Kobe J. Med. Sci., Vol. 54, No. 2, pp. E147-E158, 2008

The Efficacy of Reboxetine as an Antidepressant, a Meta-analysis of Both Continuous (Mean HAM-D Score) and Dichotomous (Response Rate) Outcomes

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Received 29 October 2007 /Accepted 9 January 2008

Key words: reboxetine, depression, antidepressants, HAMD scale, effect size, imputed SD

Reboxetine is the first selective Norepinephrine Reuptake Inhibitor (NRI). There are limited numbers of quantitative synthesis studies of the efficacy of this drug in treating depressive disorders. We have meta-analyzed the efficacy of the reboxetine using both continuous and dichotomous outcome measures. Data was collected from the Pubmed search of English-language studies published from 1997 to 2007 and manual search of retrieved articles. We have searched for controlled clinical trials of reboxetine with any other antidepressant comparator or placebo in adults with depressive disorders using HAM-D scale for the outcome measure. After 11 studies were selected, separate meta-analyses for the active drug and for the placebo were performed using random effect model. The overall effect size compared with the other antidepressants was -0.06 (95%CI: -0.19; 0.08), with placebo -1.54 (95%CI: -2.23; -0.85). It was calculated using the final mean HAM-D score (continuous outcome). The pooled SD was used when the variance was not available. Pooled odds ratios for the response rates (dichotomous outcome) were 1.04 (95%CI: 0.75; 1.46) and 2.85 (95%CI: 1.88; 4.31) for the active drug and placebo comparisons accordingly. These results suggest that the efficacy of the reboxetine and the other antidepressants (SSRI, TCA and SNRI) on both measures does not differ while it is significantly superior to placebo.

Depression is becoming a major health issue not only in the industrialized countries but also in the developing world. It is expected to become the leading cause of disability worldwide by the year of 2020 according to WHO. Pharmacotherapy is the first line treatment, and it is a practical tool not only for the specialist doctors, but also for general or primary care doctors. SSRIs are the most widely prescribed pharmacological agents. Nevertheless, other classes of antidepressants are being actively studied and introduced in the recent years. Accordingly, meta-analyses of not only SSRIs, but also other groups have been conducted. However, there is very limited number of quantitative synthesis studies of reboxetine. It is the first selective Norepinephrine Reuptake Inhibitor (NRI) that affects only α2 adrenoreceptors and does not have anticholinergic and antihistaminic actions (7, 23). The Tricyclic Antidepressants (TCA) inhibit the noradrenaline re-uptake as well. However, TCAs act as both α1 and α2 adrenoreceptors antagonists and have anticholinergic, antihistaminic actions that are responsible for their side-effects (18, 28). Reboxetine was

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synthesized in the mid-1960s and identified as a potential antidepressant. It was found that reboxetine was desensitizing the α2-receptors in a single oral dose (11).

The recent published meta-analysis on reboxetine includes only studies against SSRI and does not evaluate the efficacy of reboxetine using the mean values of the HAM-D scores (continuous variable). Instead it meta-analyzes the response and discontinuation rates (all dichotomous variables) (20). Despite its subjectivity the HAM-D rating scale has become well-validated and highly reliable tool in assessment of the severity of the depression and has been widely used in clinical trials of antidepressant drugs as a measure of their efficacy. The improvement on this scale is better indication of the efficacy of the drug being studied rather than sheer response rate as an outcome measurement.

The aim of the study was to assess the overall efficacy of reboxetine in the adult patients with depressive disorders employing meta-analyses of both continuous (mean values on HAM-D scale) and dichotomous (response rates) measures.

MATERIALS AND METHOD

Search strategy and study inclusion criteria

We have searched Medline, Cochrane database using keywords reboxetine, depression (with Boolean operator AND) and using the limitations: from 1997 to 2007; English language; all adult, randomized controlled trials. A search of review articles with the same key words also has been done in order to obtain relevant studies. The reference lists of all primarily retrieved studies and articles were manually screened for the additional studies. All potential studies have been assessed independently by two investigators according the following criteria: the study design – the controlled clinical trials, the population – all adult patients with depressive disorders (age + 18), control groups – placebo and other active agents, the outcome – the improvement on HAM-D scale either response rate or the both. Disagreements were resolved through the discussions between two investigators getting to consensus.

