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Comparison of Venlafaxine with Other Antidepressants for the Treatment of Major Depressive Disorder: A Narrative Review

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ABSTRACT

Major depression disorder is the leading cause of disability worldwide, with the number of affected people increasing substantially during the last decades. The management of this condition is primarily focused on pharmacotherapy and psychotherapy. Venlafaxine is a bicyclic phenyl phenylethylamine derivative with a robust antidepressant effect due to its mechanism of action based on presynaptic reuptake of serotonin, noradrenaline (norepinephrine) and, to a lesser extent, dopamine. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are vastly used for the treatment of major depression. Here we collect relevant evidence from scientific literature that show that venlafaxine, probably due to its dual modulation of serotonin and noradrenaline neurotransmission interaction, is more efficacious compared to both selective serotonin reuptake inhibitors and also to other dual-acting antidepressants such as desvenlafaxine.

Keywords: Major Depressive Disorder; Efficacy; Narrative Review; Selective Serotonin Reuptake Inhibitors (SSRIs); Venlafaxine; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Abbreviations: SSRIS: Selective Serotonin Reuptake Inhibitors; TCA: Tricyclic Antidepressants; MOI: Monoamine Oxidase Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; DA: Dopamine; NA: Noradrenaline; HAM-D: Hamilton Rating Scale for Depression

Introduction

Depression is the leading cause of disability worldwide. The number of people living with depression increased by around 18% between 2005 and 2015, and it is estimated that depression affects 322 million people, or about 4% of the world's population [1]. Pharmacotherapy and psychotherapy are the two mainstays of depression treatment. In particular, second-generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are the first-line options in the pharmacological management of major depression [2]. However, meta-analyses have shown that approximately only 50% of patients under psychological treatment seem to achieve normal functioning, with cognitive, interpersonal psychotherapy being the most effective approaches [3]. Tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOIs) like amitriptyline, imipramine, desipramine, isocarboxazid or phenelzine tranylcypromine have been the only available antidepressants for a long time. Despite compounds of these both classes have proven to be effective, adverse events, the use of suboptimal doses and potential drug-drug and drug-food interactions have arisen as caveats linked to these medications [4,5]. TCAs have shown non-specific serotonergic and noradrenergic activity, as well as a potential non-selectivity towards muscarinic cholinergic, α1-adrenergic and H1 histaminergic receptors, which might result in dry mouth, dizziness, blurred vision, constipation, sedation, and orthostatic hypotension and even death under overdose conditions [6-8].

In the case of MAOIs they also bind to multiple receptors and can interact with tyramine causing potentially fatal hypertension, in addition to the appearance of adverse effects such as hypotension, bodyweight gain and sexual dysfunction [6]. These factors have limited their use in patients with major depression. The introduc-

tion of SSRIs and afterwards serotonin-norepinephrine reuptake inhibitors (SNRI) was a major advance in the management of depression. Although SSRIs could have become the first-line treatment for several psychiatric diseases like uncomplicated unipolar depression and dysthymia, their effectiveness/safety balance in major depression has been questioned [9]. This narrative review examines the effectiveness of venlafaxine, as first developed SNRI, in the management of major depressive disorder, compared to SSRIs and other dual-acting antidepressants of its pharmacological class.

Material and Methods

This article is a narrative review which covers the mechanism of action of venlafaxine and a comparison in efficacy with serotonin reuptake inhibitors and other dual-acting antidepressants. A literature search was performed in PubMed based on the keywords "venlafaxine", "comparative study", "SSRI", "serotonin reuptake inhibitors", "dual-acting antidepressants" and "major depressive disorder".

