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Effects of venlafaxine extended release formulation on the clinical management of patients

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One of the issues related with antidepressant drug use is to improve patient compliance. Investigations have searched for simplified administration schedules that focus on having a significant impact on the management of depressive patients. This article has reviewed the extended release formulation characteristics and its effect on the drug pharmacokinetics and clinical assessments of depressive patients. The conclusion of this review is that venlafaxine extended release formulation represents an innovation in the treatment of depresión. This formulation provides the same total exposure to venlafaxine with a once-daily dose as the immediate release formulation with several doses, slower gastrointestinal release and smaller fluctuations between C_{max} and C_{min}. These differential characteristics result in a potential improved efficacy and a better tolerability profile. The increased compliance observed with venlafaxine extended release formulation could improve the appropriate management of depressive patients.

Key words:
Depression. Venlafaxine extended release. Compliance. Clinical management.

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Repercusión de la formulación retard de venlafaxina en el manejo clínico de los pacientes

Uno de los aspectos que deben mejorar en el uso de los fármacos antidepresivos es el adecuado cumplimiento terapéutico por parte de los pacientes. Por ello se han investigado pautas de administración simplificadas que han buscado tener un significativo impacto en el manejo del paciente depresivo. En este artículo se han revisado las características propias de la formulación retard y su repercusión sobre aspectos farmacocinéticos y evaluaciones clínicas de los pacientes con depresión. De la revisión realizada se permite concluir que la formulación retard de venlafaxina representa una innovación en el tratamiento de la depresión. Las características diferenciales de esta formulación, que proporciona en una única dosis diaria la misma exposición total a la venlafaxina que la formulación de liberación inmediata en varias dosis, y con una liberación más lenta a nivel del tracto gastrointestinal y unas menores fluctuaciones entre $C_{máx}$ y $C_{mín}$, se traducen en la clínica en una potencial mejor eficacia y un mejor perfil de tolerabilidad. La mejor adherencia terapéutica observada para el tratamiento con la formulación retard de venlafaxina podría facilitar el adecuado manejo del paciente depresivo.

Palabras clave:
Depresión. Venlafaxina retard. Cumplimiento. Manejo clínico.

INTRODUCTION

Since approximately 50 years ago, antidepressant drugs have been the first line treatment for several types of depression[1]. In spite of their extended use, treatment of depression is associated with high rates of relapses and recurrences, which reach up to 80% according to the studies[2] and frequent therapeutic failures (between 40% and 60%)[3]. Improvement in compliance could represent a clear increase in antidepressant efficacy.

Lack of compliance to drug treatment is observed very frequently in the case of depressive patients. Unipolar depression is a chronic and recurrent condition that requires acute and long-term treatment. Present treatment guidelines of depression recommend continuation of antidepressant treatment up to, at least 6-9 months after treatment of the acute phase of major depressive episode and for life in some cases of recurrent forms of the disease[4]. In spite of these recommendations, which stress the importance of continuing antidepressant treatment beyond the resolution of the acute phase symptoms, antidepressant treatment discontinuation rates are high. It has been demonstrated how compliance tends to decline over time, with treatment compliance rates that decrease from 68, 63, and 50, until 40% in weeks 3, 6, 9 and 12, respectively5. Factors directly related with antidepressant treatments and that have a negative repercussion on

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compliance include, among others, presence of adverse effects related with these treatments, delay in the onset of therapeutic effect and their administration in complicated therapeutic regimes or at suboptimum doses[6].

Inadequate compliance is partially related with the appearance of undesirable adverse effects[1,7]. Thus, it has been described how the presence of one or more moderate/severe adverse effects is associated with an increase of up to three times in the likelihood of premature discontinuation of antidepressant treatment[8]. Certain characteristics of depression, such as cognitive impairment, hopelessness and poor motivation that may lead to forgetfulness and to passive non-compliance stand out among other factors that contribute to explaining low compliance to antidepressant treatments. Furthermore, the same remission of the symptoms frequently induces the patient to think that he can handle his problem without needing medication. Even more, other aspects, such as guilty feeling, may induce the patient to consider that such treatment is not deserved, which inevitably leads to reducing motivation[0]. On the other hand, diseases, as is the case of depression, in which the relationship between compliance and recurrence is not very well defined, are more vulnerable to being associated to low compliance[9]. The high resistant depression rates reported, up to 30%, are also associated directly with low compliance[10].

