Extended-release formulation of venlafaxine in the treatment of post-traumatic stress disorder

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There is abundant evidence for abnormalities of both norepinephrine and serotonin neurotransmitter systems in post-traumatic stress disorder (PTSD). Venlafaxine extended-release formulation (venlafaxine XR) is a serotonin and norepinephrine re-uptake inhibitor with antidepressant and anxiolytic properties relevant to the pathophysiology of PTSD. Venlafaxine XR is currently approved for the treatment of panic disorder, generalized anxiety disorder and social anxiety disorder, as well as major depression in adults, based on a number of randomized, double blind, placebo-controlled clinical trials. Limited data also demonstrate that venlafaxine XR maintains a therapeutic response for more than 6 months in these anxiety disorders. Venlafaxine XR has demonstrated short- and long-term efficacy for the treatment of PTSD in two recent randomized, double-blind, placebo-controlled clinical trials, although it has not been extensively studied for PTSD, compared with other anxiety disorders. This review focuses on the potential role of venlafaxine XR in the treatment of PTSD, based on currently available evidence.

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The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have previously been the mainstay of pharmacological treatment for various anxiety disorders, including post-traumatic stress disorder (PTSD). However, since the 1980s, selective serotonin re-uptake inhibitors (SSRIs) have rapidly replaced the pivotal role of TCAs and MAOIs in the treatment of PTSD, owing to safety and tolerability issues, such as anticholinergic side effects, overdose toxicity and a propensity toward hypertensive crisis. Currently available data have demonstrated that SSRIs may be the first-line pharmacological agents for the treatment of PTSD, based on a number of randomized, double blind, placebo-controlled clinical trials (RCT), and paroxetine and sertraline have been approved for PTSD by the US FDA [1,2].

Although emerging data have established the efficacy and safety of SSRIs in the treatment of PTSD [1,2], various factors other than PTSD symptoms, such as gender, type of trauma and symptom clusters, may limit and compromise the effects of SSRIs [3]. In fact, it was not possible to separate sertraline and fluoxetine from placebo in short-term placebo-controlled clinical trials in military veterans with PTSD [3,4]. In addition, chronic PTSD was found to be less likely to respond to pharmacological treatment than new-onset cases [3].

A recent preliminary study has subclassified PTSD into noradrenergic system-sensitized and serotonin (5-hydroxytryptamine [5-HT]) system-sensitized neurobiological subgroups, suggesting that medications with different pharmacological profiles may exert different therapeutic benefits in the treatment of PTSD [5]. In this context, the extended-release (XR) formulation of venlafaxine, which is classified as a serotonin and norepinephrine re-uptake inhibitor (SNRI), may be another efficacious agent in the treatment of PTSD. This review focuses on the potential role of venlafaxine XR in the treatment of PTSD, as well as providing a brief overview on PTSD based on currently available evidence.

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Prevalence of PTSD

The estimated lifetime prevalence of PTSD is 7.8%, and prevalence is greater in women than in men [6]. The most common traumas associated with PTSD are exposure to combat and witnessing of violence among men, and rape and sexual molestation among women [6]. The lifetime prevalence of PTSD in patients within a primary care setting ranged from 12 to 25% [7,8]. Furthermore, nearly half (48%) of the patients with PTSD in general medical practice do not appear to receive appropriate and adequate psychiatric intervention, indicating that a substantial proportion of primary care patients with PTSD are receiving inadequate or no treatment [9,10].

Clinical features of PTSD

Diagnostic criteria for PTSD basically requires the development of distinctive symptom clusters, such as re-experience, avoidance and hyperarousal, following exposure to extreme traumatic events that are associated with feelings of intense fear, helplessness or horror, and resulting in functional impairment or distress [11]. Some studies have demonstrated that PTSD can continue for 6–12 months after experiencing trauma, although the longitudinal course of PTSD can vary and depends on individual vulnerability, socioenvironmental factors and psychiatric comorbidity [12,13]. Comorbidity is also common in patients with PTSD. In the National Comorbidity Survey, approximately 80% of patients with PTSD had a lifetime history of at least one other psychiatric disorder (major depression > social anxiety disorder [SAD] > dysthymia > generalized anxiety disorder [GAD]), and there were some differences between male (i.e., alcohol/drug dependence and behavioral problems) and female (i.e., panic disorder and agoraphobia) comorbidity [6]. In addition, somatic symptoms and physical illness were prevalent in patients with PTSD [14,15], especially among those with physical injury resulting from traumatic events [16]. Diverse psychiatric manifestations that may be derived from the complicated interactions of distinctive PTSD symptom clusters are presented in FIGURE 1. In addition, increased lifetime prevalence of suicidal ideation has been reported, and overall, patients with PTSD have an increased rate of attempted suicide, as much as six-times that in the general population [17,18].

Disturbance in serotonergic &/or noradrenergic neurotransmission in PTSD

Although controversy exists regarding the exact role of 5-HT in the development of PTSD, decreased platelet binding of [^{3}H]-paroxetine and defects in the 5-HT transporter system have been consistently reported [19–23]. Other supportive findings include the association of a low number of 5-HT binding sites with treatment response to SSRIs [19] and a lower level of plasma 5-HT in patients with PTSD [24].

Noradrenergic dysregulation in patients with PTSD is also observed, with increased heart rate and blood pressure when they are exposed to visual and auditory reminders of trauma. Elevated 24-h urinary noradrenaline has been consistently reported in patients with PTSD, compared with those with other psychiatric disorders and control groups [24–27]. TCAs have also demonstrated a therapeutic effect in the treatment of PTSD symptoms, such as hypervigilance and heightened attention [1,2,28,29].

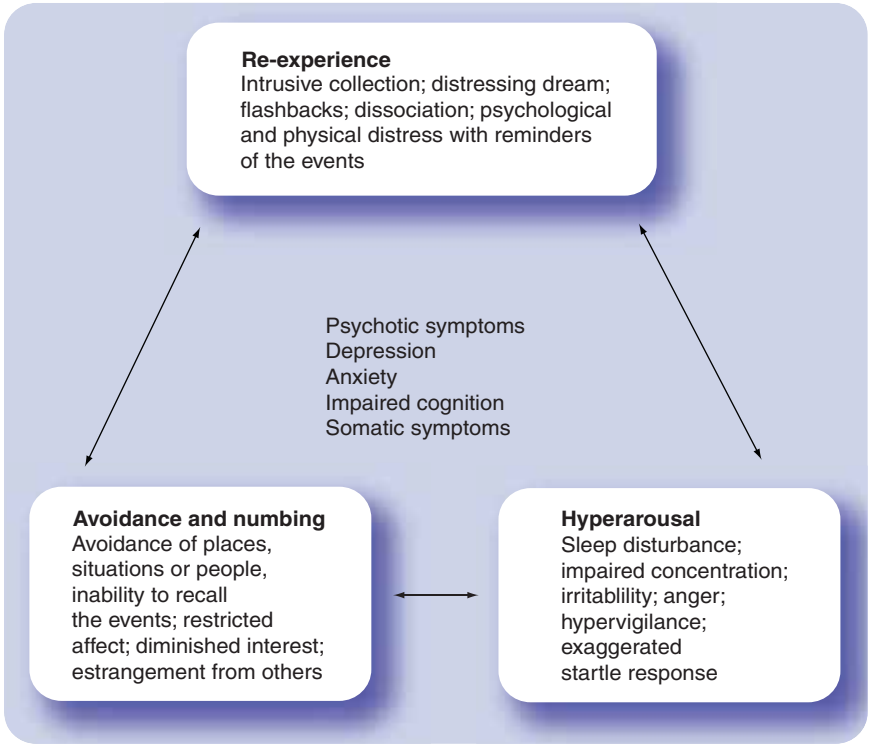


Figure 1. Psychiatric symptoms possibly derived from distinctive symptom clusters of post-traumatic stress disorder.

