and feeling tense (visit 3; Table 2). Despite her continued anhedonia and low motivation, she hired a personal trainer to increase her level of activity. However, she still had complaints of low energy levels and fatigue. At that point it was decided to increase the dose of venlafaxine XR to 225 mg/day, due to the incomplete resolution of symptoms. A month later, she had almost complete remission of symptoms, with remarkable improvement in functioning (visit 4; Table 2). Persistent symptoms included infrequent low mood days, and some difficulty with sleep and concentration. She had resumed weekly church attendance, was present at family functions, and was exercising 4 to 5 times a week. Approximately 1 year after starting treatment, she remained asymptomatic, was continuing to work with her personal trainer, and her anhedonia and poor motivation had resolved (visit 8; Table 2).

6.3.1. Expert comment

It is important to find a treatment that provides the best balance between efficacy and adverse effects and to monitor

Table 2. Summary of clinical scale scores per visit for case report 3.

Visit	Week	PHQ-9	GAD-7	SDS	BMI (kg/m^2)
1	0	23	18	20	67
2	2	20	13	16	67
3	6	13	7	9	66
4	10	7	0	0	65
8	54	3	0	0	60

GAD-7, general anxiety scale 7-item; PHQ-9, patient health questionnaire 9-item; SDS, self-rating depression scale.

both psychiatric and non-psychiatric clinical features (such as BMI). To achieve full symptomatic remission, it may be necessary to increase the dose of venlafaxine, in this case to 225 mg/day. As well illustrated in this case, venlafaxine XR was shown to have efficacy over the long term. Of note, a return to physical exercise and social activities were also an important part of recovery.

7. Expert opinion

On October 15th, 2022, an Expert Scientific Forum, sponsored by Viatris, was convened to discuss the treatment challenges at different stages of the patient journey in MDD, and the clinical utility of venlafaxine. Several barriers to treatment in MDD were identified, some of which were noted to contribute to the frequent problem of patients discontinuing treatment due to a lack of understanding of their disorder. While the specific obstacles to treatment for Major Depressive Disorder (MDD) can vary across healthcare systems, the following are commonly encountered barriers:

a. The stigma that still exists around mental health.
b. The lack of time available for patient consultations.
c. Both patients and practitioners often want a 'quick fix.'
d. Funding, availability and access to medications.
e. The heterogeneity of depression and the lack of an ideal medication for every patient.

There was a general consensus of the panel that venlafaxine XR should be considered as a first-line treatment for MDD with or without comorbid anxiety, and that there are clear pharmacodynamic signals supporting a symptom cluster-based treatment paradigm for venlafaxine XR. It was noted that if there is a need to address specific symptoms requiring increased norepinephrine transmission, higher doses of venlafaxine XR are needed. This differential dosing can be helpful in clinical practice, as venlafaxine XR can be started at a lower dose to address those symptoms that should be treated first (depressed mood, psychomotor/agitation, feelings of worthlessness and suicidality), and then residual symptoms (such as loss of energy and cognitive impairment) may be able to be treated by increasing the dose of venlafaxine XR. Moreover, venlafaxine XR is uniquely placed to target functioning and energy due to its action as an SNRI at higher doses; in patients who are improving with treatment, but in whom recovery is not complete, and there still are energy deficits, the dose of venlafaxine XR can be increased, to a maximum of 375 mg/day, whereas for a patient with MDD with anxiety as the main symptom requiring treatment, venlafaxine XR can be continued at a dose of 75 mg/day. While there may be some concern around the potential for adverse effects at these higher doses, there was a general consensus that they are unlikely to significantly alter the risk-benefit ratio for those patients who do not respond fully to lower doses. Clinical studies have provided evidence that patients with depression may transition between different subtypes of the disorder throughout their lifetime and potentially even within a single episode. According to the expert panel, an approach focused on treating symptoms and symptom clusters of depression and comorbid diagnoses, rather than relying on the identification of specific subtypes of depression (such as atypical or melancholic depression) may yield greater success. (Figure 1) [66].

Based on its pharmacological properties, venlafaxine can be considered a gold standard for treating MDD, regardless of the presence of comorbid anxiety. It is particularly suitable for patients who may benefit from targeting different symptoms with varying doses, based on the specific symptoms of depression exhibited by each individual. Adopting a personalized approach that tailors medication choice and dosage to the unique symptom profile of each patient shows promise for enhancing treatment effectiveness. While the SGAs have similar effectiveness, it is likely that there are some clinically significant differences between individual agents [67]. However, there are no studies that directly compare the impact of these drugs on symptoms of MDD such as energy, fatigue and lassitude. The experts are therefore of the opinion that this topic warrants further research through comparative studies and meta-analysis.

While a categorical classification system like the DSM is essential for diagnosis, incorporating a symptom-based approach could complement a DSM-based diagnosis, and help guide treatment decisions. Further research is required to establish this dimensional approach for medication selection and optimizing dosage. If new evidence supports the feasibility of such an approach, personalized treatment based on individual symptoms could become standard practice.

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