Following these considerations, simplified administration schedules that seek to have a significant impact on the depressive patient's management have been investigated. Commerzialitation of new formulations of antidepressants, already available on the market, could represent an innovation in depression treatment. The development of these formulations has been motivated by the intention of obtaining significant improvements for the patients, among them, mainly, a better grade of compliance and better safety profile[11].

Venlafaxine (venlafaxine hydrochloride) is an antidepressant that is not chemically related with tricyclic drugs (TCA) or selective serotonin reuptake inhibitors (SSRIs). It is a racemic compound called (R/S)-1-(2-[dimethylamino]-1-[4-methoxyphenyl]ethyl) cyclohexanol hydrochloride. Both venlafaxine and its main active metabolite, O-desmethyl-venlafaxine (ODV), are potent serotonin and norepinephrine reuptake inhibitors, weakly inhibiting dopamine reuptake[12]. Venlafaxine inhibits *in vitro* serotonin and norepinephrine reuptake, it being three-five times more potent in its activity on serotonin than on norepinephrine[13,14]. Its affinity for cholinergic, muscarinic, histaminergic, alpha-1, alpha-2 and beta-adrenergic receptors is practically null[13].

The venlafaxine immediate release formulation was first marketed in Spain in 1995. This formulation is approved for the treatment of depression and prevention of relapses of depressive episodes and recurrences of new depressive episodes. The extended release formulation (sustained release) was later marketed in 1999. This formulation is also approved in generalized anxiety disorder and in the treatment of social anxiety disorder. This new extended release formulation confers the pharmaceutical speciality innovating characteristics, on the basis of a potential clinical improvement for the patients. The characteristics of the extended release formulation and its effects on pharmacokinetic aspects and clinical evaluations of patients with depression are reviewed in this article.

CHEMICAL CHARACTERISTICS OF VENLAFAXINE EXTENDED RELEASE FORMULATION

The innovating extended release mechanism of venlafaxine is supported by the fact that each gelatin capsule contains *spheroids* that, in turn, contain the active ingredient, venlafaxine. This gelatin capsule is soluble and completely dissolves on contact with gastric fluids, releasing the spheroids that contain venlafaxine in the gastrointestinal tract. Each spheroid contains an inert and insoluble matrix in which part of the total dose of the active ingredient is dispersed. An insoluble and porous coating surrounds the matrix, forming a semi-permeable membrane through which venlafaxine is released when exposed to gastrointestinal fluids. Given that each spheroid covers the complete gastrointestinal tract, venlafaxine is progressively released. The insoluble portion of the spheroids cross the gastrointestinal tract without dissolving and is excreted.

The release mechanism depends on basic principles of concentration gradients, which are not affected by gastric pH, enzymatic activity or other factors such as gastrointestinal content, so that venlafaxine release is produced at a controlled and predictable rhythm[15].

DIFFERENTIAL PHARMACOKINETIC CHARACTERISTICS

When compared with the immediate release formulation, venlafaxine extended release formulation offers a slower release and sustained action duration, with the same total amount of active drug, allowing its administration once a day. The extended release formulation is differentiated from the immediate release one in that venlafaxine is released more slowly in the gastrointestinal tract, which delays the distribution of venlafaxine to the systemic circulation. Steady state concentrations of venlafaxine and ODV are obtained at 3 days of the administration of repeated doses.

Two open label, randomized, crossed arms, single and multiple dose studies in 24 healthy volunteers have evaluated relative bioavailability of both formulations. In the study of single doses, 2×75 mg and 150 mg doses of venlafaxine extended release formulation were compared with 50 mg doses of the immediate release formulation. The venlafaxine plasma concentration peak was reached more slowly in the case of the extended release formulations, however the total amount of venlafaxine absorbed and the ODV formation were similar for both (table 1). The steady

Table 1 Pharmacokinetic variables for venlafaxine and O-desmethylvenlafaxine following single-dose administration of venlafaxine extended release (XR) and venlafaxine immediate release (IR) to 22 healthy subjects