Some studies have suggested that the aberration of 5-HT and noradrenaline may play a role in the pathophysiology of PTSD. An interesting study used *m*-chlorophenylpiperazine (m-CPP) as a probe for serotonergic activity and yohimbine as a probe for noradrenergic activity to investigate the possibility of neurobiological subgroups of PTSD based on subclassification by 5-HT or noradrenaline predominance [5]. In that study, yohimbine-induced panic attacks appeared to occur in different patients from those with m-CPP-induced panic attacks, and only 19% of patients had panic attacks induced by both pharmacological probes, which was partly supported by a subsequent study [24].

Taken together, the alterations in noradrenaline and 5-HT might be relevant to the clinical manifestations of PTSD (i.e., so-called hypervigilance), which include exaggerated startle, irritability, autonomic hyperarousal and impulsivity [30].

However, the currently limited available evidence for alterations in 5-HT and noradrenergic neurotransmission does not enable a definite conclusion about the precise contribution of both neurotransmitters to the development of PTSD. Nevertheless, established efficacy of SSRIs and TCAs in treating this disorder suggests that medication combining 5-HT and noradrenaline effects, such as venlafaxine XR, might have potential use in the treatment of PTSD, although the exact mechanism of action of the drug for PTSD has not yet been fully elucidated.

Introduction to venlafaxine XR

The immediate-release (IR) formulation of venlafaxine was introduced to the market in 1994, as the first of a newer generation of dual-mechanism antidepressants (SNRIs), with the expectation of greater efficacy compared with single-mode action antidepressants.

Venlafaxine might be more beneficial than SSRIs in cases of treatment-resistant depression, severe depression and remission of depressive symptoms, although few quality head-to-head comparison studies are available [31–38]. With the recent advent of several new formulations of existing antidepressants to overcome their significant shortcomings, venlafaxine XR was introduced to the market in 1997, initially for treatment of major depression and with subsequent indications for GAD, SAD and panic disorder.

Comparison of venlafaxine XR & IR formulations

Drug design

Venlafaxine XR is designed as an XR capsule with a microencapsulated formulation, whereas the IR formulation is a water-soluble compressed tablet. The release of active venlafaxine XR is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent [39].

Pharmacodynamics

The pharmacodynamic profile of venlafaxine XR is no different from that of the IR formulation, although its pharmacokinetic profile has been somewhat changed. Venlafaxine and its active metabolite, *O*-desmethyl venlafaxine (ODV), inhibit presynaptic 5-HT and norepinephrine re-uptake. Unpublished manufacturer's data indicate that venlafaxine and ODV have different potencies against 5-HT and norepinephrine transporters, with ODV being relatively more potent than venlafaxine against norepinephrine [WYETH PHARMACEUTICALS INC., UNPUBLISHED DATA]. Venlafaxine has a weak effect on dopamine re-uptake. Venlafaxine and ODV have no significant affinity for muscarinic, histamine H1 or α_1-adrenergic receptors *in vitro*. Finally, venlafaxine and ODV do not possess MAO inhibitory activity [39]. The inhibition of noradrenaline re-uptake may begin at doses of 75 mg/day, thereby supporting a relevant clinical effect [40].

Pharmacokinetics

Compared with the IR formulation, venlafaxine XR releases the active drug much more slowly into the gastrointestinal tract. Venlafaxine XR has a lower peak plasma concentration (C_{max}: 150 ng/ml for XR vs 225 ng/ml for IR) and longer time to peak plasma concentration (t_{max}: 5.5 h for XR vs 2 h for IR) [39,41]. The active metabolite ODV also extends the effective half-life of venlafaxine XR, which probably accounts for the acceptability of its once-daily dosing, compared with the twice-daily dosing required for the IR formulation [39,42]. The lower C_{max} and effective half-life of venlafaxine XR might be expected to induce less nausea and dizziness at the initiation of therapy, and to possibly increase patient compliance, as well as to reduce the possibility of a dose-dependent elevation in blood pressure [42]. A higher plasma level of venlafaxine plus ODV has been significantly associated with a more rapid decrease in depressive symptoms, leading to the hypothesis that exposure to a more potent noradrenergic therapeutic agent may be beneficial for the early improvement of depression [43].

Owing to its slow release rate, venlafaxine XR has the advantage of a slower absorption rate while maintaining the same bioequivalence as the IR formulation. The bioavailability of both venlafaxine and ODV is similar between equal daily doses of venlafaxine XR and IR, but venlafaxine XR can reduce daily fluctuations in the plasma concentrations of venlafaxine and ODV that can occur with the IR formulation [39]. In summary, venlafaxine XR has a lower C_{max}, longer t_{max} and longer effective half-life than the IR formulation, while providing the same bioequivalence, which suggests the convenience of switching from the IR formulation to venlafaxine XR [44].

Drug interaction

The concomitant use of venlafaxine with drugs that potentially inhibit both cytochrome P450 (CYP) 2D6 and 3A4, the primary metabolizing enzymes for venlafaxine, has not been well studied [45]. However, it is known that the combination of venlafaxine with risperidone, haloperidol and desipramine leads to altered pharmacokinetics; therefore, the dosages of CYP2D6 substrates may need to be adjusted when administered with venlafaxine [41].

Indications

Venlafaxine XR has been approved for the treatment of major depression, SAD and GAD, and recently for panic disorder by the FDA. The IR formulation has been approved only for major depression. Venlafaxine XR has not yet been approved for the treatment of PTSD.

Comparative efficacy & safety

The efficacy and safety of venlafaxine XR (mean dose: 124–140 mg/day) and IR (mean dose: 115–125 mg/day) have been directly compared in 278 outpatients with major depression in a 12-week RCT [46]. Although both formulations demonstrated comparable antidepressant efficacy over the placebo-treated group, venlafaxine XR was superior ($p < 0.05$) to the IR formulation at week 8 based on the Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression-Severity score (CGI-S), and at week 12 based on all the efficacy measures.

The most common adverse event in each formulation group was nausea (45% in each drug-treated group vs 10% in the placebo group), which was mainly observed in the first week of treatment and decreased to approximately 10% by week 2 [46]. There were no significant differences in the frequency of adverse events between the two formulations, with the exception of a higher incidence of male sexual dysfunction with venlafaxine XR, which might be related to the sustained plasma concentrations of active metabolites in patients treated with venlafaxine XR [42,46]. A risk/benefit analysis has been conducted to compare the two formulations, using linear ratio measures for dizziness, insomnia, nausea, nervousness, somnolence and a composite of anticholinergic events [47]. In that study, a statistically significant benefit-to-risk ratio of at least 2:1 was demonstrated for venlafaxine XR over venlafaxine IR with regard to nausea and dizziness, which might cast new light on the adverse events of the two formulations [47].

Head-to-head comparisons between venlafaxine XR and IR in placebo-controlled clinical trials are too few to provide a definite conclusion as to which formulation is superior; in particular, there are no currently available RCT data related to anxiety disorders. Considering the established efficacy of both formulations compared with placebo or active comparators in several placebo-controlled clinical trials of treatment for major depression and various anxiety disorders, and given their similar pharmacodynamics, it appears that there are no differences in antidepressant and antianxiety efficacy between the two formulations. Despite the differences in pharmacokinetics between the two formulations, the current paucity of direct comparisons does not warrant any conclusive remarks concerning their differential safety and tolerability profiles. Clearly, adequately powered, well-designed placebo-controlled clinical trials should be conducted to demonstrate any differences in terms of efficacy and tolerability between the two formulations.

Clinical data for venlafaxine XR in the treatment of PTSD

Efficacy studies of venlafaxine XR in PTSD

Overview

The efficacy of venlafaxine XR for the treatment of GAD, SAD and panic disorder has been established in a number of short- and long-term (8–28 weeks) placebo-controlled clinical trials; however, there has been a limited number of placebo-controlled clinical trials for the treatment of PTSD [48,49]. In one study, venlafaxine XR was compared with sertraline and placebo in 538 outpatients for 12 weeks [48]. Patients were randomly assigned to receive placebo or flexible doses of venlafaxine XR (37.5–300 mg/day) or sertraline (25–200 mg/day). TABLE 1 presents the details of the study procedure.

