Combination therapy with reboxetine for major depression patients who are partial or nonresponders to serotonin selective reuptake inhibitors

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Tratamiento de combinación con reboxetina en pacientes con depresión mayor no respondedores o con respuesta parcial a inhibidores selectivos de la recaptación de serotonina

Summary

Introduction. *Recent studies have confirmed the usefulness of the therapeutical combination of two antidepressants from different pharmacological families in patients with single drug therapy resistant depression.*

Methods. *In this prospective 6 weeks open-labeled study, efficacy of combination strategy was evaluated. This included the addition of reboxetine to 34 outpatients with DSM-IV major depressive disorder, who had not responded previously, or who partially responded to conventional treatment in single drug therapy with serotonin selective reuptake inhibitors (SSRI). Data were analyzed on a intent-to-treat basis.*

Results. *Mean decrease in the 21 item Hamilton depression rating scale (HDRS) score was 49.4% (from 26.9 to 13.6; p < 0.0001) and in the clinical global impressions scale (CGI) was 40.4% (from 4.6 to 2.7; p < 0.0001). At the end of the treatment, 47.1% of the patients were considered in remission (HDRS ≤ 10), 55.9% evaluated as responders (HDRS ≤ 50%) and 58.8% considered as having improvement (CGI < 4). No serious side effects were observed during combination therapy, the most frequent being nervousness and the urinary hesitancy (5.9%).*

Conclusions. *The results of this study suggest that addition of reboxetine to SSRI may be an effective and well-tolerated strategy in treatment-resistant patients who have failed to adequately respond to single drug therapy with SSRI.*

Key words: *Major depression. Resistant depression. Combination treatment. Reboxetine. SSRI.*

Resumen

Introducción. *Estudios recientes han confirmado la utilidad de la terapéutica de combinación con dos antidepresivos de diferentes familias farmacológicas en pacientes con depresión resistente al tratamiento en monoterapia.*

Métodos. *En este estudio, de diseño abierto, prospectivo y de 6 semanas de duración, se ha evaluado la eficacia, como estrategia de combinación, de la adición de reboxetina a 34 pacientes con depresión mayor que previamente no habían respondido, o lo había hecho de forma parcial, al tratamiento convencional en monoterapia con inhibidores selectivos de la recaptación de serotonina (ISRS). Los datos fueron analizados mediante el método de intención de tratar.*

Resultados. *La disminución media en la puntuación de la Escala de Hamilton para la depresión de 21 ítem (HAM-D) fue del 49,4% (de 26,9 a 13,6; p < 0,0001) y en la Escala impresión clínica global (ICG) del 40,4% (de 4,6 a 2,7; p < 0,0001). Al final del tratamiento, el 47,1% de los pacientes fue considerado en remisión (HAM-D ≤ 10), el 55,9% evaluado como respondedor (HAM-D ≤ 50%) y el 58,8% considerado en mejoría (ICG < 4). No se observaron efectos adversos graves durante el tratamiento de combinación, siendo los más frecuentes el nerviosismo y la retención urinaria (5,9%).*

Conclusiones. *Los resultados de este estudio constatan que la estrategia de combinación con reboxetina es una herramienta potencialmente útil en casos de depresión resistente al tratamiento en monoterapia con ISRS.*

Palabras clave: *Depresión mayor. Depresión resistente. Tratamiento de combinación. Reboxetina. ISRS.*

INTRODUCTION

Depression is a very frequent psychiatric disorder whose prevalence, according to different studies, ranges from 5% in the National Comorbidity Survey[1] to 17% in the DEPRES (Depression Research in European Society) study[2]. In Spain, the data obtained show a weighted prevalence of 6.7%[3-4]. Such high figures confirm the serious problem that depression represents at present, not only

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exclusively from the clinical point of view but also in terms of loss of quality of life for the patient and economic cost for society (use of health care resources, loss of productivity, etc.)[5-6]. Furthermore, it is estimated that 30 to 40% of these patients do not respond adequately to antidepressive treatment with correct doses, compliance and treatment duration[7-14], although when pragmatic criteria on «treatment resistant depression» are established, these figures seem to be lower (15-20%)[15].

In spite of the importance of these data, there is presently no consensus on the definition of treatment resistant depression or refractory depression[15-18]. There are varied opinions and they consider aspects on the adequacy of the drug administered, dose, treatment duration, previous therapeutic history, etc.[12,19-20]. Thus, the sense of patients who are non-responders or partially responders to antidepressive treatment is used more and more[21]. However, there is a unanimous criterion on the negative prognosis of this type of depression that tends, to a greater degree than in the cases of positive response, to chronicness, with more frequent episodes and greater severity, and with increased suicidal risk[22].

In the approach to partially responding or non-responding patients to antidepressive treatment, several alternatives have been proposed[21,23,24], such as optimization of posological regimen[8,25], switch or change of antidepressive agent[26,27] or addition of a new drug. There are two possibilities in relationship with the last strategy of association. On the one hand, the strategy called potentiation, consisting in the association of a non-antidepressive pharmacological agent *per se*, for example, lithium salts[28,29], buspirone[30], pindolol[31,32] or psychostimulants[33,34] to the pre-existing antidepressive drug. On the other hand, combination strategy is referred to when the association of two antidepressants, generally of different pharmacological families, with a differential pharmacodynamic profile, is mentioned[11,18].

In regards to combination therapies, experience with the association of serotonin selective reuptake inhibitors (SSRI) and tricyclic antidepressants[35-39] as well as the latter with mono-amino-oxidase inhibitors (MAOI)[39-41] has been good, in spite of the possible and potentially dangerous drug interactions that may occur[42]. More recently, some previous studies have shown that the association of reboxetine to non-responder patients treated with SSRI is promising[43-45]. With this strategy, it is aimed to potentiate the two neurotransmission pathways, such as serotoninergic and noradrenergic, most implicitly related with the depressive disorders, by blocking the serotonin and noradrenaline transporters respectively used by the SSRI and reboxetine.