Data extraction

From the studies which met the above criteria and were included into meta-analysis, the following data were abstracted: number of participants in both reboxetine and control arms of the studies, response rates (the percentage of the patients having more than 50% improvement on the HAM-D scale), baseline and final (end-point) mean values on HAM-D, the estimates of the variance of it (SD), change in mean values (between endpoint and baseline), p-values and significance levels. In some studies (1, 3, 12) the value of final HAM-D scores was approximated from the provided graphs or review articles where it was indicated (2, 15).

Statistical analysis

Two outcome measures were chosen for the quantitative data synthesis: the endpoint HAM-D scores means (continuous data) and the response rates (dichotomous data). For the calculations and data synthesis, Comprehensive Meta-Analysis software package was used. The effect size for the treatment was defined as the standardized difference in mean and calculated as the difference in final (end-point) means of reboxetine and the comparator divided by the pooled standard deviation of the two groups. The final mean values on HAM-D were used instead of the change from baseline, because in most studies the standard deviation for this change was not available. Moreover, because of the withdrawals it was difficult identify the sample size which would correspond for this change in two mean values (baseline and end-point).

In order to compute the effect size or the standardized mean difference, both the raw means and the estimates of the variance were necessary. When the dispersion was not indicated (1, 2, 12, 26, 27), it was imputed as a pooled SD from the others studies, where the SDs were available. In many studies it has been shown that the imputed standard deviations do not alter the conclusions of the meta-analysis of the continuous data (9, 10, 21). The following formula was used to calculate the pooled SD:

$$SD = \sqrt{\frac{\sum (n_i - 1) SD^2}{\sum (n_i - 1)}}$$

Pooled SD for the placebo-controlled and active drug control studies were calculated using reported SD from the according groups separately (i.e. there is not only one pooled SD for all the missing SDs). The second outcome or the response rate (dichotomous variable) was used for calculating the odds ratios.

Heterogeneity assessment was performed using Q statistics and computed as:

$$Q = \sum_{i=1}^{k} W_i (T_i - \overline{T})^2$$

Where k is the number of studies included, T_i is the treatment effect estimated in the ith study, $\overline{T}$ is the weighted estimator of treatment effect, and W_i is the weight attached to that study. The Q statistics has shown that the level of heterogeneity was significant, implying that the variability between study estimates is too large to assume that they are estimating same underlying treatment effect. Thus the random effect model was chosen, which assumes that the underlying effect sizes are drawn from the distribution of effect sizes and incorporates the heterogeneity among studies.

Publication bias was assessed by calculating the fail-safe number. In order to explore the sensitivity, a meta-analytical calculation was conducted excluding the single-blind and open studies. Influence of the imputed data was explored by a separate meta-analysis excluding studies with missing data.

RESULTS

The initial search using the above mentioned limitations has produced 67 citations (without limitations 230). From that, 21 studies were identified as possible candidates for the meta-analysis and the full texts of each article were obtained. Four additional articles were identified from the reference lists of these articles as well as of the review articles (8, 15, 17) on reboxetine. Finally, 11 studies were selected for the meta-analysis as a result of assessment according to criteria. Figure 1. shows the flow of the selection process.

Studies characteristics or qualitative summarisation.

Table I. shows the main characteristics of the included studies. All 11 studies were included for the meta-analysis of the effect size as the standardized mean change in the end-point HAM-D score, since the missing SD were imputed as described before. However, for the meta-analysis of the response rate as odds ratios, 9 studies were included, because 2 studies (22, 25) did not have that outcome. Since 2 studies (2, 3) had both placebo and active drug arms, the outcomes for each subgroup were inputted separately. Hence, there are 13 comparisons for the continuous outcome meta-analysis and 11 comparisons for the binomial outcome or the response rate (Table I).

The age of the population in 9 studies was between 18-65 years old, in 2 studies more than 65 years old (12, 22) with the total of 2018 patients. The mean baseline HAM-D scores in studies ranged from 21.05 to 35.7, indicating moderate to severe levels of depressive symptoms. The dose of reboxetine was ranging from 4 mg to 10 mg, but in majority of

studies the dose of 8 mg was included. The mean reduction on the HAM-D scale with reboxetine was fluctuating between 13.0 and 23.1, whereas in the placebo groups it was between 4.5 and 8.6 (Table I).