Results

Mechanism of Action

Venlafaxine, or 1-[2-(dimethylamino)-1-(4-methoxyphenyl) -ethyl] cyclohexanol hydrochloride, is a bicyclic phenylethylamine derivative that, along with its major active metabolite O-desmethylvenlafaxine, inhibits presynaptic reuptake of serotonin (5-hydroxytryptamine; 5-HT), noradrenaline (norepinephrine; NA) and, to a lesser extent, dopamine (DA). Compared to other antidepressants, it interacts with more than one receptor site, since it affects both serotonin and norepinephrine receptors. However, it does not interact with α1-adrenergic, muscarinic cholinergic, H1 histaminergic, benzodiazepine or opioid receptors and does not inhibit monoamine oxidase. Therefore, it avoids adverse events like dry mouth, hypotension, and sedation. However, venlafaxine can interact with dopamine receptors, inhibiting its reuptake [6,9]. Therapeutic efficacy of venlafaxine lies on the fact that both serotonergic, noradrenergic and dopaminergic systems take part in the pathophysiology of major depression, thus the blockade of these uptakes might benefit patients with this major depressive disorder. Moreover, venlafaxine has demonstrated that at low doses acts as SSRI, whereas if it is used at higher doses, it acts as dual 5-HT and also NA reuptake inhibitor [6,10], conferring this drug a remarkable versatility in relation with this special antidepressant mechanism of action. The clinically significant noradrenergic effect of venlafaxine occurs fundamentally at the level of the central nervous system, and, therefore, venlafaxine has been proven safe at cardiovascular level in several studies. (Mbaya, et al. [11]) reported that venlafaxine, even at high doses above 300 mg/day (mean 346.15 mg; range 225–525 mg) did not have any clinical or statistically significant in PR, QT, QRSD and QTc interval values, neither tachycardia. More recently, (Behlke et al. [12]), in a secondary analysis of the IRL-Gray clinical trial, observed that venlafaxine did not significantly affect cardiac conduction in 169 adults older than 60 years depressed patients treated with doses up to 300 mg daily, since it did not prolong QTc or other electrocardiogram parameters, regardless of the serum concentration of this medication.

Superiority of Venlafaxine towards SSRIs as a First-Line Treatment

It is widely accepted that 5-HT, NA, and DA play an important role in mood regulation. SSRI antidepressants act selectively on serotonergic systems by blocking serotonin uptake pumps. Therefore, serotonin levels available in the space between neurons are increased, extending their effect in the brain, and thus improving mood in patients [13]. Although SSRIs are usually the first-line therapies in the pharmacological management of major depression, venlafaxine has proven to be more effective in the treatment of this condition [2]. In a randomized, double-blind trial which compared venlafaxine and fluoxetine in 382 outpatients with major depression, patients were randomly assigned to receive either medication, with the option of increasing the doses three weeks after the start of the trial if a poor response was achieved. Initially, both venlafaxine and fluoxetine reduced significantly mean Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) scores, although no significant differences were observed between groups. However, after three weeks, higher CGI-I scores (Clinical Global Impression-Improvement score of 1 or very much improved) were observed among those patients who increased their venlafaxine doses compared to fluoxetine ($p<0.05$) [14]. In a comparison study with sertraline in the treatment of major depressive disorder through an eight-week, double-blind, randomized trial, statistically significant higher response rates were observed in the venlafaxine group (83% vs 68%, $p=0.05$). In addition, a higher number of patients reported a HAM-D score lower than 10 in the patients in which venlafaxine was prescribed (68% vs 45%, $p=0.008$). Regarding remission rates, percentages stayed at 67% and 36% for venlafaxine and sertraline respectively ($p<0.05$) [15].

In an analysis performed across eight double-blind randomized clinical trials that compared venlafaxine and SSRIs among 2,045 patients with major depression disorders remission rates were 45% for venlafaxine, 35% for SSRIs and 25% for placebo ($p<0.001$ for all comparisons). In addition, effectiveness of venlafaxine was statistically higher than SSRIs and placebo from the second week onwards. Overall, a 50% greater chance of remission with venlafaxine therapy compared to SSRIs was observed (odds ratio [OR]=1.5, 95% CI: 1.3, 1.9) [16].

In a pooled analysis of 1,454 outpatients diagnosed with major depression across five double-blind, randomized studies that compared the efficacy of venlafaxine with fluoxetine for six weeks, both treatments demonstrated higher response rates compared to placebo. Superiority in response rates was observed with venlafaxine, compared to placebo, between weeks 3 and 6 ($p<0.05$).

Additionally, higher remission rates were observed in the venlafaxine group from the second week to the sixth week, since the percentages of remitter patients were greater compared to fluoxetine (9% vs 5% at week 2 and 36% vs 28% at week 6, p=0.019 and p=0.003 respectively). Both treatments proved to be superior to placebo, although significant differences were observed from week 3 onwards for venlafaxine (18% vs 10%, p=0.003) and from week 4 onwards for fluoxetine (20% vs 14%, p=0.042), suggesting a faster effect of venlafaxine. Furthermore, venlafaxine was more effective compared to fluoxetine regarding psychic anxiety (14.0% vs 8.8%, p<0.05) and sense of guilt (16.9% vs 9.6%, p<0.05). This superiority on anxiety symptoms, commonly associated to depressive symptoms in major depression, could explain the superiority of venlafaxine as antidepressant, versus fluoxetine [17] or even other SSRIs.

