Double-Blind, Placebo-Controlled Study of the Efficacy of Reboxetine and Citalopram as Adjuncts to Atypical Antipsychotics for Negative Symptoms of Schizophrenia

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ABSTRACT

Objective: In this study, we assessed the efficacy of 2 pharmacodynamically different antidepressants, citalopram (a selective serotonin reuptake inhibitor) and reboxetine (a norepinephrine reuptake inhibitor), as adjunctive therapy to risperidone and olanzapine for the treatment of negative symptoms in schizophrenia.

Method: We performed a 6-month, multicenter, double-blind, randomized, placebo-controlled clinical trial. The recruitment period was from November 2008 to December 2011. The sample comprised 90 patients with a diagnosis of schizophrenia (*DSM-IV* criteria) who exhibited negative symptoms. The patients were recruited from 10 centers in different cities of the Spanish State. The primary efficacy measure was change in score on the negative subscale of the Positive and Negative Syndrome Scale (PANSS) between baseline and 6-month assessment. Other efficacy measures were changes in the PANSS subscales and total score, as well as the Scale for the Assessment of Negative Symptoms (SANS) subscales and total score.

Results: For statistical analysis, we employed mixed-effects models. We did not find statistically significant differences between the placebo group and the 2 treatment groups at 6-month assessments for the PANSS total ($P = .6511$), any PANSS subscale (negative [$P = .5533$], positive [$P = .1723$], or general psychopathology [$P = .2083$]), or the SANS ($P = .5884$). Cohen *d* measure showed a small effect size below the 0.5 threshold for all comparisons.

Conclusions: In conclusion, our results do not support adjunctive use of citalopram or reboxetine with risperidone or olanzapine for the treatment of negative symptoms in schizophrenia.

Trial Registration: ClinicalTrials.gov identifier: NCT01300364

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Negative symptoms in schizophrenia are often regarded as the central dysfunction of the illness, and they seem to be closely linked to the global functioning of patients.[1–3] Moreover, persistent negative symptomatology is associated with cognitive dysfunction, which also impairs social functioning[4,5] and which, following some authors, may represent the core of the pathophysiology of schizophrenia.[6] Although significant progress has been made with regard to knowledge of the neurobiology of the disease, and a large array of effective antipsychotic molecules have been synthesized for treating positive symptoms (delusions, hallucinations),[7] response to treatment of schizophrenia remains rather modest, owing mainly to the persistence of negative symptoms. A critical but often difficult clinical distinction is between primary and secondary negative symptoms. The former constitute an enduring deficit state, whereas the latter can be manifestations of depressive symptoms, extrapyramidal side effects of medication, or the consequence of positive symptoms.[8] Reviews of randomized clinical trials indicate that negative symptoms respond poorly to antipsychotic drugs, and although second-generation antipsychotics may be more effective than first-generation drugs, there is no clear evidence of their efficacy for primary negative symptoms.[9,10] Most of the recent clinical guidelines do not provide clear-cut pharmacologic recommendations for the treatment of negative symptoms in schizophrenia.[11,12]

Antidepressant drugs are commonly prescribed in clinical practice as adjunctive therapy for negative symptoms in schizophrenia, although their utility is far from clear. In fact, clinical research on this issue offers conflicting results, as clinical trials to date have found positive as well as negative results.[13–17] Some of the conflicting results may be accounted for by methodological limitations: small sample, short trial length, a range of concomitan t antipsychotic regimens, or lack of exclusion of subjects with depressive symptoms.

Selective serotonin reuptake inhibitors (SSRIs) have been the most studied antidepressants in schizophrenia. Their putative utility would be explained by the serotonergic modulation of the serotonin-dopamine balance.[13,18] It is well established that activation of prefrontal cortex 5-HT_{1A} receptors increases the release of dopamine in this brain area, which would be expected to improve negative symptomatology as well as cognitive deficits.[19,20] However, this improvement appears to be an indirect effect that is also achieved by some atypical antipsychotics,[19,20] suggesting that

their beneficial effects could be attributed to an improvement of secondary negative symptoms (depressive symptoms or negative symptoms secondary to antipsychotic treatment) through the serotonergic activity. Efficacy results with SSRIs are not conclusive.[21–23] Among SSRIs, citalopram, which was chosen for our trial, has been the object of very little research in schizophrenia, in contrast to other SSRIs such as fluoxetine. In their double-blind 3-month follow-up trial, Salokangas et al[24] found moderate efficacy only for anxiety and depressive symptoms, but not for negative symptoms.