Reboxetine is the first drug of a new family of antidepressive agents; the noradrenaline reuptake selective inhibitors (NRSI)[46]. Its affinity for muscarinic cholinergic, histaminerergic H_1 and adrenergic α_1 receptors is very low[47], so that its use is not associated to the typical adverse effects of the classical tricyclic antidepressants. Comparative, multicentric, double blind and randomized clinical trials with reboxetine in patients with major depression have manifested an antidepressive efficacy superior to the placebo[46,48-49] and, in general lines, to the tricyclic antidepressants with which they have been compared (desipramine and imipramine)[50-52]. Comparative studies have also been performed with fluoxetine, observing a similar antidepressive efficacy[53-55]. A good tolerability profile is added to this clinical efficacy, verified in specific studies[56,57].

The objective of this study is to assess efficacy, as a combination strategy of the addition of reboxetine to the convention drug treatment with SSRI in patients who have not responded previously or who have done so partially during 6 weeks.

METHODS

This open designed, prospective, naturalistic, multicentric and 6 week long study included 34 out-patients of both genders (24 women and 10 men), diagnosed of major depressive disorder (MDD), according to the DSM-IV criteria, who had not responded or had done so partially to a previous treatment of at least 6 weeks of single drug therapy with SSRI (fluoxetine, n = 13; paroxetine, n = 12; sertraline, n = 4; citalopram, n = 4; fluvoxamine, n = 1). The patients, whose ages ranged from 18 to 65 years (mean: 43.4 ± 11.9 years), were selected in different health care centers of Madrid and Barcelona. Partially responding patients were considered to be those in whom a 25-50% reduction was observed in the Hamilton for depression rating scale score for the 6 weeks of single drug treatment, even at doses greater than those generally recommended in the disease. Non-responder patients were those who, under these same criteria, did not decrease their score by at least 25 %[21]. Among the exclusion criteria, pregnant or nursing women, patients with somatic disease that prevented daily life type activities and patients with significant cognitive deterioration were contemplated. During the study period, the initial antidepressive dose (generally superior to the recommended therapeutic dose) was maintained constant. The reboxetine dose added ranged from 2 to 8 mg/day (mean initiation dose of 2.8 ± 1.0 mg/day and mean maintenance dose of 4.6 ± 1.8 mg/day). All the patients enrolled in the study gave their informed consent to participate in it.

Antidepressive efficacy was assessed with the application of the 21 item Hamilton depression rating scale (HAM-D) and the clinical global impression-global improvement scale (CGI-GI) in the weeks 2, 4 and 6. Before initiating treatment with reboxetine (baseline visit: week 0), the HAM-D and CGI-disease severity scale (CGI-DS) was applied (1:normal, not ill;2: borderline case; 3:mildly ill; 4:moderately ill; 5:noticeably ill; 6:seriously ill;7:among the most serious patients). The main efficacy endpoint was defined as the absolute or percentage decrease of the score on the HAM-D scale between the last evaluation and the baseline evaluation. Response and remission indexes were contemplated as

secondary endpoints of efficacy. A responder patient was considered to be one in whom the HAM-D scale score decreased equal to or superior to 50% and patient in remission one with a total score of ≤ 10 in the HAM-D. Secondary efficacy endpoints were also considered to be the variation in the score of the CGI-GI scale (1: much better; 2:moderately better; 3:mildly better; 4:without changes; 5: mildly worse; 6: moderately worse; 7: much worse) at weeks 2, 4 and 6 of the addition of reboxetine and the percentage of patients improved (score < 4 points in the CGI-GI). A comparative analysis was performed between the two groups with the greatest number of patients (fluoxetine and paroxetine). In the adverse effects analysis, all those events occurring during the combination treatment period and that were not present in the baseline assessment were considered. At the end of the study period (week 6), a global subjective assessment of the treatment (efficacy and tolerability) was performed by both the investigator as well as the patient according to the scale: 0: very bad; 1:bad; 2: fair; 3: good; 4: very good.

An analysis of the data was performed by intent-to-treat, using the last-observation-carried-forward (LOCF) method as a tool to attribute lost values, contemplating all the patients with the baseline value and, at least, another assessment, although they had not finished the study period. Homogeneity of the sociodemographic endpoints and of the score on the different scales between the treatment groups in baseline assessment was contrasted by the analysis of variance (ANOVA). In the statistical analysis of the changes obtained in regards to the baseline determinations, the Student's *t* test for paired data was used and the Student's *t* test for independent samples was used in the comparison between groups in the comparison of frequencies. The Chi squared test (with the Yates modification when necessary) was used. A $p < 0.05$ was considered as statistical significance. In the statistical analysis, the MINITAB, version 12.21 (Minitab Inc., 1998) computer program was used

RESULTS

Table 1 shows the demographic data of the patients enrolled, according to the antidepressive drug used in the baseline visit (with its mean dose at the time of baseline assessment) as well as some characteristics of the depressive disorders (type of MDD, number of previous depressive episodes and baseline score on the HAM-D and CGI scales). A total of 70.6% of the patients were women. In relationship with the type of MDD, 70.6 % presented a recurrent episode, the mean for previous episodes being 3.2 ± 3.3. The initial mean dose of reboxetine was 2.8 ± 1.0 mg/day and the mean maintenance dose was 4.6 ± 1.8 mg/day. After the application of the analysis of the variance, no statistically significant differences were obtained between the groups in relationship with the parameters of age of the patients, baseline score on the HAM-D and CGI, and maintenance dose of reboxetine. A total of 52.9% of the patients were classified according to the score obtained in the CGI-DS, as noticeably (CGI-DS = 5) to seriously (CGI-DS: 6/7) ill (38.5% in the fluoxetine group, 50 % in the sertraline and citalopram groups, and 75 % in the paroxetine group). Some benzodiazepine was consumed during the study by 61.8% of the patients enrolled. Other psychodrugs were used in much lower proportion: antipsychotics, lithium salts and disulfiram, in one patient respectively, and thyroid hormones in two patients.