A subsequent 6-month RCT evaluated the long-term efficacy of venlafaxine XR (37.5–300 mg/day) in 329 outpatients with PTSD (TABLE 1) [49].

Results of efficacy

Short-term RCT (12 weeks)

In the first RCT, venlafaxine XR ($p = 0.015$ vs placebo) demonstrated superior efficacy to placebo by an observed difference (OD) of -7.3 over a 12-week period, based on an assessment of changes in the 17-item Clinician-administered PTSD Scale (CAPS-SX17) score from baseline to end point (last observation carried forward [LOCF]) [48]. Sertraline failed to demonstrate any efficacy ($p = 0.081$ vs placebo) based on this primary end point, while there was no significant difference compared with that of venlafaxine XR (OD = -2.1; $p = 0.494$) (FIGURE 2). A significantly greater change in the CAPS-SX17 score from baseline for venlafaxine XR compared with placebo from week 2 was found throughout the study. Regarding CAPS-SX17 cluster scores, venlafaxine XR demonstrated significantly greater improvement than placebo for avoidance/numbing ($p = 0.021$ vs placebo) and hyperarousal ($p = 0.024$ vs placebo), although there was no difference in re-experience ($p = 0$ 0.195 vs placebo). Sertraline was superior to placebo only for the avoidance cluster score ($p = 0.033$ vs placebo) (FIGURE 2) [48].

The efficacy of venlafaxine XR based on changes in the patient-rated Davidson Trauma Scale (DTS) scores was more consistent than that based on the CAPS-SX17 scores. Venlafaxine XR showed greater improvement than placebo for changes in the DTS total score (OD= -8.3, $p = 0.015$) and the intrusion (OD = -2.4; $p = 0.031$), avoidance/numbing (OD = -3.3; $p = 0.029$) and hyperarousal cluster scores (OD = -2.5; $p = 0.025$), whereas sertraline did not differ from placebo for any measured DTS scores (FIGURE 2) [48].

After 12 weeks of treatment, remission (CAPS-SX17 $\leq$20) rates were 30.2% for venlafaxine XR, 24.3% for sertraline and 19.6% for placebo. The remission rate for venlafaxine XR was significantly different from that of placebo at 12 weeks ($p < 0.05$ vs placebo), and significant rate differences between venlafaxine XR and both sertraline and placebo were observed as early as 4 weeks ($p < 0.05$ vs placebo; $p < 0.01$ vs sertraline) and 6 weeks ($p < 0.001$ vs placebo; $p < 0.05$ vs sertraline). In contrast, sertraline failed to demonstrate a significant difference in remission rate compared with placebo at any time during the study [48].

The majority of other secondary outcomes also significantly favored venlafaxine XR over placebo, with the exception of the Global Assessment of Functioning (GAF) score (Sheehan Vulnerability to the Effects of Stress Scale [SVS]: $p = 0.021$ vs placebo; Clinical Global Impression-Severity score (CGI-S: $p = 0.007$ vs placebo; 17-item Hamilton Depression Rating Scale [HAM-D-17]: $p = 0.039$ vs placebo). Sertraline demonstrated marginal significance only for changes in the CGI-S score ($p = 0.046$ vs placebo) [48].

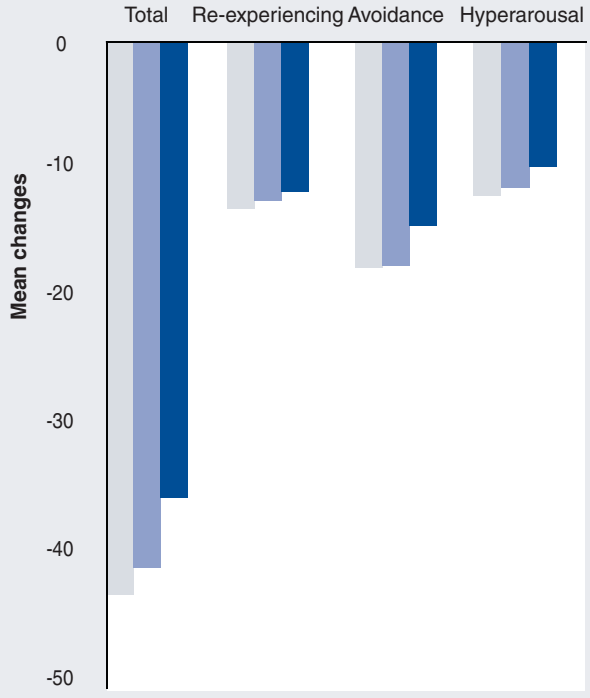
Patient self-rating of functioning, satisfaction and quality of life, as measured by total and cluster scores on the Quality of Life Enjoyment and Life Satisfaction Short Form (Q-LES-Q-SF), showed greater improvement with venlafaxine XR than with placebo for the total score (OD = 2.7; $p = 0.033$) and the cluster scores on general activities (OD = 2.5; $p = 0.029$) and overall life satisfaction (OD = 0.3; $p = 0.002$). Changes in the total (OD = -2.0; $p = 0.025$) and social life cluster (OD = -0.7; $p = 0.025$) scores on the Sheehan Disability Scale (SDS) were also

CAPS-SX17

ES	Total	Re-experiencing	Avoidance	Hyperarousal
vs PBO	0.27	0.14	0.25	0.25
vs SRT	0.08	0.10	0.08	0.08
SRT vs PBO	0.19	0.07	0.24	0.17

DTS scores

ES	Total	Intrusion	Avoidance	Hyperarousal
vs PBO	0.27	0.24	0.24	0.25
vs SRT	0.13	0.17	0.09	0.10
SRT vs PBO	0.1	0.07	0.15	0.14



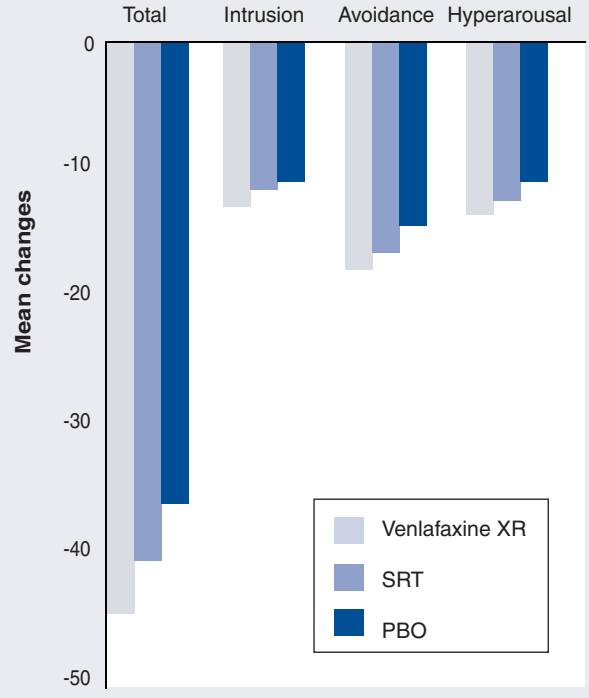


Figure 2. Changes in primary (CAPS-SX17 total score) and major secondary end point (CAPS-SX17 cluster scores and DTS total and cluster scores) in a 12-week randomized, controlled clinical trial of venlafaxine XR for patients with post-traumatic stress disorder (last observation carried forward analysis).
*$p < 0.05$, not significant unless otherwise remarked.
CAPS-SX17: Clinician-administered Post-traumatic Stress Disorder Scale; DTS: Davidson Trauma Scale; ES: Effect size; PBO: Placebo; SRT: Sertraline; Data taken from [48].

significantly greater with venlafaxine XR than with placebo, but there were no statistical differences in work/school or family/home cluster scores compared with placebo [48].