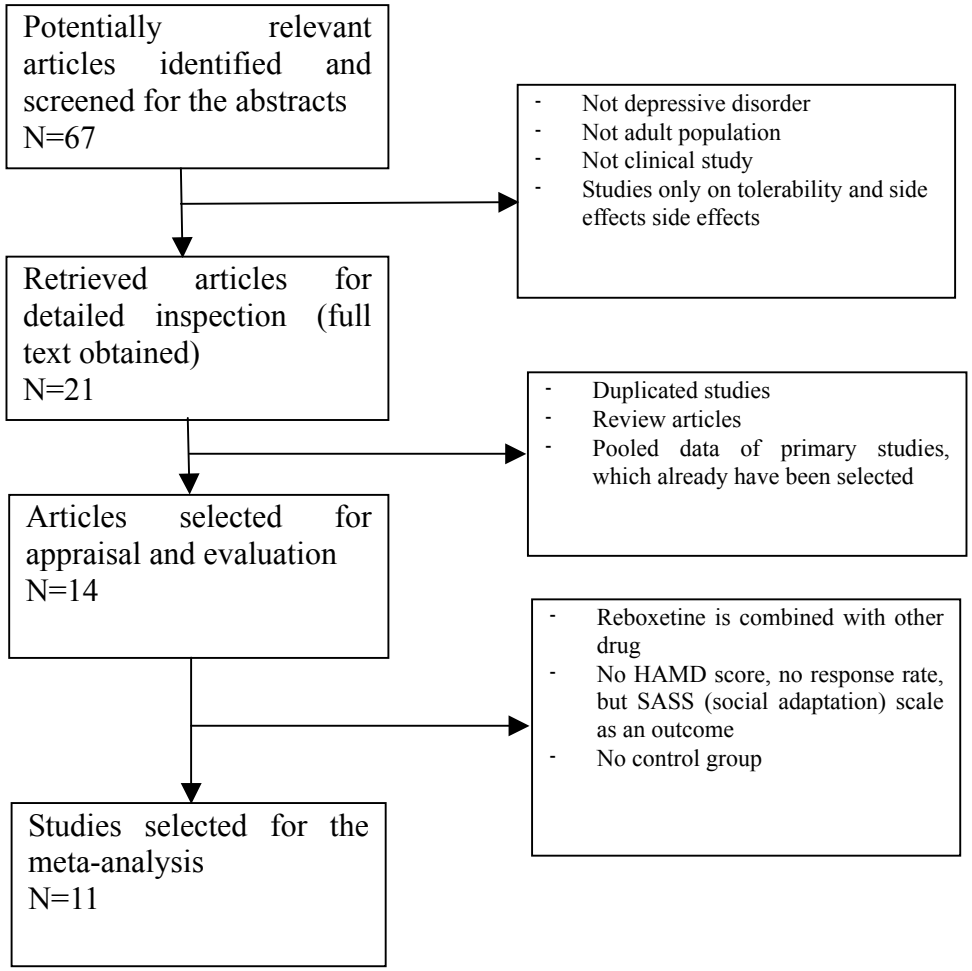


Fig. 1. The selection flow of the primary studies

TABLE I. Studies included into Meta-analysis and review

No	Study	Smpl. size, *n*	Age, *years*	Duration, *weeks*	Dose of RBX	Control or Comparator, *mg*	Main or primary Outcome measure	Additional Outcome measures	HAMD at baseline RBX/CPR	Mean reduction in HAMD score RBX/CPR	End-point HAMD RBX/CPR	Response rate RBX/CPR
1	Berzewski et al, 1997	256	mean 43.9	6	8 mg	Imipramine, 150	reduction in HAMD score	responce, remission rates	28.8(±4.8) 28.0(±5.2)	15.8 (C.I.,12.5–16.1) 14.3 (C.I., 12.5–16.1)	9.6(±7.5) 10.4(±8.2)	0.685/0.562
2	Ban et al, 1998	258	18–65	4	4–8 mg	Desapramine, 100–200	reduction in HAMD score	MADRS, ZUNG, CGI-SI	29.89(0.56)		16.35(±6.62) 17.5(±6.75) graph	0.60/0.35 0.60/0.48
			18–65	4	4–8 mg	Placebo	reduction in HAMD score	MADRS, ZUNG, CGI-SI	29.89(0.56)		16.35(±6.62) 19.54(±7.91)	0.60/0.35 0.60/0.48
3	Massana et al, 1999	168	18–65	8	8–10 mg	Fluoxetine, 20–40	reduction in HAMD score	responce, remission rates	28.6(5.3) 27.4(4.1)	19.2 (C.I.,17.3–21.2) 16.8 (C.I.,14.9–18.6)	9.4(±7.3) 10.6 (±8.7)	0.94/ 0.106
4	Versiani, Mehilane et al, 1999	283	18–65	46	4–8 mg	Placebo	reduction in HAMD score	responce rate	29.1(5.5) 29.7(5.7)	18.2 – short term 0.8 / +4.8–long term	7.9 13.9	0.609/0.402