Treatment	C_{max} (ng/ml)	T_{max} (h)	$t^1/_2$ (h)	AUC_T (ng • h/ml)	AUC (ng • h/ml)
Venlafaxine					
2 × 75 mg extended release	107 ± 42	6.1 ± 1.5	11.8 ± 6.9	1,587 ± 1,165	1,775 ± 1,206
1 × 150 mg extended release	101 ± 36	5.7 ± 1.5	10.3 ± 4.4	1,621 ± 1,253	1,777 ± 1,423
1 × 50 mg immediate release	82 ± 28	3.0 ± 1.4	5.0 ± 3.2	571 ± 442	625 ± 470
O-desmethylvenlafaxine					
2 × 75 mg extended release	163 ± 53	10.5 ± 3.0	13.2 ± 3.3	4,132 ± 1,491	4,516 ± 1,523
1 × 150 mg extended release	167 ± 49	12.3 ± 9.2	14.6 ± 4.2	4,268 ± 1,293	4,787 ± 1,551
1 × 50 mg immediate release	120 ± 30	5.5 ± 3.4	9.6 ± 2.5	1,558 ± 465	1,758 ± 494

C_{max}: maximum plasma concentration; T_{max}: time to reach C_{max}; $t^1/_2$: elimination half-life; AUCT: area under the plasma concentration-time curve at the last observable time. Values are expressed as mean ± SD. Adapted from Troy et al., 1997[16].

state half-life of venlafaxine and ODV was 5 ± 3.2 and 9.6 ± 2.5 hours, respectively, after the administration of the immediate release formulation (1 × 50 mg), thus needing the administration of 2 or 3 daily doses to maintain adequate plasma levels. In the case of the extended release formulation, the steady state half-life of venlafaxine and ODV was 11.8 ± 6.9 and 13.2 ± 3.3 hours, respectively (2 × 75 mg), and 10.3 ± 4.4 and 14.6 ± 4.2 hours, respectively (1 × 150 mg), which makes it possible to administer a once-daily dose[16].

In the multiple dose study (table 2), the maximum plasma concentrations of venlafaxine and ODV were lower in the case of the extended release formulation but the area under the curve was similar for both formulations, observing smaller C_{max} to C_{min} fluctuation for the extended release formulation compared with the conventional one[16]. In addition, no differences were observed in the venlafaxine plasma levels after administration of both formulations, extended or immediate release, in the morning or at night. The pharmacokinetics were also not influenced in any of the formulations by food intake[17].

In conclusion, bioavailability studies show that equal doses of the extended release formulation (administered in a

Table 2 Pharmacokinetic variables for venlafaxine and O-desmethylvenlafaxine following multiple-dose administration of venlafaxine extended release (XR) and venlafaxine immediate release (IR) to 24 healthy subjects

Treatment	C_{max} (ng/ml)	T_{max} (h)	$t^1/_2$ (h)	AUCT (ng • h/ml)	R_f
Venlafaxine					
75 mg immediate release q12h	225 ± 86	2,0 ± 0,7	50 ± 35	2.604 ± 1.325	1,86 ± 0,68
2 × 75 mg extended release q24h	155 ± 71	5,4 ± 1,4	51 ± 37	2.246 ± 1.216	1,23 ± 0,40
2 × 75 mg extended release q24h	157 ± 71	5,8 ± 1,6	50 ± 37	2.240 ± 1.218	1,27 ± 0,34
1 × 150 mg extended release q24h	149 ± 79	5,4 ± 1,1	41 ± 44	2.222 ± 1.403	1,21 ± 0,35
O-desmethylvenlafaxine					
75 mg immediate release q12h	290 ± 117	3,1 ± 1,5	167 ± 69	5.402 ± 2.131	0,54 ± 0,20
2 × 75 mg extended release q24h	256 ± 108	7,8 ± 2,4	148 ± 61	5.036 ± 2.115	0,50 ± 0,14
2 × 75 mg extended release q24h	266 ± 105	9,2 ± 2,7	144 ± 65	5.019 ± 2.055	0,57 ± 0,22
1 x 150 mg extended release q24h	260 ± 109	9,0 ± 2,6	150 ± 62	5.052 ± 2.087	0,51 ± 0,14

C_{max}: maximum plasma concentration; T_{max}: time to reach C_{max}; $t^1/_2$: elimination half-life; AUCT: area under the plasma concentration time curve at the last observable time; R_f: steady-state fluctuation ratio (C_{max}-C_{min}/C_{mean}); qnh = every n hours. Values are expressed as mean ± SD. Adapted from Troy et al., 1997[16].

once-daily dose) and the immediate release formulation (administered in multiple doses) of venlafaxine provide the same total exposure to venlafaxine and ODV. The pharmacokinetic bioequivalence between both formulations makes it possible to establish dose-dose equivalences when substituting the immediate release formulation treatment by the extended release one. Although both formulations are bioequivalent from a pharmacokinetic point of view, the extended release formulation offers other differential advantages that clinically result in a better management of the depressive patient, aspects that are commented in the following sections of this review. Even more, the pharmacokinetic characteristics of the extended release formulation offer the possibility of reducing the appearance of withdrawal syndrome, as a result of its apparent longer half life[18].