Recently, in an eight-week, multicenter, randomized, single-blind, active-controlled trial among 184 postmenopausal women with major depressive disorder, a higher reduction in HAMD-24 anxiety/somatization factor scores was observed with venlafaxine compared to fluoxetine (least-squares mean difference -2.22, 95% CI: -7.08, -0.41, p=0.001). These results translated to a greater baseline-to-eight-week least-squares mean change of the anxiety/somatization factor scores (p<0.05 for all). Although both treatments achieved better results compared to placebo, authors concluded that venlafaxine led to an overall greater improvement in the treatment of postmenopausal major depression [18].

Regarding meta-analysis, (Einarson, et al. [19]) reported from 44 trials involving 4,033 patients that venlafaxine had the highest mean success rate (73.7%) compared to SSRIs (61.1%) and tricyclic antidepressants or TCAs (57.9%). The statistical analysis showed that these differences were significant (p<0.001). Concerning risk/benefit balance, it is worth noting that the dropout rates due to adverse event and also due to lack of efficacy were numerically lower in favor of venlafaxine, in comparison with SSRIs and TCAs. (Nemeroff, et al. [20]) reported in a meta-analysis with 34 randomized double-blind studies in which remission rates in the treatment of depression were analyzed, that venlafaxine was statistically superior to SSRIs as a class. Remission rates of venlafaxine over different SSRIs were superior in 28 of the 34 studies, with remission rate differences ranging from -7% to 31%. Overall, venlafaxine treatment was associated with a 5.9% advantage over the SSRI class (95% CI: 0.038, 0.081).

In another meta-analysis by (Bauer, et al. [21]) including 63 clinical trials, an overall random effect OR of 1.15 (95% CI: 1.02, 1.29) across 29 studies was observed, which indicated that venlafaxine was significantly more effective compared to SSRI. In addition, a greater effectiveness in remission rates in the venlafaxine group was also reported, with random effects OR of 1.19 (95% CI: 1.06, 1.34). Finally, in another meta-analysis which included 26 randomized, double-blind clinical trials, a greater response rate with venlafaxine compared to SSRIs was reported, with an overall OR of 1.17 (range 0.65-2.78, 95% CI: 1.03, 1.34, p=0.02). Regarding remission rate, it also proved to be superior in those patients who received venlafaxine in comparison with SSRIs, with a mean OR of 1.13 (range 0.27-2.62, 95% CI: 1.0, 1.28, p=0.05). Individual comparisons reported that venlafaxine was relevantly superior towards fluoxetine regarding response rates (OR=1.28, 95% CI: 1.05, 1.55, p=0.01) [22]. In conclusion, as per our review, venlafaxine seems to be superior to SSRIs in terms of efficacy in first-line treatment of major depression. As a compilation of all the above, the results obtained in the clinical trials are summarized in Table 1 [14-18]; and the ones from the meta-analyses in Table 2 [19-22].

Table 1: Summary of clinical trials comparing venlafaxine towards SSRIs as first-line treatment.

Study	Methodology	Results
(Costa e Silva [14]).	Design: Eight-week, multicenter, randomized, double-blind, parallel-group study of the efficacy and tolerability of venlafaxine and fluoxetine. Patients: 382 participants with major depression according to Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), a minimum score of 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D), and depressive symptoms for at least one month. Intervention: Patients were randomly assigned to 37.5 mg venlafaxine twice daily or 20 mg fluoxetine once daily. Primary objective: Final on-therapy scores on the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impressions Severity of Illness (CGI-S) and Improvement (CGI-I) scales.	After three weeks, higher CGI-I scores observed among in patients who increased their venlafaxine doses compared to fluoxetine (p<0.05)
(Mehtonen, et al. [15]).	Design: Pooled analysis of five double-blind, randomized studies. Patients: 1454 outpatients DSM-IV major depressive disorder and a baseline 21-item Hamilton Rating Scale for Depression (HAM-D) score of at least 18. Intervention: Patients were randomly assigned to 37.5 mg b.i.d. venlafaxine or 50 mg sertraline, once daily. From day 15 onwards, doses could be increased to 75 mg b.i.d. venlafaxine or 50 mg b.i.d. sertraline. Primary objective: Comparison of the efficacy and tolerability of venlafaxine and sertraline.	At week 8, the HAM-D response rate was 83% and 68% for venlafaxine and sertraline respectively (p=0.05). 68% and 45% of patients with venlafaxine and sertraline achieved a HAM-D score less than 10 (p=0.008). Among participants in which doses were increased, remission rates were 67% and 36% for venlafaxine and sertraline (p<0.05).