Secondary analysis showed no significant effect of the HAM-D severity score at baseline on the CAP-SX17 score ($F = 1.85$; $p = 0.159$) and no significant interaction between the treatment and the baseline HAM-D-17 severity score ($F = 0.31$; $p = 0.872$), indicating that the improvement in depressive symptoms did not affect the efficacy of venlafaxine XR for PTSD symptoms. The mean total CAPS-SX17 score at baseline ($F = 7.18$; $p = 0.008$) and the type of treatment ($F = 3.26$; $p = 0.039$) accounted for a statistically significant effect on the improvement of the total CAPS-SX17 score, which clearly suggests that the effect of venlafaxine XR on PTSD core symptoms is not mediated by the improvement of depressive symptoms [48]. TABLE 2 summarizes the details of the changes in outcome measures other than CAPS-SX17 and DTS, from the baseline to the end point (LOCF).

Long-term RCT (24 weeks)

A long-term RCT of venlafaxine XR (75–300 mg/day) was conducted for 6 months in 329 outpatients with PTSD [49]. Compared with placebo, venlafaxine XR showed a significantly greater change in the total CAPS-SX17 score from baseline to end point (LOCF), with an OD of -8.9 over 24 weeks ($p = 0.006$), along with earlier improvement seen from week 4 onward (LOCF), which agrees with the short-term RCT result (OD = -7.3) (FIGURE 3) [48].

The CAPS-SX17 cluster scores showed inconsistent results, demonstrating significant differences in the changes from baseline to end point in the cluster scores for re-experience (OD = 8.0; $p = 0.008$) and avoidance/numbing (OD = 11.5; $p = 0.006$), but not for hyperarousal (OD = 9.8; $p = 0.06$). By contrast, the results of the short-term RCT, which indicated significant superiority in the cluster scores for avoidance/numbing ($p = 0.021$) and hyperarousal ($p = 0.024$), but not for re-experience. The remission

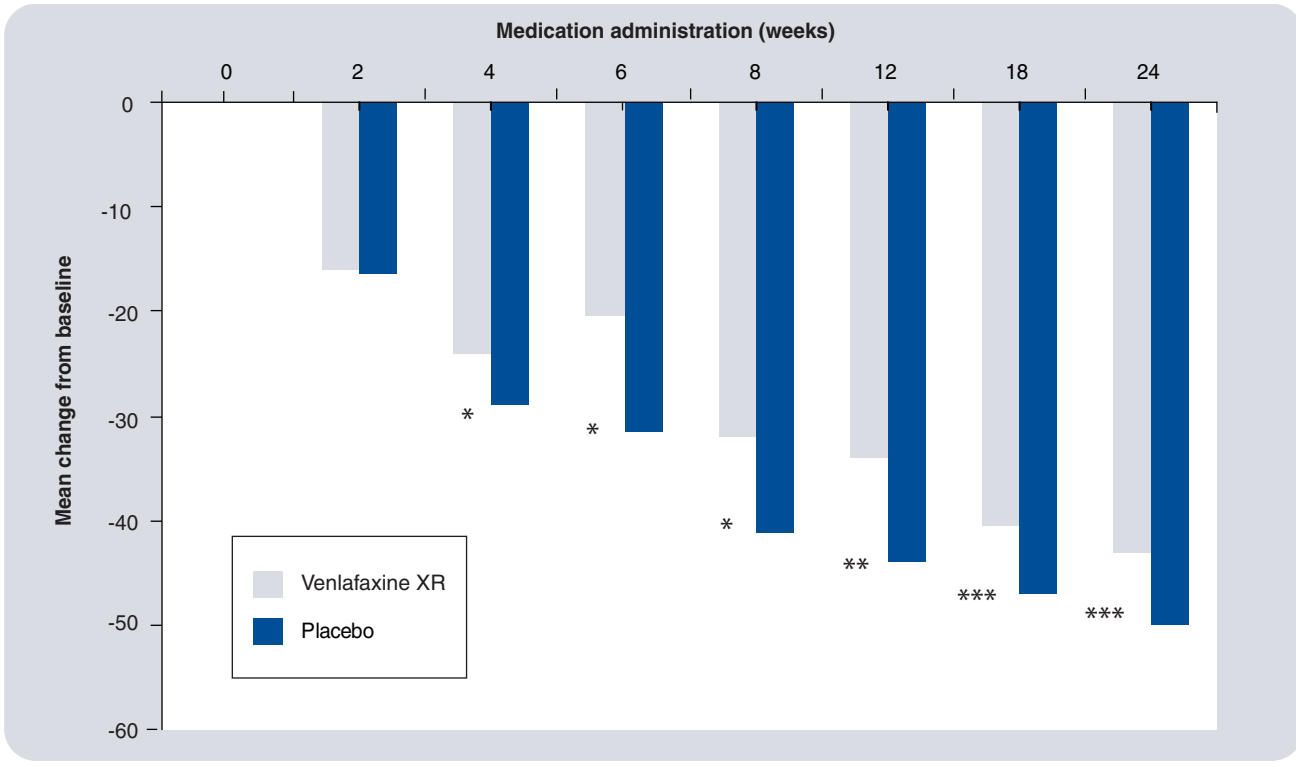


Figure 3. Change in total score on the Clinician-administered Post-traumatic Stress Disorder Scale (CAPS-SX17) in 24-week randomized controlled clinical trial of venlafaxine XR for patients with post-traumatic stress disorder (last observation carried forward [LOCF]).
*p < 0.05 vs placebo; **p < 0.001 vs placebo; ***p < 0.01 vs placebo.
Data taken from [49].

(CAPS-SX17 ≤20) rates were 50.9% (82 of 161) and 37.5% (63 of 168) for venlafaxine XR and placebo, respectively (p = 0.01) at week 24 (LOCF).

Venlafaxine XR also demonstrated significantly greater improvement than placebo at the end point for all other reported outcome measures, including changes in the total scores for CGI-S (OD = -0.5; p = 0.004), GAF (OD = 3.3; p = 0.03), HAM-D-17 (OD = -1.4; p = 0.007), Connor–Davidson Resilience Scale (CD-RISC: OD = 6.7; p = 0.002), SVS (OD = 0.9; p = 0.01), Q-LES-Q-SF (OD = 3.7; p = 0.007) and SDS (OD = –2.0; p = 0.03), although some inconsistent results were noted in the analysis of the cluster scores on Q-LES-Q-SF and SDS compared with those in the short-term RCT. Thus, venlafaxine XR has demonstrated greater improvements in overall quality of life and disability in comparison with placebo. However, patient satisfaction, especially the cluster score in Q-LES-Q-SF, was not significantly improved in either the short- or long-term RCT of venlafaxine XR [48,49].

Comments on efficacy data

When comparing the data from placebo-controlled clinical trials of venlafaxine XR with those of SSRIs, the changes in the primary end point for the short- and long-term placebo-controlled clinical trials of venlafaxine, as measured by the CAPS-SX17 total score, ranged from -42 to -52. These changes are greater than the changes (from -33 to -40) reported from the registration placebo-controlled clinical trials of sertraline [50,51] and paroxetine [52,53], conducted for FDA approval in treating PTSD. However, this is unlikely to be meaningful since these differences are more likely to arise from differences in subject characteristics, trauma type or placebo response (i.e., extremely severe groups [~81–84] for venlafaxine XR [48,49] and severe groups [~73–77] for sertraline [50,51] and paroxetine [52,53] based on mean baseline total CAPS-SX17 score) and do not necessarily indicate different efficacy between individual agents.