The mean score on the HAM-D in the baseline visit was 26.9 ± 6.2 points, decreasing to 13.6 ± 9.1 in week 6 (49.4% reduction; $p < 0.0001$) (table 2). The differences in the decrease of the HAM-D score were significant in week 2 after reboxetine was added, both in the total group as well in the two subgroups of patients analyzed (fluoxetine and paroxetine). No statistical differences were found between both groups in any of the intermediate visits or at the end of the treatment (fluoxetine: –15.3 ± 10.7; paroxetine: –14.2 ± 7.7) (figs. 1 and 2). The percentage of responder patients (HAM-D (50%) (table 3)

TABLE 1. Demographic and psychiatric data

	Fluoxetine	*Paroxetine*	*Sertraline*	*Citalopram*	*Fluvoxamine*	*Total*
n	13	12	4	4	1	34
Age (years)	45.4 ± 12.5	43.3 ± 11.9	34.5 ± 6.6	45.0 ± 15.6	47	43.3 ± 11.9
Gender						
W (%)	6 (46.15)	10 (83.33)	4 (100)	3 (75)	1 (100)	24 (70.59)
M (%)	7 (53.85)	2 (16.67)	0 (0)	1 (25)	0 (0)	10 (29.41)
MDD type						
Single episode	2	3	2	3	—	10
Recurrent episode	11	9	2	1	1	24
No. of episodes*	2.5 ± 2.7	4.4 ± 4.4	3	2	3	3.2 ± 3.3
Mean dose**	25.4 ± 8.8	29.2 ± 11.6	75.0 ± 28.9	42.5 ± 12.6	300.0	—
HAM-D	26.9 ± 6.9	29.6 ± 4.7	26.5 ± 3.9	22.2 ± 4.4	14.0	26.9 ± 6.2
CGI-DS	4.4 ± 0.8	4.9 ± 0.7	4.7 ± 0.9	4.5 ± 0.6	3.0	4.6 ± 0.8

W: women; M: men; HAM-D: 21 item Hamilton depression rating scale; CGI-DS: global clinical impression-disease severity. *Number of previous depressive episodes. **Mean dose (mg/day) of antidepressant used before combination treatment.

TABLE 2. Mean score (± SD) in the HAM-D score on baseline visit (week 0) and in the last determination (week 6)

	Week 0	*Week 6*			
		LOCF		*DC*	
Fluoxetine	26.92 ± 6.933	11.62 ± 10.08	p < 0.0001	7.80 ± 8.01	p < 0.0001
Paroxetine	29.58 ± 4.68	15.42 ± 8.96	p < 0.0001	10.71 ± 5.99	p < 0.0001
Sertraline	26.50 ± 3.87	18.00 ± 7.83	p = 0.108	14.67 ± 5.03	p = 0.043
Citalopram	22.25 ± 4.43	13.75 ± 7.37	p = 0.205	11.00 ± 7.94	p = 0.16
fluvoxamine	14.00	3.00	—	3.00	—
Total	26.88 ± 6.18	13.59 ± 9.10	p < 0.0001	9.71 ± 7.03	p < 0.0001

LOCF: Last-Observation-Carried-Forward analysis. DC: analysis by complete data or by protocol.

and those in remission (HAM-D ≤ 10 points) (table 4) in week 6 was 55.9% and 47.1%, respectively. No differences existed between the treatment subgroups in regards to the number of responder patients (fluoxetine: 8 [61.5%]; paroxetine: 6 [50%]; sertraline: 2 [50%]; citalopram: 2 [50%]; $\chi^2 = 0.423$, ddl = 3; p = 0.935) and those in remission (fluoxetine: 8 [61.5 %]; paroxetine: 4 [33.3 %]; sertraline: 1 [25 %]; citalopram: 2 [50 %]; $\chi^2 = 2,776$; ddl = 3; p = 0.427).

At the end of the treatment, a mean decrease was obtained in the score of the CGI-GI scale of –1.85 ± 1.46 (40.4% of reduction versus baseline values, p < 0.0001). The paroxetine group patients showed a lower reduction in the CGI score, obtaining significant differences in week 2 (*versus* fluoxetine, p = 0.0049) (fig. 3). The percentage of patients with improvement (absolute value in the CGI-GI < 4 points) at the end of the treatment was 58.8 %, no statistical differences being observed between the different treatment subgroups (fluoxetine: 8 (66.7 %); paroxetine: 6 (50 %); sertraline: 3 (75 %); citalopram: 2 (50 %); χ^2=0.957; ddl = 3; p = 0.812).

In the patient subpopulation classified as noticeably to seriously ill in the baseline visit (CGI-GI ≥ 5; n = 18), mean decrease in the total HAM-D score was –4.8 ± 10.3,

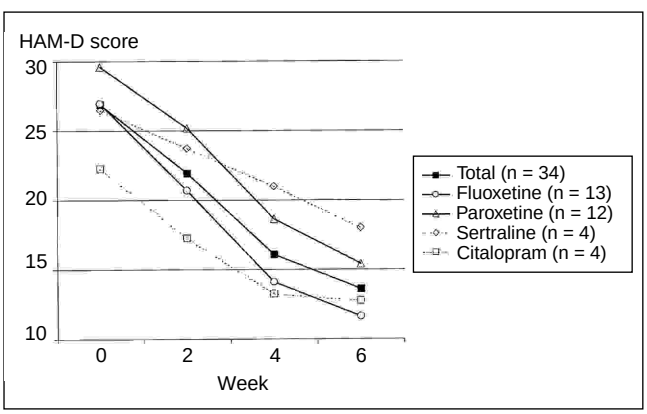

Figure 1. Decrease in total score of the HAM-D scale of the baseline evaluation at week 6 (LOCF analysis).