(Thase, et al. [16]).	Design: Analysis of eight double-blind randomized clinical trials comparing venlafaxine and selective serotonin reuptake inhibitors (SSRI) during the development of immediate-release (IR) and extended-release (XR) formulations of venlafaxine. Patients: 2045 participants with major depression disorders remission rates. Intervention: Doses were 75-375 mg/day venlafaxine IR, 75-225 mg/day venlafaxine XR, fluoxetine 20-80 mg/day, 20-40 mg/day paroxetine, and 100-200 mg/day fluvoxamine. Primary objective: Compare remission rates during treatment with SSRIs or venlafaxine.	Final remission rates were 45% for venlafaxine, 35% for SSRIs and 25% for placebo ($p<0.001$ for all comparisons). Effectiveness of venlafaxine was statistically higher than SSRIs and placebo from the second week and third weeks onwards respectively. An odds-ratio (OR) of 1.5 (95% CI: 1.3, 1.9) was observed, with a 50% greater chance of remission with venlafaxine compared to SSRIs.
(Davidson, et al. [17]).	Design: Integrated comparative analysis of five double-blind, randomized, multisite (United States, Canada, and Europe) studies. Patients: 1454 outpatients with a DSM-III-R or DSM-IV diagnosis of major depression. Intervention: Venlafaxine doses ranged from 75 to 375 mg/day and fluoxetine ones from 20 to 80 mg/day. Primary objective: Evaluate the short-term (6 weeks) efficacy of venlafaxine compared with fluoxetine.	Response rates were higher in both treatments compared to placebo starting at week 2, with venlafaxine being statistically superior from week 2 to 6 ($p<0.001$) and fluoxetine only at weeks 2 and 6 ($p<0.05$). Higher remission rates were observed in the venlafaxine group from week 2 to 6. Percentages of remission patients were higher compared to fluoxetine (9% vs 5% at week 2 [$p=0.019$] and 36% vs 28% at week 6 [$p=0.003$]). Venlafaxine was more effective in the treatment of psychic anxiety (14.0% vs 8.8%, $p<0.05$) and sense of guilt (16.9% vs 9.6%, $p<0.05$).
(Zhou, et al. [18]).	Design: Eight-week, multicenter, randomized, single-blind, active-controlled trial conducted at a psychiatric hospital (Beijing Anding Hospital) and a general hospital (Beijing Chaoyang Hospital) between April 2013 and September 2017. Patients: 184 postmenopausal female outpatients aged ≥50 with a Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for MDD as determined by the Mini International Neuropsychiatric Interview (MINI). Intervention: Patients were 1:1 randomized to 75 mg/day oral venlafaxine or 20 mg/day oral fluoxetine. Primary objective: Mean change in HAMD-24 scores from baseline to week 8.	Higher reduction in HAMD-24 anxiety/somatization factor scores with venlafaxine compared to fluoxetine (least-squares mean difference -2.22, 95% CI: -7.08, -0.41, $p=0.001$), which lead to a greater baseline-to-eight-week least-squares mean change of the anxiety/somatization factor scores ($p<0.05$ for all).

Table 2: Summary of meta-analyses comparing venlafaxine towards SSRIs as first-line treatment.