Reboxetine, a selective norepinephrine reuptake inhibitor with scarce activity on the 5-HT transporter[25] and a clinical activating profile (ie, greater effectiveness for depressive symptoms such as anhedonia), has also been studied as an adjunct for negative symptoms in schizophrenia. The neurobiological rationale is based on recent observations that part of the cortical dopamine originates in noradrenergic axons, where dopamine is a synthesis intermediate of norepinephrine.[26] Studies with reboxetine are scarce and offer conflicting results. An open study[27] of 16 patients with schizophrenia in which reboxetine was added to first- and second-generation antipsychotics reported an improvement of negative symptoms, whereas a double-blind, placebo-controlled 6-week study[28] failed to find any improvement when reboxetine was used adjunctively with haloperidol.

The objective of our clinical trial was to evaluate the efficacy of 2 antidepressants (citalopram and reboxetine) for negative symptoms in schizophrenia when used as adjuncts of 2 widely used second-generation antipsychotics (risperidone and olanzapine). We chose these 2 antidepressants because they both have activity on neurotransmitter systems that may play a role in negative symptoms, they have different mechanisms of action and have a high selectivity for their respective neurotransmitter systems, and they both have a low potential for pharmacokinetic interactions. Our aim was to compare the 2 antidepressants with placebo and with each other.

- Reboxetine and citalopram seem not to be effective as adjunctive treatment for negative symptoms of schizophrenia.
- The use of polypharmacy in clinical practice in the treatment of patients with schizophrenia should be avoided unless it is supported by evidence from clinical trials.

Clinical Points

METHOD

Design and Sample

Our study was a multicenter, double-blind, randomized, placebo-controlled clinical trial of 6 months' duration. All of the participating subjects from the different centers who fulfilled inclusion and exclusion criteria and signed an informed consent statement were randomly assigned by the Parc Sanitari Sant Joan de Déu trial pharmacy to 1 of the 3 treatment groups in a 1:1:1 proportion on the basis of a random number list. The preparation of the medication was performed by the Sant Joan de Déu Pharmacy Department. Placebo, reboxetine, and citalopram tablets were prepared so that they were identical in appearance. All study personnel and participants remained blind to treatment assignment for the duration of the study. Parc Sanitari Sant Joan de Déu was the coordinating center.

The recruitment period was from November 2008 to December 2011. A total of 98 patients diagnosed with schizophrenia (*DSM-IV* criteria) were recruited from 10 centers in different cities of the Spanish State: Barcelona (4), Madrid (4), Valencia (1), and Victoria (1). A final sample of 90 subjects was obtained after the remainder dropped out of the study following recruitment (Figure 1). Inclusion criteria were diagnosis of schizophrenia; age between 18 and 65 years; treatment with a stable dose of either olanzapine or risperidone for at least 60 days prior to inclusion in the study; and presence of significant negative symptoms, defined as 1 or more negative symptom with a severity score greater than 4 on the PANSS negative scale.[29] Exclusion criteria were substance use/dependence disorders in the previous 6 months; mental retardation; antidepressant or mood stabilizer use in the previous 4 months; and use of more than 1 antipsychotic or use of antipsychotics other than olanzapine or risperidone (except levomepromazine 100 mg/d, clotiapine 40 mg, chlorpromazine 100 mg, and quetiapine 200 mg, since they were used as hypnotics). We also excluded patients with scores greater than 20 on the Hamilton Depression Rating Scale (HDRS)[30]; pregnant and lactating women; and subjects with severe renal failure (serum creatinine > 5 mg/dL), history of hemorrhagic disorders, or intolerance or allergy to reboxetine or citalopram.