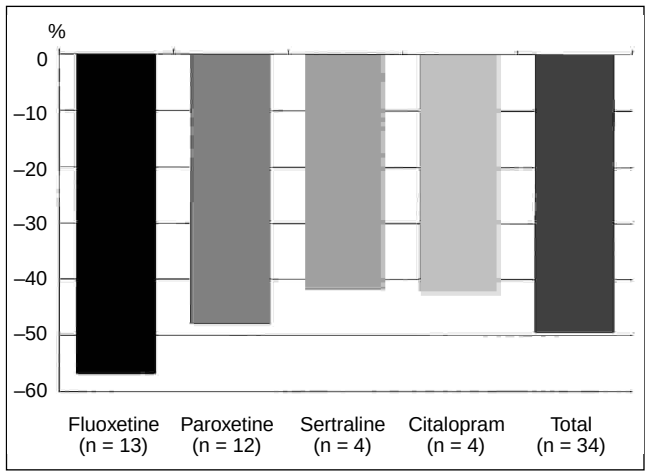

Figure 2. Percentage of decrease in total score on HAM-D scale, according to treatment subgroups (LOCF analysis).

a figure similar to that obtained in the total sample (–13.3 ± 9.3). The decrease in the CGI-GI score was also similar (–2.17 ± 1.42 *versus* –1.85 ± 1.49). The percentage of patients with improvement (55.6% *versus* 58.8%, p = 0.821), responders (55.6 % *versus* 55.8%; p = 0.982) and those in remission (38.9 % *versus* 47.1%; p = 0.569) was slightly less at the end of the treatment in this subgroup of patients.

The data on the subjective evaluation of efficacy and tolerance of the treatment by the investigators and the patients were filled out in 27 cases. A total of 65.4% of the investigators and 59.2% of the patients considered that the efficacy of the treatment was good or very good while tolerance was graded as bad-very bad by only 11.1% of the investigators and patients (fig. 4).

During the development of the study, there were 10 treatment withdrawals; one patient from the paroxetine subgroup withdrew due to absence of efficacy, five due to adverse effects (two in the fluoxetine subgroup, two in the paroxetine subgroup and one in the citalopram subgroup) and four for personal reasons that were not related with the study. In the analysis by complete data or by protocol (excluding withdrawals), the statistical differences obtained in the LOCF analysis are maintained (tables 2, 3 and 4).

The adverse effects reported during the 6 weeks of the study are shown in table 5. All of the adverse effects were listed as mild or moderate intensity, including the five patients who withdrew from treatment for this reason. Of them, four were related by the investigators with reboxetine (two cases of nervousness with insomnia, one case of urinary hesitancy and one case of periorbital edema). Urinary hesitancy and nervousness were the most frequently reported adverse effects (5.9 %). The rest of the adverse effects were only reported in one case each one (hypersweating, mouth dryness, tremors, insomnia, asthenia, etc.). Specific drug treatment of these adverse effects was not necessary at any time.

TABLE 3. Number of responder patients (percentage) (HAM-D ≤ 50 %) after addition of reboxetine

	Week 2	*Week 4*		*Week 6*	
	LOCF	*LOCF*	*DC*	*LOCF*	*DC*
Fluoxetine	2/13 (15.38)	7/13 (53.85)	7/11 (63.64)	8/13 (61.54)	8/10 (80)
Paroxetine	1/12 (8.33)	4/12 (33.33)	3/10 (30)	6/12 (50)	5/7 (71.43)
Sertraline	0/4	0/4	0/3	2/4 (50)	2/3 (66.67)
Citalopram	1/4 (25)	2/4 (50)	2/4 (50)	2/4 (50)	2/3 (66.67)
Fluvoxamine	0/1	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Total	4/34 (11.76)	14/34 (41.18)	13/29 (44.83)	19/34 (55.88)	18/24 (75)

LOCF: Last-Observation-Carried-Forward analysis. DC: analysis by complete data or by protocol.

DISCUSSION

The results of this study, in spite of its open design, suggest that the addition of reboxetine in patients who are non-responders or partially responders to treatment in single drug therapy with SSRI, can be an effective and well tolerated therapeutic strategy. It is obvious that the results of the open studies, without a control group, are methodologically questionable. However, the use of placebo in this type of patients is also questionable from the ethical point of view, given that the risk of suicidal behaviors is notoriously greater[58]. In the same way, the limited sample size of some treatment subgroups in our study (sertraline, citalopram and fluvoxamine) prevents an adequate comparative analysis, so that, in this sense, we have confined ourselves from a merely descriptive point of view to those subpopulations having greater sample size.

On the other hand, it must be stated that the interpretation of the results of the studies on the treatment of patients with resistant depression is not easy because, to a large degree, of the variability of the methodology used and lack of consensus in the conceptualization of resistant depression[16,59]. In this way, different inclusion/exclusion criteria of patients have been applied and there is a large divergence in the consideration of the time used to define the resistance condition as well as in seriousness, number and duration of depressive episodes[19-20]. Furthermore, use of different assessment scales of the antidepressive response and establishment of different posological regimes make it difficult to understand the problem[18,60].

Given the lack of consensus, in this study, we have considered patients resistant to antidepressive treatments, as stated by Lam and collaborators[18] as those patients who are non-responders or partially responders, according to the Hirschfeld et al. criteria[21] to a previous single drug treatment with SSRI for a 6 week period, the time considered «adequate» to assess the antidepressive response for most of the authors[59].

Recent revisions verify that 36% of the patients with MDD enrolled in double-blind, placebo controlled clinical trials and in open studies do not respond to antidepressive treatment or do so partially, even at the highest doses of the recommended therapeutic range[16]. In regards to the usual clinical practice, it is estimated that more than 50% of depressive patients have an inadequate response to single drug therapy antidepressive treatment[8,15-16] and the depression acquires a chronic character in 20 % of the cases after several pharmacological interventions[61-62]. In relationship with SSRI, O'Reardon et al.[63] state that 30% of depressive patients do not obtain an adequate response to the initial treatment and 60-70 % do not achieve complete remission. In any event, and in general lines, it is assumed that one third of the patients generally respond adequately to antidepressive treatment, another third generally respond partially and finally, another third of the patients do not respond to initial antidepressive treatment. It is the last two thirds in

TABLE 4. Number of patients (percentaje) in remission (HAM-D ≤ 10) after addition of reboxetine

	Week 2	*Week 4*		*Week 6*	
	LOCF	*LOCF*	*DC*	*LOCF*	*DC*
Fluoxetine	1/13 (7.69)	8/13 (61.54)*	8/11 (72.73)**	8/13 (61.54)	8/10 (80)
Paroxetine	0/12	3/12	3/10 (30)	4/12 (33.33)	4/7 (57.14)
Sertraline	0/4	0/4	0/3	1/4 (25)	1/3 (33.33)
Citalopram	1/4 (25)	1/4 (25)	1/4 (25)	2/4 (50)	2/3 (66.67)
Fluvoxamine	0/1	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)
Total	2/34 (6.88)	13/34 (38.24)	13/29 (44.83)	16/34 (47.06)	16/24 (66.67)

LOCF: Last-Observation-Carried-Forward analysis. DC: analysis by complete data or by protocol. * p = 0.047 versus paroxetine; ** p = 0.031 *versus* paroxetine.