Interestingly, there were inconsistent findings regarding the effect of venlafaxine XR on the CAPS-SX17 cluster scores for re-experience and hyperarousal in the short- versus long-term placebo-controlled clinical trials, similar inconsistencies were found in trial results for sertraline (no effect on re-experience and better good response on psychological symptoms than on somatic symptoms) [50,54] and for fluoxetine (no effect on avoidance) [55], but not for paroxetine [52,53]. The inconsistencies in these results indicate that the currently available SNRIs and SSRIs might have limited effects on the entire sphere of PTSD symptoms, suggesting the possibility that another major neurotransmitter may be responsible for the pathogenesis of PTSD or that weaknesses or rater biases may exist in the PTSD symptom assessments currently used in clinical trials [49]. Given the inconsistent findings with

Table 1. Summary of two randomized, placebo-controlled trials of venlafaxine XR for post-traumatic stress disorder.

Demographic/method	Short-term trial [48]	Long-term trial [49]
Trial duration (weeks)	12	24
Patients screened	889	442
Outpatients with PTSD	538	329
Completion of study	350 of 531 (66%)	224 of 329 (68%)
Drugs compared	Venlafaxine XR (n = 179; 37.5–300 mg/day) vs sertraline (n = 173, 25–200 mg/day) vs placebo (n = 179)	Venlafaxine XR (n = 161 [female n = 89; 55.3%]; 37.5–300 mg/day) vs placebo (n = 168 [female n = 89; 53.0%])
Types of trauma (%)		
Accidental injury	11.9	18.2
Adult sexual abuse	15.8	12.5
Childhood sexual abuse	14.9	14.9
Combat	9.0	12.2
Nonsexual abuse	26.2	28.6
Unexpected death	12.6	13.4
Primary end point		
Baseline-to-end point change in total 17-item clinician-administered PTSD Scale (CAPS-SX17) score (LOCF)	Yes	Yes
Secondary end points		
17-item Hamilton Depression Rating Scale (HAM-D-17)	Yes	Yes
CAPS-SX17 symptom cluster scores for re-experiencing/intrusion, avoidance/numbing and hyperarousal	Yes	Yes
Clinical Global Impression-Severity score (CGI-S)	Yes	Yes
Connor–Davidson Resilience Scale (CD-RISC)	No	Yes
Davidson Trauma Scale (DTS) total score and symptom cluster scores for avoidance/numbing, hyperarousal and re-experiencing/intrusion	Yes	No
Frequency of remission (CAPS-SX17 $\leq$ 20)	Yes	Yes
Gobal Assessment of Functioning (GAF)	Yes	Yes
Sheehan Vulnerability to the Effects of Stress Scale (SVS)	Yes	Yes
Time to remission	No	Yes
Health outcomes		
Adverse events were assessed, and use of concomitant treatments were recorded at all visits	Yes	Yes
Quality of Life Enjoyment and Life Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)	Yes	Yes
Sheehan Disability Scale (SDS)	Yes	Yes

LOCF: Last observation carried forward; PTSD: Post-traumatic stress disorder; Venlafaxine XR: Venlafaxine XR.

venlafaxine XR and the worsening of hyperarousal in a case report of duloxetine treatment [56], the role of noradrenergic effects of SNRIs are inconclusive in the treatment of PTSD symptoms to date.

The remission rate for PTSD after 6 months of treatment with venlafaxine XR was 50.9%. This rate is higher than the rates for GAD (43%) [57] and SAD (31%) [58] reported from placebo-controlled clinical trials of venlafaxine XR, which suggests that venlafaxine XR might be potentially more effective in the treatment of PTSD than other anxiety disorders. However, more data are needed to draw firm conclusions about the different remission rates with venlafaxine XR in PTSD, GAD and SAD. It is also worth noting that the remission rate in the 6-month trial was 20.7% higher than that in the short-term, 12-week RCT. As observed in long-term treatment with venlafaxine XR, continuous treatment with sertraline for PTSD has also demonstrated a lower relapse rate than placebo treatment (5 vs 26%). Relapse in patients who received placebo was 6.4-times greater than in those treated with sertraline [59]. Furthermore, a high pretreatment CAPS-SX17 score (>75) was associated with a late response to treatment, which may be likely to occur after 12 weeks, indicating a delayed treatment effect [60]. Taken together, these results clearly demonstrate that continuous treatment of PTSD is mandatory in clinical practice [49,59].

Significant improvement in the primary end point (i.e., the change in the total CAPS-SX17 score from baseline) versus placebo was observed at 2–6 weeks in placebo-controlled clinical trials of sertraline [50], paroxetine [52] and fluoxetine [55], which is in agreement with the venlafaxine XR data [48,49]. Therefore, the currently available RCT data do not support an earlier onset of efficacy for venlafaxine XR compared with that for SSRIs in the treatment of PTSD. This contrasts with previous placebo-controlled clinical trials for major depression in which venlafaxine demonstrated an earlier antidepressant action (within 4–7 days of treatment) [61–63] and trials in which venlafaxine exhibited rapid onset of action in comparison with SSRIs [64].

In the studies of venlafaxine XR for PTSD, efficacy was not affected by gender, indicating equal efficacy of the drug in men and women with PTSD [49].

Open-label studies have also suggested the effectiveness of the IR formulation, which eventually prompted the placebo-controlled clinical trials of venlafaxine XR for PTSD

Table 2. Summary of change scores and effect sizes for the outcome measures other than CAPS-SX17 and DTS from the baseline to the end point (LOCF) in a 12-week randomized, controlled trial.

	VFX (n = 179)	SRT (n = 173)	PBO (n = 179)	Effect size		
				VFX vs SRT	*VEX vs PBO*	*SRT vs PBO*
SVS	-2.6	-2.4	-1.8	0.08	0.26*	0.18
CGI-S	-1.6	-1.5	-1.2	0.08	0.30**	0.22*
GAF	14.2	13.6	11.4	0.04	0.22*	0.18
HAM-D-17	-7.1	-6.4	-5.5	0.10	0.22*	0.13
Q-LES-Q-SF						
Total score	11.5	11.2	8.8	0.03	0.24*	0.21
General activities	8.6	8.2	6.1	0.04	0.24*	0.21
Medication satisfaction	0.3	0.6	-0.1	0.26	0.42	0.68*
Overall life satisfaction	0.9	0.9	0.6	0.03	0.34**	0.31**
SDS						
Total score	-8.5	-8.2	-6.5	0.05	0.25*	0.20
Family/home	-2.9	-2.8	-2.3	0.03	0.21	0.17
Social life	-3.2	-3.0	-2.4	0.06	0.24*	0.18
Work/school	-2.5	-2.5	-1.9	0.01	0.18	0.19

Note: All p-values were based on pairwise comparisons from the analysis of covariance (LOCF).
*p < 0.05; **p < 0.01 (not significant unless otherwise remarked).
CAPS-SX17: Clinician-administered Post-traumatic Stress Disorder Scale; CGI-S: Clinical Global Impression-Severity score; DTS: Davidson Trauma Scale; GAF: Global Assessment of Functioning; HAM-D-17: 17-item Hamilton Depression Rating Scale; LOCF: Last observation carried forward; PBO: Placebo; Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; SDS: Sheehan Disability Scale; SF: Quality of Life Enjoyment and Life Satisfaction Short Form; SRT: Sertraline; SVS: Sheehan Vulnerability to the Effects of Stress Scale; VFX: Venlafaxine XR.
Modified from [48].

[65,66]. Despite its methodological weakness, a case report has indicated that the IR formulation might be effective for the treatment of patients with PTSD who do not respond to several SSRIs, suggesting a potential role for venlafaxine in refractory PTSD [66]. Head-to-head comparison or switching studies between venlafaxine XR and other antidepressants, such as SSRIs, will be of interest for addressing these practical clinical issues, as has already been partly demonstrated in the treatment of patients with treatment-resistant depression.

Dosing of venlafaxine XR in patients with PTSD

The two placebo-controlled clinical trials for the treatment of PTSD assigned 37.5 mg/day as a starting dose of venlafaxine XR. This is the same initiation dosage for panic disorder, whereas 75 mg/day is a starting dose for GAD, SAD and major depression [39,48,49]. The mean average daily dosages of venlafaxine XR were 164.4 and 181.7 mg/day in the short- [48] and long-term placebo-controlled clinical trials [49], respectively, with mean average daily maximum dosages of 224.6 and 221.5 mg/day in the respective placebo-controlled clinical trials. In the short-term RCT, approximately 47% (84 of 179) of patients received the maximum dose, and 35.4% (57 of 161) and 23.0% (37 of 161) of patients took 300 and 225 mg/day, respectively, in the long-term trial [48,49].