The study (ClinicalTrials.gov identifier: NCT01300364) received institutional review board approval. We received the approval of the Spanish Agency for Treatments (Agencia Española del Medicamento), as well as that of the local ethics committees of each of the participating centers.

The patients provided informed consent in accordance with the procedures outlined by the local institutional review board and were informed that they could withdraw from the study at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions.

Interventions

Ninety subjects were randomly assigned to complete a 6-month period of adjunctive treatment with reboxetine, citalopram, or placebo. Participants received citalopram (23 patients), reboxetine (34 patients), or placebo (33 patients) from the Parc Sanitari Sant Joan de Déu pharmacy. Medication doses were citalopram 30 mg/d and reboxetine 8 mg/d. The initial doses were 15 mg/d for citalopram and 4 mg/d for reboxetine, and the doses were titrated up to the final dosage within 1 week and maintained without changes throughout the study. Changes in antipsychotic dose were not allowed until the end of the study. Use of benzodiazepines and biperiden was permitted.

Outcomes

The diagnosis was made through the Structured Clinical Interview for *DSM-IV* Axis I Disorders, which was conducted by research fellows and reviewed by the principal investigators in each subcenter of the study. Sociodemographic as well as clinical variables were analyzed. Psychopathologic symptoms were assessed at baseline, week 12, and week 24 by administering the Positive and Negative Syndrome Scale (PANSS)[31] and the Scale for the Assessment of Negative Symptoms (SANS).[32] Side effects were analyzed with the UKU Side Effect Rating Scale[33] and the Simpson-Angus Scale.[34] The assessing researchers have extensive experience in the use of clinical scales and were trained in the scales of the study. An interrater reliability analysis of the PANSS was performed. The result was an index > 0.80 in all the subscales.

Adherence was estimated as the percentage of tablets taken out of the total tablets for each individual during the study period.

Statistical Analysis

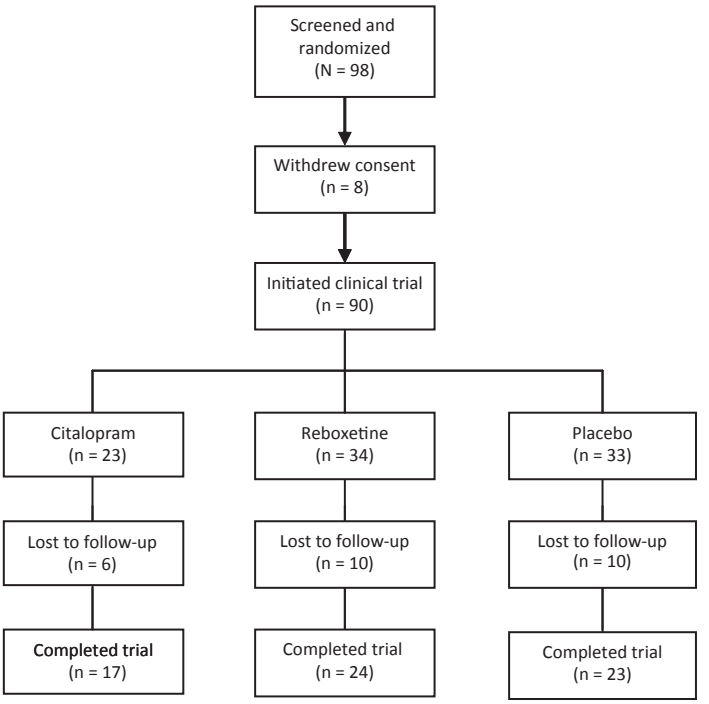
Comparisons of baseline categorical characteristics between groups were performed using the χ^2 test. The distributions of adherence and antipsychotic drugs doses were analyzed by means of the Kruskal-Wallis *H* test. Doses were converted to the equivalent doses of oral risperidone.[35] Other continuous data at baseline were compared with analysis of variance. Analyses were carried out on an intention-to-treat basis. Linear mixed-effects models were used to compare the differences in time course for the 4 scales regarding treatment groups. An unstructured correlation matrix was used to take into account the correlation among repeated measures for each subject. Whereas the last-observation-carried-forward method has been shown to produce biased results,[36–38] mixed-effects modeling provides unbiased estimates in the presence of missing data and allows the analysis of repeated measures collected at several time points.[36,38,39] Assessments at baseline and 3 and 6 months were the dependent variable in the models. Treatment group and time were the covariates as well as an interaction treatment-by-time term, also tested to assess whether time modified intervention effect. When the interaction was statistically not significant, it was removed, and the model was computed without it. All estimates were performed under a missing at random assumption. Effect size was estimated by means of the Cohen *d* measure.