Study	Methodology	Results
(Einarson, et al. [19])	Design: Randomized, double-masked, controlled trials involving at least one of the following drugs in at least one arm: venlafaxine XR; the SSRIs citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; and the tricyclic antidepressants (TCA) amitriptyline, imipramine, desipramine, and nortriptyline. Patients: 4033 participants with a Montgomery-Asberg Depression Rating Scale (MADRS) of ≥18 or any version of the Hamilton Rating Scale for Depression (HAM-D) of ≥15.	Mean success rates were 73.7% for venlafaxine (range 66.7-81.3%), 61.1% for SSRIs (range 38.8-100.0%) and 57.9% for TCAs (range 20.0-93.5%; $p<0.001$). Mean dropout rates were 10.9% for venlafaxine (range 10.2-12.2%), 17.4% for SSRIs (range 6.7-40.9%) and 23.1% for TCAs (range 8.0-44.4%).
(Nemeroff, et al. [20].)	Design: 34 randomized, double-blind treatment studies with evaluation of a standard dependent measure, such as the Hamilton Rating Scale for Depression (HAM-D). Patients: 8877 participants meeting criteria for major depressive disorder, as determined by the Diagnostic and Statistical Manual of Mental Disorders (edition III-R or IV) or International Disease Classification–10 criteria.	Remission rate differences for venlafaxine compared with each specific SSRI ranged from 3.4% to 14.1%. Results vs fluoxetine were statistically significant (6.6% [95% CI: 0.030, 0.095]; $p<0.001$). Venlafaxine treatment was associated with a 5.9% advantage over the SSRI class (95% CI: 0.038, 0.081).
(Bauer, et al. [21]).	Design: 63 randomized, controlled trials completed up to April 2007 comparing venlafaxine with other antidepressant drugs in the treatment of major depression.	Venlafaxine showed higher treatment response rates (random effects odds ratio 1.15, 95% CI: 1.02, 1.29), remission rates (random effects odds ratio 1.19, 95% CI: 1.06, 1.34) compared to SSRIs.
(de Silva & Hanwella [22])	Design: 26 randomized, double-blind clinical trials with head-to-head comparison of venlafaxine with a SSRI (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, or sertraline) in the acute treatment of major depressive disorder in adults between January 1990 and September 2010.	Venlafaxine was superior to SSRIs in achieving response (OR=1.17, 95% CI: 1.03, 1.34; $p=0.02$) and remission (OR=1.13, 95% CI: 1.00, 1.28; $p=0.05$).

Superiority of Venlafaxine Compared to SSRIs in Refractory Patients to First-Line Treatment

Disease remission is the main treatment clinical aim of major depressive disorder. However, estimations indicate that only about 50% of these patients respond to the treatment of SSRI, with around 30% of them only achieving response or partial remission [23-25]. Since switching to a second SSRI in refractory patients has proven to achieve from variable to any response [26-30], a clinical strategy often employed is prescribing patients with an antidepressant with a different mechanism of action. In such a scenario, venlafaxine might represent an interesting option for these refractory patients according to the data available in the scientific literature.

In a multicenter, randomized, double-blind, double-dummy, dose-ranging, parallel-group trial that compared extended release venlafaxine with citalopram among 406 patients with depression who had been unresponsive to eight weeks of monotherapy with an adequate regimen of SSRI other than citalopram, a non-significant difference in the mean change from baseline to the final on-therapy evaluation on the HAM-D21 total score was observed (-17.0 for venlafaxine vs -16.5 for citalopram, p=0.4778) for the overall population. However, when analyzing the clinically relevant subset of patients who had a CGI-I score of 1 (very much improved) after 12 weeks, statistically significant superiority was observed in the venlafaxine group (p=0.024). Sub-analyses of the HAM-D21 scores showed that among the patients who were more severely affected by reporting baseline scores greater than 31, venlafaxine group was significantly superior in comparison with citalopram group on the estimated longitudinal change in the total score from baseline (least squares mean of 14.25 vs 17.78; p=0.0121). This difference was also observed in the CGI-S (Clinical Global Impression-Severity) scores (1.94 vs 1.53, p=0.0359) [31].

Finally, in a five-year retrospective analysis which compared switching to venlafaxine or other SSRI after treatment failure with a SSRI, it was observed that the rate of patients achieving a CGI-S score of 2 or less (1 = normal, not at all ill; or 2 = borderline mentally ill) after the different treatments was statistically higher in the venlafaxine group (68.1% vs 58.9%, p=0.02) [32]. To summarize, and in view of the reviewed evidence, venlafaxine could be more effective than SSRIs also for the treatment of refractory to first-line patients diagnosed of major depression.