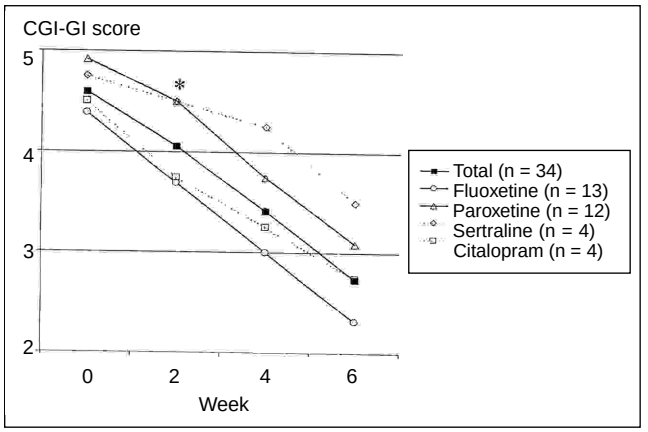

Figure 3. Score on CGI scale of the baseline evaluation at week 6 (LOCF analysis). *p = 0.0049 *versus* fluoxetine.

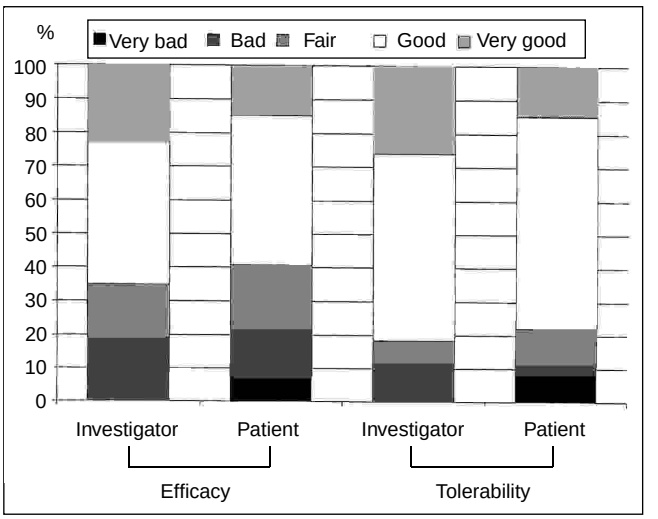

Figure 4. Global subjetive evaluation of the efficacy and tolerability of the reboxetine + SSRI combination (percentage of patients and investigators) (n = 27).

whom the mechanisms necessary to achieve improvement of the therapeutic results should be implemented, either by optimizing the posological regimen of the agent that has been used or by switching it, or by adding another drug, antidepressive (combination strategy) or not (potentiation strategy).

Compared to the switching strategy, the combination strategy should be considered when there is a partial response of the drug used as first choice, since, this would prevent gradual discontinuation of the treatment underway, conserving the partial beneficial effects obtained[11]. On the other hand, lack of response in 4 weeks, at therapeutic doses, is a predictive factor of poor prognosis when substituting the medication in the successive weeks[64-66]. Furthermore, the combination strategy has another series of advantages: it minimizes the demoralizing psychological effect of failure for the patient, avoids the appearance of the symptoms of an antidepressive discontinuation syndrome, permits the possibility of using lower doses of the two antidepressants used, reducing the possibility of adverse effects, the possibility of complementing certain symptoms that are not resolved by the first antidepressant, and «improves» some adverse effects induced by it and the possibility of achieving a faster response than that obtained by the substitution strategy[18]. However, the possibility that drug interactions can appear as well as the increase of adverse effects must be considered. These precautions should be taken into consideration, especially in the case of tricyclic antidepressants, the monitoring of plasma levels being recommendable. Thus, in non-responder or partially responder patients ones susceptible to being treated with both antidepressive drugs in combination, the following should be kept in mind: a benefit/risk ratio, a greater incidence of adverse effects versus a decrease of morbidity and/or mortality by suicide and the possibility of a «decrease of the therapeutic response» after repeated treatment failures[13].

The best documented combination strategies in the literature and that contribute the best results of clinical efficacy are those of SSRI with tricyclic antidepressants[35-39,67], SSRI with mirtazapine[68,69] and SSRI with bupropion[70-72]. More anecdotal data also sustain the combinations of venlafaxine with tricyclic antidepressants[73], while the combination with several SSRI is debatable, although some pilot studies, with a small number of patients, point to the efficacy of the combinations of citalopram with

TABLE 5. Adverse effects (percentage) reported after the addiction of reboxetine

	Fluoxetine	*Paroxetine*	*Sertraline*	*Citalopram*	*Fluvoxamine*	*Total*
Urinary hesitancy	1 (7.69)	1 (8.33)				2 (5.88)
Nervousness	1 (7.69)			1 (25)		2 (5.88)
Increased sweating	1 (7.69)			1 (25)		1 (2.94)
Mouth dryness		1 (8.33)				1 (2.94)
Tremor	1 (7.69)					1 (2.94)
Insomnia				1 (25)		1 (2.94)
Asthenia	1 (7.69)					1 (2.94)
BP abnormality	1 (7.69)					1 (2.94)
Periorbital edema		1 (8.33)				1 (2.94)

fluvoxamine[74] and citalopram with fluoxetine[75]. Recently, several studies have been published that indicate the adequacy of the association between SSRI and reboxetine[43-45], with very promising results.