5	Katona et al, 1999	347	>65	8	4–6 mg	Imipramine, 50–100	reduction in HAMD score	GCI scale, responce rate	27.9(4.9) 26.9(5.4)	only graph, about >10	15.0 13.5 graph	0.55 /0.57
6	Versane, Amin et al, 2000	52	18–65 mean 40.85	6	4–8 mg	Placebo	reduction in HAMD score	responce rate, Zung, GSI	35.7 35.1	23.1/4.5 p<0.0001	12.6 30.6	0.74/ 0.20
7	Andreolli et al, 2002	128	18–65	8	8–10 mg	Fluoxetine, 20–40	reduction in HAMD score	responce and remission rate	26.9 (3.6)	13.4/13.3	13.60	0.556/ 0.563
			18–65	8	8–10 mg	Placebo	reduction in HAMD score	responce and remission rate	27.6(3.6)	13.4/8.6	18.80	0.556 /0.35
8	Rampello et al, 2005	31	>65	16	4 mg	Placebo	reduction in HAMD score	BDI	24.06(1.52) 24(1.31)		9.26 (±2.15) 22.73(±2.4)	
9	Langworh et al, 2006	359	16–71 mean 42.8/ 41.5	24	8–10 mg	Citalopram, 20–40	change in HAMD score	responce, remmision rate	>25	19.6 /17.8, p<0.034	17 (±8.3) 19 (±7.7)	0.90/ 0.92 graph
10	Akkaya et al, 2006	93	18–65 mean 40.4/ 42.0	10	8mg	Venlafaxine, 150	change in HAMD score	responce, remission rate	21.9(4.3) 20.6 (4.3)	no statistical significant difference F=0.640, p>0.05	9.2 10.0 graph	0.64 /0.86
11	Taner E et al, 2006	43	18–65 mean 36.84	8	8–10 mg	Fluoxetine, 20–40	change in HAMD score	CGI-SI, GAF	21.41(± 3.28) 21.05(± 3.2)		8.07(±6.94) 6.65(±3.11)	

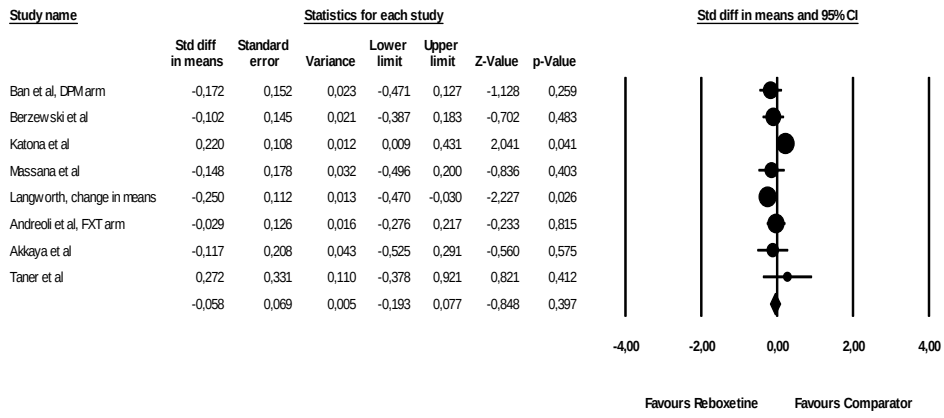
RBX-reboxetine; CPR-Comparator; DPM-desapramin;

Quantitative data synthesis.