Based on the results of the two placebo-controlled clinical trials, the dosage of venlafaxine XR for the treatment of PTSD would be in the range of 150–225 mg/day, which is similar to the FDA-approved venlafaxine XR dosage established in placebo-controlled clinical trials for other psychiatric disorders. Whether higher doses of venlafaxine XR are needed for more severe cases of PTSD remain uncertain, and a fixed-dose RCT of venlafaxine XR is not yet available for patients with PTSD. However, clinical experience and complicated treatment responses in PTSD have suggested that certain patients who do not respond to the usual therapeutic dose may benefit from increases to the maximum dosage, with upward titration by 75 mg/day at intervals of 2 weeks or longer.

Safety & tolerability

The most commonly observed adverse events (AEs) in the placebo-controlled clinical trials of venlafaxine XR for the treatment of anxiety disorders are nausea, headache, insomnia, dry mouth, sexual dysfunction, sweating, somnolence and asthenia [39]. In the 12- and 24-week placebo-controlled clinical trials of venlafaxine XR for PTSD, the most common AE was headache (28.6–29.0% with venlafaxine XR vs 26.2–29.0% with placebo), followed by nausea (21.7–24.0% with venlafaxine XR vs 11.3–14.0% with placebo). The overall AE profile and attrition rate (nearly 10%) were not significantly different from the data of placebo-controlled clinical trials for panic disorder (7%), GAD (18%) and SAD (17%) [48,49]. In the placebo-controlled clinical trials of venlafaxine XR for other anxiety disorders, the most common AE leading to treatment discontinuation was nausea, followed by dizziness [49], which is comparable to the AEs in the placebo-controlled clinical trials for PTSD. Treatment-emergent AEs (≥10% of patients in at least one of the active treatment groups) in the short-term RCT of venlafaxine XR for PTSD are given in TABLE 3.

Sexual dysfunction, with no difference in incidence versus placebo (5 vs 3.6%), has also been reported in the 24-week RCT of venlafaxine XR for PTSD [49]. Overall, the rate of sexual dysfunction with venlafaxine tended to fall between the rates with SSRIs and moclobemide (32–50%) [67].

Table 3. Treatment-emergent adverse events in the 12-week randomized, controlled trial of venlafaxine XR for post-traumatic stress disorder.

Adverse event	Venlafaxine XR (n = 179)	Sertraline (n = 173)	Placebo (n = 179)
Headache	53 (29)	57 (32)	55 (29)
Nausea	45 (24)	39 (23)	27 (14)
Diarrhea	22 (12)	47 (26)	25 (13)
Dry mouth	34 (18)	26 (15)	27 (15)
Somnolence	21 (12)	18 (10)	24 (13)
Fatigue	19 (11)	24 (14)	17 (9)
Dizziness	24 (13)	21 (12)	14 (8)
Insomnia	24 (13)	18 (10)	16 (9)
Constipation	21 (12)	12 (7)	18 (10)
Anorexia	21 (12)	13 (8)	11 (6)

Data indicate numbers (%) of subjects. Data from [48].

In the placebo-controlled clinical trials of venlafaxine XR for anxiety disorders, some doses (200–375 or >300 mg/day) were associated with a mean change in heart rate of 8.5 bpm, compared with 1.7 bpm with placebo [39]. In this context, in January 2006, the FDA issued safety labeling revisions for venlafaxine XR to warn of the risk of sustained hypertension associated with its use in some patients. Therefore, pre-existing hypertension should be controlled before treatment with venlafaxine XR, and blood pressure should be monitored regularly in patients taking this medication. For patients who experience a sustained increase in blood pressure while taking venlafaxine, either dose reduction or discontinuation should be considered [39,101]. However, no clinically significant changes in laboratory values were noted in either RCT for PTSD [48,49]. For example, the mean increment of systolic and diastolic blood pressure was below 2.5 mm Hg, the heart rate change was no more than 3 bpm, and the mean change in cholesterol level was less than 0.2 nmol/l [48,49].

Venlafaxine XR is not associated with clinically problematic weight gain or loss, and a number of placebo-controlled clinical trials for other anxiety disorders and major depression have demonstrated little effect of venlafaxine XR on body weight [39]. Consistent with previous findings, the mean weight changes from baseline were -0.5 and 0.6 kg in the 12 and 24-week placebo-controlled clinical trials for PTSD [48,49].

Although not reported in the placebo-controlled clinical trials of venlafaxine XR for PTSD, venlafaxine-associated hyponatremia, activation of mania/hypomania, seizure, serotonin syndrome and abnormal bleeding, which have all been reported by the manufacturer, should also be considered when treating patients who have potential risk factors for these conditions [39].

The use of venlafaxine XR during pregnancy is rated as category C, similar to most SSRIs, except for paroxetine (category D). Venlafaxine XR has not been associated with congenital malformations in animal studies. However, because animal reproduction studies are not always predictive of human responses, venlafaxine XR should be used during pregnancy only if the clinical benefit clearly outweighs the risk [39].

The FDA has issued a public health advisory notice regarding worsening depression and suicidal ideation in pediatric and adult patients being treated with ten newer antidepressants, including venlafaxine XR. Hence, careful observation should be exercised for the emergence of suicidal ideation and self-injury in all patients treated with antidepressants, especially at the times of treatment initiation and dose increase. Venlafaxine XR has not been approved for use in pediatric patients [39,68].

Expert commentary

Whether venlafaxine XR demonstrates different efficacy and acceptability as a first-line agent (or adjunctive therapy) for patients with PTSD, compared with other pharmacological agents, will depend on further well-designed placebo-controlled clinical trials. Studies with different designs, including head-to-head comparisons, dosing studies and treatment-response predictor analyses, as well as trials with different trauma groups, different age groups, patients with comorbidity and refractory cases, will provide important information about the role of venlafaxine XR in the treatment of PTSD.

Patients with PTSD are considered to have increased risk for somatization, as well as being sensitive to physical symptoms [69]. Patient medication satisfaction with venlafaxine XR was not significantly different from that with placebo in the 12- and 24-week placebo-controlled clinical trials for PTSD, whereas satisfaction with sertraline was different from that with placebo in the 12-week RCT. Hence, the common and troublesome side effects of venlafaxine XR should be kept in mind during the treatment of patients with PTSD.

The recommended minimum treatment period for chronic PTSD is 12–24 months, as supported by mounting evidence favoring long-term treatment of PTSD [49,59,60]. Thus, clinicians should persuade patients to remain on maintenance treatment for as long as possible. A favorable profile of drug discontinuation symptoms for venlafaxine XR, compared with the IR formulation, has not yet been established. Considering the proven risk of withdrawal syndrome for the IR formulation and the need for continuous treatment for PTSD [39], patients should be advised against abrupt or relatively rapid withdrawal of venlafaxine XR; in fact, venlafaxine is associated with more withdrawal symptoms than SSRIs (i.e., escitalopram) [70].

Patients with PTSD represent a greater risk for suicidal behavior. When prescribing venlafaxine XR for patients who have potential suicidal risk factors, a clear-cut evaluation of the risks and benefits should be completed in advance, because of the relatively more serious overdose toxicity of venlafaxine XR compared with SSRIs [71].

Further pooled analyses of the two available placebo-controlled clinical trials [48,49] of venlafaxine XR for PSTD are currently underway to explore potential predictors of response and remission, including gender and type of trauma, which will be useful in better understanding the role of venlafaxine XR in the treatment of PTSD [48,49].