Descriptive and bivariate analyses were performed in a first stage using SPSS 20 (IBM; Armonk, New York). For mixed-effects modeling, given that the statistical analyst had proven expertise in modeling and programming with SAS software, we used SAS V.9.2 (SAS Institute; Cary, North Carolina).

Sample Size

The sample size for this study was determined in advance. The first calculation of 249 individuals was based on the assumption of a variance of 27 points within groups and a difference of 1.5 points between groups for the PANSS negative subscale, power of 80%, and a type I error of 0.05. An insufficient capacity of recruitment during the study period led the team to recompute the sample size. The final calculation of 90 subjects allows capture of a difference of at least 3 points between treatment groups when comparing baseline and final assessment, keeping a power of 80% and a statistical confidence of 95%.

Figure 1. Trial Profile[a]



[a]A total of 64 patients completed the study (dropout rate of 29%). At 3-month follow-up, 78 patients remained in the study (dropout rate of 14%). The dropout rates showed no statistical difference between groups (citalopram 26%, reboxetine 29%, placebo 30%). The main reason for dropout was patient decision.

RESULTS

The percentage of total dropout was 29%. No statistical difference in dropout was seen between groups (citalopram 26%, reboxetine 29%, placebo 30%). The main reason for dropout was patient decision.

Baseline Demographic and Clinical Characteristics

Demographic information is shown in Table 1. There were no statistical differences between the 23 patients in the citalopram group, the 34 patients in the reboxetine group, and the 33 patients in the placebo group with regard to gender, age, age at onset, psychiatric comorbidity, current antipsychotic (or other) medication, or mean daily dose of antipsychotic. The sample was also homogeneous among the 3 groups with respect to baseline PANSS and SANS total and subscale scores. We did not find differences among the 3 groups in the HDRS baseline scores, and the mean HDRS scores were less than 10 in the 3 groups.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Citalopram, Reboxetine, and Placebo Groups (N = 90)

	Citalopram	Reboxetine	Placebo	Total n	*P* Value[a]
Sex, n (%)					.43
Male	18 (78.3)	27 (79.4)	22 (66.7)	67	
Female	5 (21.7)	7 (20.6)	11 (33.3)	23	
Age, mean (SD), y	42.47 (10.62)	40.02 (13.46)	44.15 (12.36)		.39
Age at onset, mean (SD), y	24.52 (9.57)	25.21 (8.30)	28.48 (7.43)		.19
Main antipsychotic, n (%)					.82
Olanzapine	7 (30.4)	13 (38.2)	12 (36.4)	32	
Risperidone	16 (69.6)	21 (61.8)	21 (63.6)	58	
Secondary antipsychotic, n (%)					.31
Yes	3 (13.0)	1 (2.9)	2 (6.1)	6	
No	20 (87.0)	33 (97.1)	31 (93.9)	84	
Benzodiazepines, n (%)					.52
Yes	5 (21.7)	12 (35.3)	11 (33.3)	28	
No	18 (78.3)	22 (64.7)	22 (66.7)	62	
Biperiden, n (%)					.08
Yes	1 (4.3)	6 (17.6)	9 (27.3)	16	
No	22 (95.7)	28 (82.4)	24 (72.7)	74	
Psychiatric comorbidity, n (%)					.05
Yes	5 (21.7)	7 (21.2)	15 (46.9)	27	
No	18 (78.3)	26 (78.8)	17 (53.1)	61	
Dosage of antipsychotic mg/d,[b] median (range)	4.5 (1–45)	6.0 (0.5–40)	6.0 (0.5–20)		.57
HDRS score, mean (SD)	8.13 (3.57)	8.09 (3.70)	8.15 (4.54)		.99
Baseline PANSS score, mean (SD)					
Total	73.13 (10.31)	72.06 (15.15)	75.06 (18.62)		.72
Positive subscale	12.78 (3.89)	12.79 (5.18)	13.57 (6.29)		.79
Negative subscale	25.91 (5.15)	25.50 (6.77)	26.21 (6.37)		.89
General subscale	34.43 (7.73)	33.76 (8.28)	35.27 (11.13)		.80
Baseline SANS score, mean (SD)					
Total	61.17 (17.94)	61.56 (19.72)	62.30 (19.24)		.97
Affective flattening or blunting	18.30 (6.71)	17.5 (8.68)	18.36 (7.95)		.88
Alogia	9.86 (5.47)	10.17 (5.39)	9.39 (4.66)		.82
Avolition/apathy	10.47 (4.64)	11.38 (3.75)	11.18 (3.75)		.67
Anhedonia/asociality	17.00 (5.34)	17.02 (5.13)	17.54 (5.44)		.90
Attentional impairment	5.52 (2.57)	5.47 (2.99)	5.81 (3.92)		.89