HAM-D scale mean values or standardized mean difference. (Fig. 2; Fig. 3)

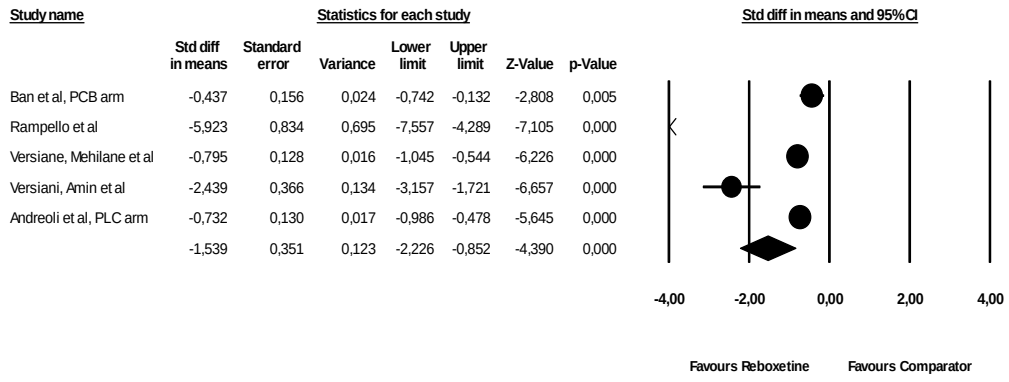
The meta-analysis of the studies comparing the reboxetine with the active drugs based on the continuous scale of the mean values has given the pooled effect size of -0.06 (95%CI: -0.19; 0.08) (Fig.2), which indicates no difference in the treatment effect between reboxetine and other antidepressants. The exclusion of the open and the single-blinded studies (1, 21) did not change this conclusion: -0.07 (95%CI: -0.22; 0.08). The pooled effect size of the studies comparing reboxetine with the placebo was -1.54 (95%CI: -2.23; -0.85, p<0.0001) (Fig.3), indicating that reboxetine has significantly favourable effect than placebo. The overall effect size for all studies is -0.5 (95%CI: -0.8; -0.2) (Fig.6); excluding the abovementioned 2 studies, the effect size is -0.59 (95%CI: -0.94;-0.26).

Fig. 2



Meta-Analysis of effect sizes (Reboxetine vs alternative Antidepressants)

Fig.3



Meta-Analysis of effect sizes (Reboxetine vs Placebo)

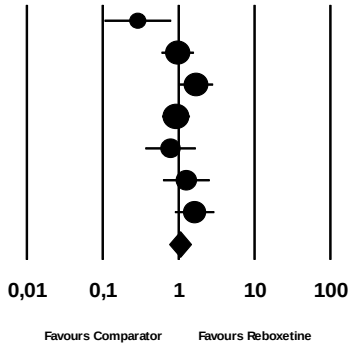
Response rate or odds ratio. (Fig. 4; Fig. 5)

For the quantitative synthesis of the binomial outcome, 9 studies provided with 11 comparisons. The pooled OR (odds ratio) of the studies with the active drug comparator was 1.04 (95%CI: 0.75; 1.46) (Fig.4), indicating no significant difference between reboxetine and other drugs. For the placebo comparisons the pooled OR was 2.85 (95%CI: 1.88; 4.31) (Fig.5), which shows that reboxetine has significantly better response rate than the placebo. The overall pooled OR for all comparisons was 1.5 (95%CI: 1.03; 2.18) in favour of reboxetine. Exclusion of the open study (1) did not alter those conclusions: OR of 1.16 (95%CI: 0.90; 1.48) for active drug comparisons and overall OR for all studies 1.67(95%CI: 1.18; 2.36).

The results suggest that the reboxetine was significantly superior in the treatment of the depressive disorders compared to the placebo measured on both continuous and dichotomous outcomes, while it did not differ from the other antidepressant drugs being compared in those studies.