In general, the combination strategies are usually effective in 50-60% of the cases, although this varies based on the agent used[27]. In our study, the results confirm these data, with a 58.8% percentage of «improved» patients, 55.9 % of responders to combination treatment and 47.1% of patients in remission. Similar results can be observed in the three open studies published up to now with reboxetine, although the number of patients included is inferior to that supplied by us. Lucca et al.[44] obtain very significant results with a sample of 14 patients diagnosed of MDD or bipolar disorder, non-responders to a conventional treatment with SSRI, alone or in combination with pindolol, at the end of 2 weeks of the association of reboxetine at subtherapeutic doses (2-4 mg/day). In our study, the percentage of responder patients reaches 11.8% at 2 weeks, and 41.2% at 4 weeks. Even more recently, this same group[45] published the results obtained in a larger series of patients (27 subjects with diagnosis of MDD, without (n = 24) or with (n = 3) psychotic features), following the previously described methodological procedure. A total of 44.4% of the patients in all the sample showed complete remission, 29.6% partial remission and 26% did not improve. In this sense, patients with psychotic features, two of whom had to discontinue to medication due to therapeutic inefficacy, stand out negatively.

On their part, Hawley et al.[76] presented data from a series of 24 patients with incomplete response to SSRI, treated in combination with reboxetine. These authors obtained a 62.5 % decrease in the score on the Montgomery-Asberg for depression scale (MADRS) in the 6th week of treatment and complete remission (MADRS < 10 points) in nine patients (37.5 % of the sample). More specific data have been supplied by Devarajan and Dursun[43]; four patients diagnosed of drug treatment resistant depression (more than two SSRI, a tricyclic antidepressant, potentiation therapy with lithium, thyroid hormones and psychotherapy, and venlafaxine) or even to electroconvulsive therapy (in three cases). These patients were treated with a dose of 20-60 mg/day of citalopram and 4-6 mg/day of reboxetine, for 16 weeks, obtaining, at the end of the treatment, reductions in the HAM-D scale score ranging from 73 to 88.8 %. Finally, and from the experimental point of view, Harkin et al.[77] verified that the combination of sertraline and reboxetine made it possible to obtain a faster pharmacological response than with each one of the antidepressants alone in animal models of depression.

The results of these preliminary studies, together with those supplied by us, make it possible to anticipate the interest of the combination therapy in non-responder patients to conventional treatment with SSRI, as the action mechanisms of these agents affect the different neurotransmission pathways[78]. In this sense, it has been proposed that the antagonism of the presynaptic α_2-adrenoreceptors can complement the action of the serotonin noradrenaline reuptake inhibitors, increasing the clinical response[79]. On their part, Lucca et al.[44] hypothesize that long term treatment with subtherapeutic doses of reboxetine could cause a desensitization of the presynapitc α_2-adrenergic heteroreceptors in serotoninergic neurons, a fact that would be translated into a potentiation of the serotoninergic neurotransmission.

On the other hand, the limited incidence of adverse effects observed in the combination studies with reboxetine, even ours, could be correlated with the pharmacokinetic profile of this drug[80]. In relationship with this aspect, it is worth mentioning that the *in vitro* studies (human microsomes) performed up to now show that reboxetine, at concentrations that are eight times higher than their C_{max}, do not inhibit any of the principal isoforms of CYP450, as the CYP2D6, CYP3A4, CYP1A2, CYP2C9 and CYP2C19[81], nor does it have *in vivo* capacity to induce the isoform CYP3A4[82]. Recent *in vivo* studies give validity to these data. Avenoso et al.[83] confirm that the administration of reboxetine to healthy volunteers (at therapeutic doses) does not modify the biotransformation of dextromethorphan to dextrorphane, a widely used substrate to assess the inhibitory capacity of the CYP2D6 isoenzyme. In the same way, the addition of 50 mg of quinidine, an inhibitor agent of isoenzyme CYP2D6, to healthy volunteers treated with 1 mg of reboxetine, does not modify the pharmacokinetic parameters of the antidepressant[84]. All these data seem to verify that serious drug interactions with reboxetine, translated into a greater incidence of adverse effects, are not predictable, when this must be associated to another antidepressive drug. In this sense, in a recent randomized design and double-blind study[85], the potentiality of possible interactions between reboxetine and fluoxetine was evaluated in 30 healthy volunteers. The subjects received 8 mg/day of reboxetine and 20 mg/day of fluoxetine for 8 days, and it was manifested that there were not statistically significant differences in different pharmacokinetic parameters in the patients simultaneously treated with both antidepressants versus each one of them administrated individually. The authors conclude that the concomitant administration of both antidepressants is well tolerated and no clinical impact can be expected in depressive patients who should be treated with this combination strategy.

In conclusion, we should insist that combination strategy with reboxetine seems to be a potentially useful tool in cases of resistant depression to treatment with SSRI. However, future controlled studies are necessary to determine the efficacy of the association of reboxetine to treatment with SSRI in single drug therapy in non-responder or partially responder patients.

REFERENCES

1. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the national comorbidity survey. Am J Psychiatry 1994;151:979-86.