Superiority of Venlafaxine Towards Other Dual-Acting Antidepressants

Desvenlafaxine is the main active metabolite of venlafaxine. It has proven to inhibit neuronal uptake of both serotonin and norepinephrine and, to a lesser degree, dopamine [33,34]. Several placebo-comparative clinical trials have established the efficacy of this compound for major depressive disorder [35-37]. However, there is no evidence that its effectiveness is superior to that observed in other antidepressant therapies [38,39]. In comparison with venlafaxine, in a post-hoc pooled analysis of two double-blind, multicenter, placebo-controlled, parallel-group, venlafaxine extended release-referenced trials, venlafaxine showed overall better results than desvenlafaxine. After an eight-week treatment, the change from baseline of HAM-D17 scores were -14.26 and -14.56 for the 75-150 mg/day and 150-225 mg/day doses of venlafaxine, respectively; -14.21 for desvenlafaxine (200-400 mg/day); and -11.87 for placebo with both treatments showing statistically significant differences towards placebo (p<0.001). However, venlafaxine, especially at the 150-225 mg/day dose, showed a more rapid separation from placebo in terms of HAM-D17 score temporary change, suggesting a faster onset of the antidepressant effect. Interestingly, statistical and -from our point of view- also clinically significant differences were observed concerning both doses of venlafaxine towards placebo regarding response rates (64% for 75-150 mg/day and 57% for 150-225 mg/day, p=0.033 and p=0.017 respectively) and remission rates for the patients that received the 150-225 mg/day dose (36%, p=0.003). Such venlafaxine differences in comparison with placebo were not observed in favor of desvenlafaxine, neither in terms of response nor in remission rates, suggesting a weaker antidepressant effect of desvenlafaxine, in comparison with venlafaxine [39].

It is worth noting that the 200-400 mg/day dose range of desvenlafaxine in the previous pooled analysis is much higher than the authorized dose range for desvenlafaxine in Spain (50-200 mg/day) [40]. Relevantly, and regarding regulatory issues, the proprietary company decided to withdraw desvenlafaxine through the centralized process of marketing authorization approval via EMA (European Medicines Agency) due to, during the assessment procedure, EMA expressed concerns and held a provisional opinion that the drug could not be approved for the treatment of major depressive disorder [41]. As a result, at this moment desvenlafaxine is marketed and available for prescription in only 3 European countries through national authorization procedures, including Spain [42].

Discussion

Individuals diagnosed with major depression disorder are usually difficult to treat, so an effective management of these patients as early as possible is crucial to achieve the best possible outcomes. Although narrative reviews have inherent limitations due to their design (mainly inclusion of heterogenous studies, each of them with a different design and study protocols, and selection bias of the reviewers), most studies addressed in this narrative review included large groups of patients and, therefore, the results have the sufficient statistical power to detect clinically meaningful differences. From our analysis, we have observed a clear trend of venlafaxine superiority in different treatment scenarios or clinical research methodologies, which, in our view, could help to overcome the mentioned methodology limitations. Results included in this narrative review point towards the fact that venlafaxine treatment is significantly more effective than

SSRIs in the treatment of first major depressive episodes with no major adverse effects added. Furthermore, it showed some benefits against some other dual-acting antidepressants such as desvenlafaxine in the management of depression by triggering earlier and superior responses in patients. In addition, the benefits of venlafaxine against SSRIs in refractory patients, which pose an exceptional challenge to prescribers, is of special clinical meaningfulness. In the clinical management of major depression, the clinical success of the first line treatment is very important since it avoids therapeutic failures and medication changes, including washout periods which can lengthen periods of treatment without clinical effectiveness and, hence, jeopardize adherence and increase the burden of illness. In this context, the proven and robust anxiolytic effect of venlafaxine is an added value in the treatment of major depression. All of the above, as per our review of its risk/benefit balance, venlafaxine can be considered as option of choice for the treatment of major depression disorder. Finally, in order to reduce pharmacological burden, help to ensure adherence to treatment, and facilitate progressive dose titration, extended-release oral pharmaceutical forms of venlafaxine which can allow a once-a-day posology including a wide range of different therapeutic dosages should be preferred.

Conclusion

This narrative review indicates that venlafaxine could present a better efficacy profile for the treatment of major depressive disorder, not only compared to treatments based on SSRIs, but also to some other dual-acting antidepressants such as desvenlafaxine.

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