Fig. 4

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Akkaya	0,289	0,105	0,797	-2,399	0,016
Andreoli 2	0,972	0,592	1,597	-0,112	0,911
Berzewski	1,695	1,009	2,847	1,993	0,046
Katona	0,922	0,603	1,409	-0,375	0,708
Langworth	0,783	0,363	1,689	-0,624	0,532
Massana,Moller	1,264	0,622	2,568	0,646	0,518
Ban DPM	1,625	0,889	2,970	1,578	0,114
	1,044	0,748	1,459	0,255	0,799



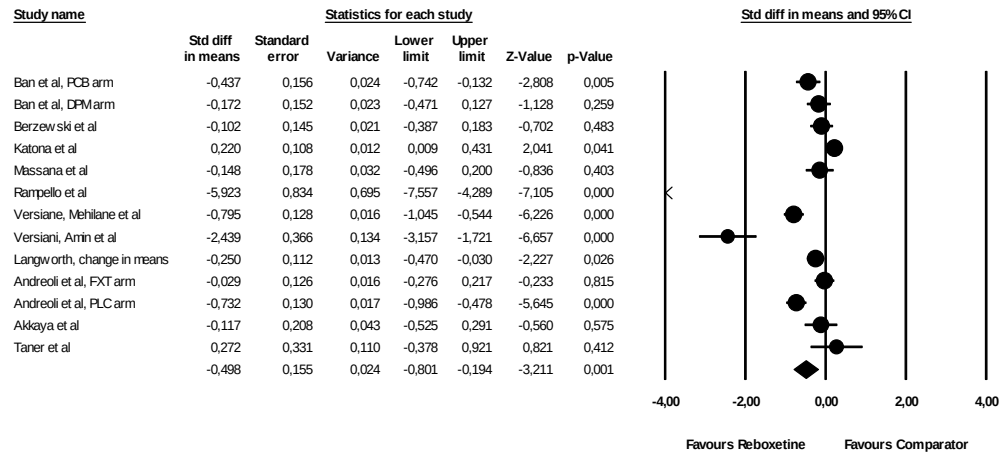
Meta-Analysis of responce rates (Reboxetine vs alternative Antidepressants)

Fig. 5

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Andreoli 1 PLC	2,475	1,489	4,113	3,496	0,000
Ban PLC	2,786	1,493	5,198	3,219	0,001
Versiane, Amin PLC	11,385	3,091	41,932	3,656	0,000
Versiani, Mehilane PLC	2,317	1,442	3,722	3,475	0,001
	2,847	1,882	4,306	4,953	0,000

Meta Analysis of responce rates (Reboxetine vs Placebo)

Fig. 6



Meta-Analysis of effect sizes (all studies)

DISCUSSION

Reboxetine as an active antidepressant has been introduced relatively recently, despite being synthesized earlier. Comparing to other classes of the antidepressants, there are significantly less controlled clinical studies of reboxetine that can be used for the meta-analysis. Because of this situation we have considered that in this meta-analysis we include all controlled studies of reboxetine both with placebo and any other alternative antidepressants. Moreover, the target group consists of patients not only with major depressive disorder, but also with any other depressive conditions, being the baseline HAM-D score >16 as the criteria for inclusion. Although this situation creates more heterogeneity, the aim of the study was to find out the overall efficacy of the reboxetine in depressive disorders when both inclusion criteria and the outcome have employed the HAM-D scale (the response rate also is calculated on the basis of the HAM-D scale as 50% improvement). As it was mentioned before, the previous quantitative review on reboxetine used only the response rate (dichotomous outcome) for the drug efficacy analyzing, but not the mean values of the scores themselves (continuous outcome) (20). Nevertheless, the pooled odds ratio for the active drugs comparison from our study does follow the findings from the previous study, stating that there is no significant difference in response between reboxetine and SSRI treated groups.

Since the mean change of the HAM-D scores after the active antidepressant drug treatment would be greater than after the placebo, we have conducted the quantitative synthesis (statistical combination and calculations) separately for the studies with the active drug comparator and separately for the studies with placebo control or arm. As a result, there are altogether 4 different submeta-analyses: reboxetine versus alternative antidepressant and reboxetine versus placebo, with continuous (mean values on HAM-D score) and dichotomous (response rate or odds) outcomes for each combination (Fig.2, Fig.3, Fig.4, Fig.5).