2. Lepine JP, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European Study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol 1997;12:19-29.
3. Estudio sociológico Libro Blanco: La depresión en España. Madrid: Gabinete de Estudios Sociológicos Bernard Krief, 1982.
4. Vázquez-Barquero J, Díez-Manrique J, Peña C. A community mental health survey in Cantabria: a general description of morbidity. Psychol Med 1987;17:227-41.
5. López-Ibor JJ, Álamo C, López-Muñoz F. Evolution of the management of depression in Spain from the psychiatrist's perspective. A comparative analysis: 1997 vs 1982. Eur Psychiatry 2000;15:362-9.
6. López-Ibor JJ, Álamo C, López-Muñoz F. A comparative analysis of depression management in primary care practice in Spain: 1997 vs 1982. Prim Care Psychiatry 1999; 5:133-45.
7. Roose SP, Glassman AH, Walsh BT. Tricyclic nonresponders: phenomenology and treatment. Am J Psychiatry 1986; 143:345-8.
8. Nieremberg AA, Amsterdam JD. Resistant depression: definition and treatment approaches. J Clin Psychiatry 1990; 51:S39-47.
9. Dinan TG. Lithium augmentation in sertraline-resistant depression: a preliminary dose-response study. Acta Psychiatry Scand 1993;88:300-1.
10. Fawcett J. Antidepressants: partial response in chronic depression. Br J Psychiatry 1994;165:37-41.
11. Sokolov STH, Joffe RT. Practical guidelines for combination drug therapy of treatment-resistant depression. CNS Drugs 1995;4:341-50.
12. Thase ME, Rush AJ. Treatment-resistant depression. En: Bloom FE, Kupfer DJ, editores. Psychopharmacology: the fourth generation of progress. New York: Raven Press, 1995; p. 1081-97.
13. Amsterdam JD, Horning-Rohan M. Treatment algorithms in treatment-resistant depression. En: Horniz-Rohan M, Amsterdam JD, editores. Treatment-resistant depression. Psychiatric Clinics North America. Philadelphia: Saunders Publ Co, 1996; p. 371-86.
14. Nemeroff CB. Augmentation strategies in patients with refractory depression. Depression 1997;4:169-81.
15. Burrows GD, Norman TR, Judd FK. Definition and differential diagnosis of treatment-resistant depression. Int Clin Psychopharmacol 1994;8(Suppl 2):5-10.
16. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996; 19:179-200.
17. Scheweitzer I, Tuckwell V, Johnson G. A review of the use of augmentation therapy for the treatment of resistant depression: implications for the clinician. Austr NZ J Psychiatr 1997;31:340-52.
18. Lam RW, Wan DDC, Cohen NL. Combining antidepressants for treatment-resistant depression: a review. J Clin Psychiatry 2002;63:685-93.
19. Souery D, Amsterdam J, de Montigny C. Treatment resistant depression: methodological overview and operational criteria. Eur Neurpsychopharmacol 1999;9:83-91.
20. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62(Suppl 16): 10-7.
21. Hirschfeld RM, Montgomery SA, Aguglia E. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. J Clin Psychiatry 2002; 63:826-37.
22. Schatzberg AF, Cole JO, Cohen BM. Survey of depressed patients who have failed to respond to treatment. En: Davis JM, Maas JW, editores. The affective disorders. Washington: American Psychiatric Press, 1983; p. 73-85.
23. Fava M. New approaches to the treatment of refractory depression. J Clin Psychiatry 2000;61(Suppl 1):26-32.
24. Nelson JC. Augmentation strategies in depression. J Clin Psychiatry 2000;61(Suppl 2):13-9.
25. Fava M, Rosenbaum JF, Cohen L. High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. J Affect Disord 1992;25: 229-34.
26. Kelsey JE. Switching drug class after initial SSRI failure. J Clin Psychiatry 1997;58:326-7.
27. Joffe RT. Substitution therapy in patients with major depression. CNS Drugs 1999;11:175-80.
28. Rouillon P, Gorwood A. The use of lithium to augment antidepressant medication. J Clin Psychiatry 1993;59:S32-9.
29. Zullino D, Baumann P. Lithium augmentation in depressive patients not responding to selective serotonin reuptake inhibitors. Pharmacopsychiatry 2001;34:119-27.
30. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. J Clin Psychopharamcol 1998; 18:465-9.
31. Moreno FA, Gelenberg AJ, Bachar K. Pindolol augmentation of treatment-resistant depressed patients. J Clin Psychiatry 1997;18:465-9.
32. Blier P, Bergeron R. The use of pindolol to potentiate antidepressant medication. J Clin Psychiatry 1998;59(Suppl 5):16-23.
33. Ayd FJ Jr, Zohar J. Psychostimulant (amphetamine or methylphenidate) therapy for chronic and treatmen-resistant depression. En: Zohar J, Belmaker RH, editores. Treating resistant depression. New York: PMA Publishing, 1987; p. 343-55.
34. Stoll AL, Pillay SS, Diamond L. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. J Clin Psychiatry 1996;57:72-6.
35. Weilburg JB, Rosenbaum JF, Biederman J. Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. J Clin Psychiatry 1989;50:447-9.
36. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry 1994;151:1372-4.
37. Zajecka JM, Jeffriess H, Fawcett J. The efficacy of fluoxetine combined with a heterocyclic antidepressant in treatment-resistant depression: a retrospective analysis. J Clin Psychiatry 1995;56:338-43.
38. Szegesi A, Wetzel H, Leal M. Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety and tolerability data. J Clin Psychiatry 1996;57:257-64.
39. Amsterdam JD, García-España F, Rosenzwig M. Clomipramine augmentation in treatment-resistant depression. Depression Anxiety 1997;5:84-90.
40. Davidson J, McLeod M, Law-Yone B. A comparison of electro-convulsive therapy and combined phenelzine-amitriptyline in refractory depression. Arch Gen Psychiatry 1978;35:639-42.
41. Berlanga C, Ortega-Soto HA. A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/ tricyclic combination. J Affect Disord 1995;34:187-92.
42. Álamo C, López-Muñoz F, Cuenca E. Interacciones farmacológicas potenciales en psicofarmacología. En: Pichot P,