CLINICAL ASSESSMENT AND ITS REPERCUSSION

In this section, the main studies that have conducted a clinical assessment are reviewed, comparing the repercussion on the patients of the administration of both venlafaxine formulations, both from the efficacy as well as safety and tolerability point of view.

The first study reviewed is a double-blind, randomized, placebo controlled, 12 week long study in out-patients of 18 years or more with major depressive episode according to the Diagnostic and Statistical Manual of Mental Diseases (DSM-III-R or IV) criteria. The following were considered as study inclusion criteria: minimum score of 20 on the 21 item Hamilton Depression scale ($HAM\text{-}D_{21}$) and no more than 20% decrease on the score between screening and baseline values and depression symptoms of at least 1 year long before entering the study19. The objectives were to assess and compare efficacy and safety of both venlafaxine formulations. Efficacy was assessed using the $HAM\text{-}D_{21}$ scale, the Montgomery-Asberg Depression Scale (MADRS) and the Clinical Global Impression scale (CGI). Patients were randomized to receive venlafaxine immediate release, 37.5 mg, twice a day administered in the morning and at night; venlafaxine extended release, 75 mg in the morning plus placebo at night; or placebo twice a day, for 14 days. After day 14, the venlafaxine dose for both formulations was increased up to 150 mg/day on the investigator's judgement. A total of 278 patients were included in the intention to treat analysis.

The mean reductions in all the main efficacy endpoints (total scores on HAM-D and MADRS, depressive mood item on the HAM-D and score on the CGI-S) were significantly higher with both venlafaxine formulations than with placebo at week 12. Similarly, the reductions in the total HAM-D scores were significantly higher among the patients treated with both venlafaxine formulations than those receiving placebo at week 2 and from weeks 4 to 12 ($p < 0.001$ and 0.05 vs placebo, respectively). Reductions in the MADRS scores were significantly higher in the active treatment groups than in those receiving placebo from weeks 3 to 12 ($p < 0.05$). Furthermore, sustained response rates based on the total scores of HAM-D and MADRS and on the CGI-M were significantly higher with both venlafaxine formulations than with placebo ($p < 0.05$).

The reductions in the total HAM-D and CGI-S scores from baseline were significantly higher in patients treated with venlafaxine extended release than with venlafaxine immediate release at week 8 (–13.7 and –1.86 vs –11.1 and –1.38, respectively; $p < 0.05$). Furthermore, reductions from baseline were significantly higher in patients who received venlafaxine extended release in the four efficacy endpoints at week 12 ($p < 0.05$). Both venlafaxine formulations significantly reduced the score of the depressive mood item of HAM-D in comparison with placebo from weeks 2 ($p < 0.01$) to 12. The response rates based on the HAM-D and MADRS scales were significantly higher in patients treated with venlafaxine extended release than those treated with venlafaxine immediate release ($p < 0.05$) or placebo ($p < 0.001$) at week 12 (fig. 1). Response rates based on CGI-S criteria were significantly higher among those who received venlafaxine extended release than among those receiving placebo from weeks 3 to 12 ($p < 0.01$-$p < 0.001$).

One of the adverse effects reported in the study was nausea. The greatest incidence of nausea was observed during the first week, it being lower in the case of extended release formulation (27%) when compared with the immediate release one (37%). This incidence rapidly decreased to 12% during the second week in both groups, with additional decreases over time. The accumulative likelihood of developing nausea was less for the extended release formulation when compared with the immediate release one. Dropouts due to an unsatisfactory clinical response were significantly more frequent ($p=0.01$) among patients receiving placebo (12%) than among those receiving venlafaxine