However, the non-active substance does have the “placebo” effect, which is important in psychological patients and can be influential on the treatment effect. Taking into account this

consideration, we have additionally conducted one more calculation for the effect size including data from both drug-control and placebo-control studies altogether in one quantitative synthesis (Fig. 6). It has been done to determine whether the favorable treatment effect of the reboxetine, compared to the placebo, would be significantly overlapped by the treatment effect of the alternative drugs.

This meta-analysis indicates that the efficacy of reboxetine and alternative antidepressants from the TCA and SSRI groups does not differ both on continuous and categorical measurements. The previous meta-analysis had shown that the discontinuation rate of the reboxetine was greater than the SSRIs, also that the side-effect profiles differ: SSRI-treated patients were more likely to experience nausea, hypersomnia, and fatigue whereas reboxetine-treated patients were more likely to experience constipation, difficulty urinating, and insomnia (20). However, there are studies that found that reboxetine is effective in patients who are resistant to the SSRI (14, 24). As well as this, some studies reported lower prevalence of sexual dysfunction in patients treated by reboxetine compared to SSRIs (5). Furthermore, two studies have shown that reboxetine is improving the social adaptation in patients greater than SSRIs (6, 16).

There are some reviews of placebo-controlled studies of reboxetine, however they are not systematic, including only limited number of studies and do not have the quantitative data synthesis or the meta-analysis itself (8, 17).

One of the main limitations of current meta-analysis is the heterogeneity. This review includes studies comparing the effects of reboxetine with both placebo and the other active drugs. To deal with it we have calculated the pooled effects separately. There is heterogeneity in the population (2 studies with the elderly patients) as well as in the length of the trials (2 studies were lasting 24 and 42 weeks).

Meta-analysis is dependent on the quality of the primary studies. As it was mentioned before, there are limited numbers of clinical studies on reboxetine. Because of it, our selection includes not only blind, but also one single-blind and one open study. However, the sensitivity analysis excluding these 2 studies did not influence the pooled results. Meta-analysis of the continuous outcome measure was more difficult because of missing data. For such, the final HAMD score means in some studies were estimated from the graphs (1, 12). When the variance estimate was not available, the standard deviation was calculated as pooled SD from those available ones.

The publication bias is the other limitation of this study. To estimate it we have calculated the fail-save number according to the Orwin's method (19), using effect size or the standardized mean difference of the continuous outcome measure. We have determined how many hidden studies are required to reduce the effect size.

$$N_{fs}=N_0 (d_0-d_c)/dc-d_{fs}$$

N_{fs}- the number of nil-null studies needed to reverse the statistically significant findings

N_0 - the number of studies used in the meta-analysis

d_0 -the mean effect size obtained for the meta-analysis (the value)

d_c -the criterion effect size value of the fail-safe studies (0.2-small; 0.5-medium; 0.8-large)

d_{fs} -the mean effect size of the fail-safe studies, usually assigned a value of 0
(the file-drawer studies are hypothezed to have effect size of 0)

Fig. 7. Orwin's fail-safe number analysis using effect sizes

In order to change the effect size of 1.5 from the placebo control studies to the small effect size of 0.2 we would need 38.5 articles.

As there are limited numbers of controlled trials on reboxetine especially double-blind, there is a need for more studies with both placebo and active drug arms. For the active drug comparators, antidepressants other than SSRIs should be studied. For instance, there are no published clinical trials comparing reboxetine with the duloxetine (SNRI) and bupropion (NDRI). Furthermore, taking into account the results of this study and the previous meta-analysis, it is recommended to study reboxetine mainly with connection to the SSRI resistant depression or with the primary focus on the side effects and discontinuation rate. Finally, considering the recent attention to the economic aspects in drug approvals, we would suggest conducting cost-effectiveness studies of reboxetine along with the RCTs. As we can see, the overall efficacy of the reboxetine does not differ greatly from other antidepressants, thus such kind of studies might reveal some advantages for wider prescription of reboxetine.

ACKNOWLEDGEMENTS

We wish to thank Dr. Daisuke Sugiyama and Mr. Suguru Hyodo for the advice and assistance.

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