editor. Psicofarmacología: de los mecanismos básicos a la respuesta clínica. Madrid: Aula Médica, 1999; p. 637-62.
43. Devarajan S, Dursun SM. Citalopram plus reboxetine in treatment-resistant depression. Can J Psychiatry 2000;45: 489-90.
44. Lucca A, Serretti A, Smeraldi E. Effect of reboxetine augmentation in SSRI resistant patients. Human Psychopharmacol Clin Exp 2000;15:143-5.
45. Serretti A, Lucca A, Cusin C, Smeraldi E. Associazione di reboxetina nella depressione resistente a SSRI G. Ital Psicopatol 2001;7:9-14.
46. Montgomery SA. Reboxetine: additional benefits to the depressed patient. J Psychopharmacol 1997;11(Suppl 4):9-15.
47. Wong EHF, Sonders MS, Amara SG. Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. Biol Psychiatry 2000;47:818-29.
48. Versiani M, Mehilane L, Gaszner P, Arnaud-Castiglioni R. Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. J Clin Psychiatry 1999;60:400-6.
49. Versiani M, Mohammed A, Guy CH. Double-blind, placebo-controlled study with reboxetine in impatients with severe major depressive disorder. J Clin Psychopharmacol 2000;20:28-34.
50. Berzewski H, Van Moffaert M, Gagiano CA. Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. Eur Neuropsychopharmacol 1997;7(Suppl 1): 37-47.
51. Ban TA, Gaszner P, Aguglia E. Clinical efficacy of reboxetine: a comparative study with desipramine, with methodological considerations. Hum Psychopharmacol 1998; 13:S29-39.
52. Katona C, Bercoff E, Chiu E. Reboxetine versus imipramine in the treatment of elderly patents with depressive disorders: a double-blind randomised trial. J Affect Disord 1999;55:203-13.
53. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol 1997; 11(Suppl 4):17-23.
54. Massana J. Reboxetine versus fluoxetine: an overview of efficacy and tolerability. J Clin Psytriatry 1998;59:8-10.
55. Massana J, Möller HJ, Burrows GD, Montenegro RM. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. Int Clin Psychopharmacol 1999; 14:73-80.
56. Mucci M. Reboxetine: a review of antidepressant tolerability. J Psychopharmacol 1997;11(Supp 1):33-7.
57. Tanum L. Reboxetine: tolerability and safety profile in patients with major depression. Acta Psychiatr Scand 2000;101(402):37-40.
58. Stanley B. An integration of ethical and clinical considerations in the use of placebo. Psychopharmacol Bull 1988; 24:180-220.
59. Berman RM, Narasimhan M, Charney DS. Treatment-refractory depression: definitions and characteristics. Depression Anxiety 1997;5:154-64.
60. Phillips KA, Nierenberg AA. The assessment and treatment of refractory depression. J Clin Psychiatry 1994;55 (Suppl 2):20-6.
61. Keller MB, Klerman GL, Lavori PW. Long-term outcome of episodes of major depression: clinical and public health significance. JAMA 1984;252:788-92.
62. Paykel ES. Epidemiology of refractory depression. En: Nolen WA, Zohar J, Rosse SP, et al., editores. Refractory depression: current strategies and future directions. New York: John Wiley and Sons, 1994; p. 3-18.
63. O'Reardon JP, Brunswick DJ, Amsterdam JD. Treatment-resistant depression in the age of serotonin: evolving strategies. Curr Opin Psychiatry 2000;13:93-8.
64. Nieremberg AA, McLean NE, Alpert JE. Early nonresponse to fluoxetine as a predictor of poor 8-week outome. Am J Psychiatry 1995;152:1500-3.
65. Quitkin FM, McGrath PJ, Stewart JW. Chronological milestones to guide drug changes: when should clinicians switch antidepressants? Arch Gen Psychiatry 1996;53:785-92.
66. Howland RH, Thase ME. What to do with SSRI nonresponders? J Pract Psychiatr Behav Health 1999;5:216-23.
67. Nelson JC, Mazure CM, Bowers MB, et al. A preliminary open study if the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303-7.
68. Carpenter LL, Jocic Z, Hall JM. Mirtazapine augmentation in the treatment of refractory depression. J Clin Psychiatry 1999;60:45-9.
69. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mitazapine. Biol Psychiatry 2002;51:183-8.
70. Bodkin JA, Lasser RA, Wines JD. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry 1997;58: 137-45.
71. Spier SA. Use of bupropion with SRIs and venlafaxine. Depression Anxiety 1998;7:73-5.
72. Kennedy SH, McCann SM, Masellis M. Combining bupropion SR with velafaxine, paroxetine, of fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. J Clin Psychiatry 2002; 63:181-6.
73. Gómez-Gómez JM, Perramón CT. Combined treatment with venlafaxine and tricyclic antidepressants in depressed patients who had partial response to clomipramine or imipramine: initial findings. J Clin Psychiatry 2000;61:285-9.
74. Bondolfi G, Chautems C, Rochat B. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacology 1996;128:421-5.
75. Bondolfi G, Lissner C, Kosel M. Fluoxetine augmentation in citalopram non-responders: pharmacokinetic and clinical consequences. Int J Neuropsychopharmacol 2000;3:55-60.
76. Hawley CJ, Sivakumaran T, Ochocki M, Bevan J. Coadministration therapy with reboxetine and serotonin specific reuptake inhibitors in twenty-four patients with major depression. 13th Congress of European College of Neuropsychopharmacology. Munich, september 9-13, 2000.
77. Harkin A, Kelly JP, McNamara M. Activity and onset of action of reboxetine and effect of combination with sertraline in an animal model of depression. Eur Pharmacol 1999;364:123-32.
78. Nelson JC. Synergistic benefits of serotonin and noradrenaline reuptake inhibition. Depression Anxiety 1998; 7(Suppl 1):5-6.
79. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. Lancet 2000;355:911-8.
80. Cuenca E, Álamo C, López-Muñoz F, Coullaut-Jáuregui J. Perfil farmacodinámico y farmacocinético de un nuevo antidepresivo: reboxetina. Psiquiatría Biol 1999;6: 86-90.
81. Brosen K. Reboxetine: pharmacokinetics in humans. Abstract Boooklet Simposio. Cerdeña, Italia, 1-3 may, 1998.

82. Pellizzoni C, Poggesi I, Jorgensen NP. Pharmacokinetics of reboxetine in healthy volunteers: single vs repeated oral doses and lack of enzymatic alterations. Biopharm Drug Dispos 1996;17:623-33.
83. Avenoso A, Facciolà G, Scordo MG, Spina E. No effect of the new antidepressant reboxetine on CYP2D6 activity in healthy volunteers. Ther Drug Monit 1999;21:577-9.
84. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. Clin Pharmacokinet 2000;39: 413-27.
85. Fleishaker JC, Herman BD, Pearson LK. Evaluation of the potential pharmacokinetic/pharmacodynamic interaction between fluoxetine and reboxetine in healthy volunteers. Clin Drug Invest 1999;18:141-50.