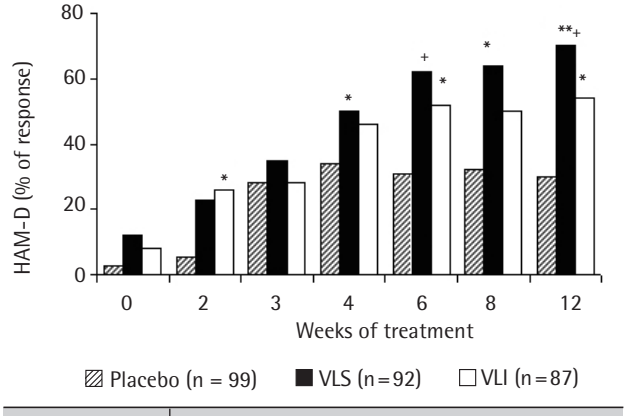

Figure 1 *HAM-D response rates for patients treated with placebo, venlafaxine IR, or venlafaxine XR. VLS: venlafaxine extended release XR; VLI: venlafaxine immediate release IR: *p < 0.05 y +p < 0.001 VSR and VIR vs placebo; **p < 0.05 VSR vs VIR. Adapted from Cunningham, 1997[19].*

extended release (2%) or venlafaxine immediate release (4%). Premature discontinuation rate due to adverse effects was inferior in the case of extended release formulation when compared with that of the immediate release (11% and 13%, respectively).

According to the results of this study, it can be concluded that the extended release formulation of venlafaxine is significantly more effective than the immediate release one at weeks 8 and 12, reaching significantly better scores on all the antidepressant efficacy endpoints at week 12 in patients diagnosed of major depressive episode. This formulation is associated with better tolerability, lower nausea incidence during the first week of treatment and lower accumulative likelihood of presenting them during the treatment.

In the second study reviewed, safety and tolerability of venlafaxine extended release formulation were assessed[20]. In all, 728 depressed patients were analyzed: 357 patients included in the placebo-controlled trials and 371 in open label, long term studies; 164 patients received approximately 6 months of treatment[19, 21]. The safety and tolerability data of 728 patients treated with venlafaxine extended release formulation were compared with the data of 2,897 patients treated in clinical trials with venlafaxine immediate release formulation22 to determine any difference in their respective safety profiles.

The pooled analysis of the placebo controlled studies showed how the incidence of the most frequently reported adverse effects was consistently lower in the treatment with venlafaxine extended release formulation when compared with the immediate release formulation. The greatest incidence of nausea was observed during the first week of treatment (27% and 37%, extended and immediate release formulations, respectively). The incidence decreased to 12% in the second week of treatment for both formulations and continued decreasing over time. Among the patients who experienced nausea during the first week of treatment and completed the study, the incidence of nausea in the later weeks was significantly inferior in those treated with venlafaxine extended release formulation. The lower incidence and better adaptation to nausea observed for venlafaxine extended release formulation have also been demonstrated in pharmacokinetic studies. According to these studies, immediate release formulation causes a dose-dependent nausea increase, with maximum intensity of nausea that is reached before reaching the plasma concentration peak. Delay in reaching the maximum peak after administration of the extended release formulation is therefore followed by a decrease in intensity and frequency of the nausea[23].

In the global comparative analysis, interruption of treatment for any reason was lower with venlafaxine extended release formulation when compared with the immediate release formulation (31% vs 52%). Discontinuation due to lack of efficacy (6% vs 11%) or due to adverse effects (12% vs 18%) was also lower. In the placebo controlled trials, venlafaxine extended release formulation was also associated with a significantly lower number of drop-outs, due to any reason (28% vs 54%), lack of efficacy (6% vs 11%) or adverse effects (10% vs 19%), when compared with the immediate release formulation. Table 3 summarizes the discontinuation rates for both formulations reported in the studies analyzed.

In conclusion of the study, venlafaxine extended release formulation seems to offer advantages over the immediate release formulation, based on a lower rate of overall discontinuations, both due to inefficacy and adverse effects, a consistently lower incidence of the most frequently reported adverse effects with venlafaxine, a faster adaptation to nausea, a superior tolerability profile and a potential better treatment compliance.

The traditional analysis of the clinical trial data with antidepressant drugs assesses the efficacy and tolerability re-

Table 3 **Discontinuation rate (%) with venlafaxine XR and venlafaxine from placebo-controlled trials**

Study event	Total database		Placebo-controlled trials			
			Venlafaxine XR		Venlafaxine IR	
	Venlafaxine XR (n = 728)	Venlafaxine IR (n = 2.897)	Placebo (n = 285)	Venlafaxine XR (n = 357)	Placebo (n = 609)	Venlafaxine IR (n = 1.033)
Any reason	31%	52%	37%	28%	58%	54%
Lack of efficacy	6%	11%	16%	6%	23%	11%
Adverse effects	12%	18%	4%	10%	6%	19%