Although currently available data clearly suggest that SSRIs such as paroxetine, sertraline and fluoxetine should be the first-choice agents in the treatment of PTSD, two recently published 12- and 24-week placebo-controlled clinical trials have established the efficacy and safety of venlafaxine XR for patients with PTSD. Thus, clinicians may have another effective treatment option for PTSD.

Five-year view

The number of placebo-controlled clinical trials examining the comparative efficacy between venlafaxine XR and SSRIs, or of switching to venlafaxine XR in patients with PTSD who were not responding to adequate treatment with SSRIs, has been lacking until now. Subsequent placebo-controlled clinical trials may address this issue in the treatment of PTSD and will provide useful and practical strategies regarding the pharmacological treatment of refractory PTSD patients.

Future research should also include investigations of possible neurogenesis associated with venlafaxine XR treatment for PTSD. This unexplored field will help clinicians integrate the role of 5-HT and norepinephrine re-uptake inhibition in the treatment of PTSD (i.e., neurogenesis of PTSD-related brain regions, or the ratio of occupancy rate in 5-HT and norepinephrine transporters at therapeutic or minimally effective doses).

As has been asserted by some researchers, venlafaxine may have the benefit of rapid onset of treatment response [72]. Therefore, it is worth investigating whether there are any differences in clinical outcome related to intervention time after a traumatic event, especially given that a large proportion of PTSD studies have failed because of a large gap between trauma and treatment.

A pharmacoeconomic study comparing actual medical costs between venlafaxine XR and other first-line agents would provide information helpful to both clinicians and patients in terms of managing therapeutic tactics and strategies. However, such studies are implausible while venlafaxine is in its product life cycle.

In conclusion, venlafaxine XR continues to be widely used for the treatment of major depression and various anxiety disorders in clinical practice. The future widespread use of venlafaxine XR for PTSD may depend on the availability of further data regarding its benefits in relation to consistent efficacy or acceptable tolerability, particularly for continuous and maintenance treatment. Conflicts with health insurance, availability of generic products, evidence-based consensus or treatment guidelines, and regulatory issues are also likely to have an impact on the use of venlafaxine XR for the treatment of PTSD.

Key issues

- Extended-release venlafaxine (venlafaxine XR) is associated with lower peak plasma concentration (C_{max}), longer time to peak plasma concentration (T_{max}) and prolonged elimination half-life than the immediate-release (IR) formulation, while the bioequivalence remains the same as with the IR formulation, which suggests that switching from the IR formulation to venlafaxine XR is convenient.
- Despite the distinctive differences in pharmacokinetics between the two formulations (i.e., advantageous C_{max} and half-life time for venlafaxine XR), the current paucity of direct comparison between the two formulations could not warrant any conclusive remark on the differential safety and tolerability profiles.
- Venlafaxine XR has already been approved for the treatment of major depression and three anxiety disorders (generalized anxiety, social anxiety and panic disorders) and has demonstrated the efficacy for the treatment of post-traumatic stress disorder (PTSD) through short- (12-week) and long-term (24-week) randomized controlled trials.
- Currently available data suggest that there is no evidence of differences in efficacy between venlafaxine XR and other first-line pharmacological agents, such as selective serotonin re-uptake inhibitors, for the treatment of PTSD.
- The side-effect profile of venlafaxine XR is largely similar to that of SSRIs, but the potential for discontinuation syndrome and cardiovascular side effects, such as increasing blood pressure, appear to be slightly higher than with SSRIs.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst. Rev.* (1), CD002795 (2006).

•• Excellent review of pharmacological treatment for post-traumatic stress disorder (PTSD).

2 Asnis GM, Kohn SR, Henderson M, Brown NL. SSRIs versus non-SSRIs in post-traumatic stress disorder: an update with recommendations. *Drugs* 64(4), 383–404 (2004).

3 Hertzberg MA, Feldman ME, Beckham JC, Kudler HS, Davidson JR. Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans. *Ann. Clin. Psychiatry* 12(2), 101–105 (2000).

4 Zohar J, Amital D, Miodownik C *et al.* Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J. Clin. Psychopharmacol.* 22(2), 190–195 (2002).

5 Southwick SM, Krystal JH, Bremner JD *et al.* Noradrenergic and serotonergic function in posttraumatic stress disorder. *Arch. Gen. Psychiatry* 54(8), 749–758 (1997).

• Good review of neurobiology in PTSD.

6 Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch. Gen. Psychiatry* 52(12), 1048–1060 (1995).

7 Stein MB, McQuaid JR, Pedrelli P, Lenox R, McCahill ME. Posttraumatic stress disorder in the primary care medical setting. *Gen. Hosp. Psychiatry* 22(4), 261–269 (2000).

8 Gillock KL, Zayfert C, Hegel MT, Ferguson RJ. Posttraumatic stress disorder in primary care: prevalence and relationships with physical symptoms and medical utilization. *Gen. Hosp. Psychiatry* 27(6), 392–399 (2005).

9 Rodriguez BF, Weisberg RB, Pagano ME *et al.* Mental health treatment received by primary care patients with posttraumatic stress disorder. *J. Clin. Psychiatry* 64(10), 1230–1236 (2003).

10 Stein MB, Sherbourne CD, Craske MG *et al.* Quality of care for primary care patients with anxiety disorders. *Am. J. Psychiatry* 161(12), 2230–2237 (2004).

11 American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders Text Revision.* American Psychiatric Press, WA, USA (2000).

12 McFarlane AC. The longitudinal course of posttraumatic morbidity. The range of outcomes and their predictors. *J. Nerv. Ment. Dis.* 176(1), 30–39 (1988).

13 Heinrichs M, Wagner D, Schoch W *et al.* Predicting posttraumatic stress symptoms from pretraumatic risk factors: a 2-year prospective follow-up study in firefighters. *Am. J. Psychiatry* 162(12), 2276–2286 (2005).

14 Cohen H, Jotkowitz A, Buskila D *et al.* Post-traumatic stress disorder and other co-morbidities in a sample population of patients with irritable bowel syndrome. *Eur. J. Intern. Med.* 17(8), 567–571 (2006).

15 Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. *Ann. NY Acad. Sci*. 1032, 141–153 (2004).

16 Grieger TA, Cozza SJ, Ursano RJ *et al.* Posttraumatic stress disorder and depression in battle-injured soldiers. *Am. J. Psychiatry* 163(10), 1777–1783; quiz 1860 (2006).

17 Bernal M, Haro JM, Bernert S *et al.* Risk factors for suicidality in Europe: results from the ESEMED study. *J. Affect. Disord.* (2006) (Epub ahead of print).

18 Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch. Gen. Psychiatry* 56(7), 617–626 (1999).

19 Fichtner CG, Arora RC, O'Connor FL, Crayton JW. Platelet paroxetine binding and fluoxetine pharmacotherapy in posttraumatic stress disorder: preliminary observations on a possible predictor of clinical treatment response. *Life Sci.* 54(3), PL39–PL44 (1994).

20 Fichtner CG, O'Connor FL, Yeoh HC, Arora RC, Crayton JW. Hypodensity of platelet serotonin uptake sites in posttraumatic stress disorder: associated clinical features. *Life Sci.* 57(2), PL37–PL44 (1995).

21 Arora RC, Fichtner CG, O'Connor F, Crayton JW. Paroxetine binding in the blood platelets of post-traumatic stress disorder patients. *Life Sci.* 53(11), 919–928 (1993).

22 Maes M, Lin AH, Verkerk R *et al.* Serotonergic and noradrenergic markers of post-traumatic stress disorder with and without major depression. *Neuropsychopharmacology* 20(2), 188–197 (1999).

23 Maguire K, Norman T, Burrows G, Hopwood M, Morris P. Platelet paroxetine binding in post-traumatic stress disorder. *Psychiatry Res.* 77(1), 1–7 (1998).

24 Spivak B, Vered Y, Graff E *et al.* Low platelet-poor plasma concentrations of serotonin in patients with combat-related posttraumatic stress disorder. *Biol. Psychiatry* 45(7), 840–845 (1999).