XR: extended release; IR: immediate release. Adapted from Hackett, 1997[20].

sults separately. Another form of analyzing the data is to simultaneously assess these criteria through benefit/risk analyses. This way of conducting the statistical analyses of the clinical trial data represents an advance when the treatment results are assessed by incorporation of clinically relevant measurements of efficacy and safety. In the analysis conducted by Entshuah and Chitra[24], the results obtained in a double blind, placebo controlled study in out-patients with major depression were evaluated. This study included 278 patients: 92 with venlafaxine extended release, 87 with venlafaxine immediate release and 99 with placebo. The patients received 37.5 mg of venlafaxine immediate release twice a day; 75 mg of venlafaxine extended release in the morning and placebo in the afternoon, or placebo, twice a day. After day 14, the doses of both venlafaxine formulations could be increased up to 150 mg/day on the investigator's judgement. This study's main efficacy and safety results have been previously commented on[19].

For the benefit/risk analysis, the individual data of these patients in regards to efficacy and related adverse events for the venlafaxine extended and immediate release formulations were grouped into five different categories. Efficacy was defined as the final score of the patients under treatment in the CGI-I of 1 (very much better) or 2 (much better). A treatment related adverse event was defined as any new adverse event or any adverse event that existed at baseline and whose severity had increased with the treatment. Benefit/risk was assessed using a linear measure and ratio for dizziness, insomnia, nausea, nervousness, drowsiness and a composite of anticholinergic events.

The benefit/risk analysis demonstrated a consistent favorable tendency of venlafaxine extended release formulation for all the adverse effects analyzed. The differences were significant for dizziness (p = 0.03), nausea (p = 0.09) and drowsiness (p = 0.046). The benefit/risk ratio for nausea and dizziness was statistically significant, of at least 2:1 for the venlafaxine extended release formulation, when compared with the immediate release formulation. Figure 2 shows the benefit/risk ratio with venlafaxine extended release and venlafaxine immediate release for the most frequently reported adverse effects. As a conclusion, venlafaxine extended release formulation, when compared with the immediate release formulation, has a consistent tendency to a lower incidence of adverse effects, better adaptation in time and a consistent and greater benefit/risk relationship, more marked in the case of nausea and dizziness.

It can be concluded from the review of these studies that the innovating characteristics of the extended release formulation confer some differential pharmacokinetic characteristics to venlafaxine when compared with the immediate release formulation, which are clinically translated into a more adequate management of the depressive patient, due to a potential greater efficacy and better compliance, greatly due to a more comfortable dosage and better safety profile.

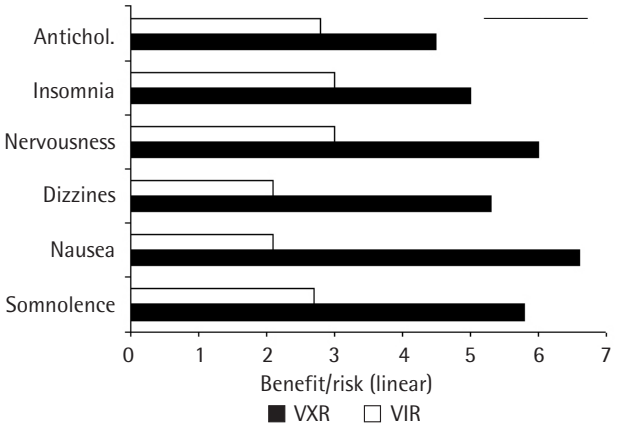

Figure 2 *Benefit/risk values for venlafaxine XR and venlafaxine IR for the most common adverse events. XR: extended release; IR: immediate release; p < 0.05 VXR vs VIR (dizziness, somnolence and nausea). Adapted from Entsuah and Chitra, 1997[24].*

CONCLUSIONS

The differential characteristics of the extended release formulation, which provides the same total exposure to venlafaxine and ODV in a once-daily dose when compared with the immediate release formulation, although with a slower release into the gastrointestinal tract and smaller fluctuations between C_{max} and C_{min} result in a better efficacy potential and better tolerability profile. The better compliance observed for the treatment with venlafaxine extended release formulation could facilitate an adequate management of the depressive patient.

The review of all the studies commented on makes it possible to conclude that venlafaxine extended release formulation may be considered as a technological innovation when compared with the immediate release formulation, considering as an innovation the positive impact that it seems to have on the management of the depressive patient.

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