25 Lemieux AM, Coe CL. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. *Psychosom. Med.* 57(2), 105–115 (1995).

26 Yehuda R, Southwick S, Giller EL, Ma X, Mason JW. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. *J. Nerv. Ment. Dis.* 180(5), 321–325 (1992).

27 Kosten TR, Mason JW, Giller EL, Ostroff RB, Harkness L. Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. *Psychoneuroendocrinology* 12(1), 13–20 (1987).

28 Denolle T, Sassano P, Allain H *et al.* Effects of nicardipine and clonidine on cognitive functions and electroencephalography in hypertensive patients. *Fundam. Clin. Pharmacol.* 16(6), 527–535 (2002).

29 Kinzie JD, Leung P. Clonidine in Cambodian patients with posttraumatic stress disorder. *J. Nerv. Ment. Dis.* 177(9), 546–550 (1989).

30 Southwick SM, Paige S, Morgan CA III *et al.* Neurotransmitter alterations in PTSD: catecholamines and serotonin. *Semin. Clin. Neuropsychiatry* 4(4), 242–248 (1999).

31 Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. *Depress. Anxiety* 16(1), 4–13 (2002).

32 Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br. J. Psychiatry* 180, 396–404 (2002).

33 Rudolph RL. Achieving remission from depression with venlafaxine and venlafaxine extended release: a literature review of comparative studies with selective serotonin reuptake inhibitors. *Acta Psychiatr. Scand.* (415), 24–30 (2002).

34 Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br. J. Psychiatry* 178, 234–241 (2001).

35 Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J. Clin. Psychiatry* 62(11), 869–877 (2001).

36 Einarson TR, Arikian SR, Casciano J, Doyle JJ. Comparison of extended-release venlafaxine, selective serotonin reuptake inhibitors, and tricyclic antidepressants in the treatment of depression: a meta-analysis of randomized controlled trials. *Clin. Ther.* 21(2), 296–308 (1999).

37 Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. *Biol. Psychiatry* 52(12), 1166–1174 (2002).

38 Gutierrez MA, Stimmel GL, Aiso JY. Venlafaxine: a 2003 update. *Clin. Ther.* 25(8), 2138–2154 (2003).

39 Venlafaxine XR, prescribing information. Wyeth Pharmaceuticals Inc., PA, USA .

40 Bitsios P, Szabadi E, Bradshaw CM. Comparison of the effects of venlafaxine, paroxetine and desipramine on the pupillary light reflex in man. *Psychopharmacology (Berl.)* 143(3), 286–292 (1999).

41 Owen JR, Nemeroff CB. New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine. *Depress. Anxiety* 7(Suppl. 1), 24–32 (1998).

42 Olver JS, Burrows GD, Norman TR. The treatment of depression with different formulations of venlafaxine: a comparative analysis. *Hum. Psychopharmacol.* 19(1), 9–16 (2004).

43 Gex-Fabry M, Balant-Gorgia AE, Balant LP *et al.* Time course of clinical response to venlafaxine: relevance of plasma level and chirality. *Eur. J. Clin. Pharmacol.* 59(12), 883–891 (2004).

44 Norman TR, Olver JS. New formulations of existing antidepressants: advantages in the management of depression. *CNS Drugs* 18(8), 505–520 (2004).

• Good review regarding newer formulations of antidepressants.

45 Muth EA, Haskins JT, Moyer JA *et al.* Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cyclohexanol derivative. *Biochem. Pharmacol.* 35(24), 4493–4497 (1986).

46 Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. *Ann. Clin. Psychiatry* 9(3), 157–164 (1997).

47 Entsuah R, Chitra R. A benefit–risk analysis of once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. *Psychopharmacol. Bull.* 33(4), 671–676 (1997).

48 Davidson J, Rothbaum BO, Tucker P *et al.* Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J. Clin. Psychopharmacol.* 26(3), 259–267 (2006).

•• Pivotal short-term study in PTSD.

49 Davidson J, Baldwin D, Stein DJ *et al.* Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch. Gen. Psychiatry* 63(10), 1158–1165 (2006).

•• Pivotal long-term study in PTSD.

50 Brady K, Pearlstein T, Asnis GM *et al.* Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA* 283(14), 1837–1844 (2000).

51 Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch. Gen. Psychiatry* 58(5), 485–492 (2001).

52 Tucker P, Zaninelli R, Yehuda R *et al.* Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J. Clin. Psychiatry* 62(11), 860–868 (2001).

53 Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am. J. Psychiatry* 158(12), 1982–1988 (2001).

54 Davidson JR, Landerman LR, Farfel GM, Clary CM. Characterizing the effects of sertraline in post-traumatic stress disorder. *Psychol. Med.* 32(4), 661–670 (2002).

55 Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. *J. Clin. Psychiatry* 63(3), 199–206 (2002).

56 Deneys ML, Ahearn EP. Exacerbation of PTSD symptoms with use of duloxetine. *J. Clin. Psychiatry* 67(3), 496–497 (2006).

57 Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. *Br. J. Psychiatry* 179, 15–22 (2001).

58 Stein MB, Pollack MH, Bystritsky A, Kelsey JE, Mangano RM. Efficacy of low and higher dose extended-release venlafaxine in generalized social anxiety disorder: a 6-month randomized controlled trial. *Psychopharmacology (Berl.)* 177(3), 280–288 (2005).

59 Davidson J, Pearlstein T, Londborg P *et al.* Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am. J. Psychiatry* 158(12), 1974–1981 (2001).

60 Londborg PD, Hegel MT, Goldstein S *et al.* Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. *J. Clin. Psychiatry* 62(5), 325–331 (2001).

61 Derivan A, Entsuah AR, Kikta D. Venlafaxine: measuring the onset of antidepressant action. *Psychopharmacol. Bull.* 31(2), 439–447 (1995).

62 Schweizer E, Weise C, Clary C, Fox I, Rickels K. Placebo-controlled trial of venlafaxine for the treatment of major depression. *J. Clin. Psychopharmacol.* 11(4), 233–236 (1991).

63 Guelfi JD, White C, Hackett D, Guichoux JY, Magni G. Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. *J. Clin. Psychiatry* 56(10), 450–458 (1995).

64 Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J. Affect. Disord.* 56(2–3), 171–181 (1999).

65 Smajkic A, Weine S, Djuric-Bijedic Z *et al.* Sertraline, paroxetine, and venlafaxine in refugee posttraumatic stress disorder with depression symptoms. *J. Trauma. Stress* 14(3), 445–452 (2001).

66 Hamner MB, Frueh BC. Response to venlafaxine in a previously antidepressant treatment-resistant combat veteran with post-traumatic stress disorder. *Int. Clin. Psychopharmacol.* 13(5), 233–234 (1998).

67 Kennedy SH, Eisfeld BS, Dickens SE, Bacchiochi JR, Bagby RM. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *J. Clin. Psychiatry* 61(4), 276–281 (2000).

68 Pae CU, Patkar AA. Paroxetine: current status in psychiatry. *Expert. Rev. Neurother.* 7(2), 107–120; Erratum in: *Expert Rev. Neurother.* 7(3), 313–314 (2007).

69 Andreski P, Chilcoat H, Breslau N. Post-traumatic stress disorder and somatization symptoms: a prospective study. *Psychiatry Res.* 79(2), 131–138 (1998).

70 Baldwin DS, Montgomery SA, Nil R, Lader M. Discontinuation symptoms in depression and anxiety disorders. *Int. J. Neuropsychopharmacol.* 1–12 (2005).

71 Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *QJM* 96(5), 369–374 (2003).

72 Montgomery SA. Rapid onset of action of venlafaxine. *Int. Clin. Psychopharmacol.* 10(Suppl. 2), 21–27 (1995).

Website

101 Safety labeling changes approved by FDA Center for Drug Evaluation and Research (CDER) – January 2006. www.fda.gov/medwatch/SAFETY/2006/jan06_quickview.htm

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