[a]*P* values are derived from 1-way analyses of variance.
[b]Antipsychotic drug doses are expressed as risperidone equivalence.
Abbreviations: HDRS = Hamilton Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

The citalopram, reboxetine, and placebo groups showed no differences in terms of treatment adherence. A minimum of 80% adherence was observed for all participants, and treatment groups did not show statistically significant difference ($P = .916$).

Symptoms

The primary efficacy measure was the score change of the PANSS negative subscale between onset of treatment and follow-up at 6 months. Our results (Table 2) showed no statistically significant differences between groups during the intended follow-up with respect to PANSS negative subscale scores ($P = .553$). The following PANSS scores also showed no significant differences between groups in change in course: positive subscale ($P = .172$), general psychopathology subscale ($P = .208$), and total PANSS score ($P = .651$). With regard to the SANS, we also found no significant differences for the total score among the 3 groups over time ($P = .588$). We also did not find statistically significant differences with respect to the SANS subscales and their change in course along the 3-point assessment regarding treatment group: affective flattening or blunting ($P = .227$), alogia ($P = .658$), avolition/apathy ($P = .441$), anhedonia/asociality ($P = .267$), attentional impairment ($P = .517$). As shown in Table 2, none of the scores showed significant differences for the main effect of the treatment group. Cohen *d* values show a small effect size below 0.5 for all comparisons (Table 3).

Side Effects

Regarding side effects, no significant difference was observed between treatment groups over time for the total measure of the Simpson-Angus Scale total ($P = .296$), nor did we find differences for each UKU dimension surveyed (psychological, $P = .143$; neurologic, $P = .719$; autonomic, $P = .548$; other symptoms, $P = .435$).

Three patients who experienced an acute exacerbation (2 on reboxetine and 1 on citalopram) were dropped from the study. We did not record other adverse effects.

DISCUSSION

The main result of our clinical trial is that citalopram and reboxetine added to 2 widely employed second-generation antipsychotics (risperidone and olanzapine) that have different mechanisms of action are not more efficacious than placebo for the treatment of negative symptoms in schizophrenia as assessed with the PANSS negative subscale as well as with the SANS subscales.

Table 2. Baseline, 3-Month, and Final Values of Follow-Up for PANSS and SANS[a]

Measure	Citalopram			Reboxetine			Placebo			Effect				
										Time × Group		Group[b]		
	Baseline	3 Mo	6 Mo	Baseline	3 Mo	6 Mo	Baseline	3 Mo	6 Mo	*F*	*P*	*F*	*P*
PANSS negative	25.91 (5.15)	21.59 (4.50)	19.82 (4.99)	25.50 (6.77)	21.44 (7.85)	19.67 (8.41)	26.21 (6.37)	22.92 (5.81)	22.65 (5.54)	0.83	.553	0.43	.649
SANS													
Total	61.17 (17.94)	50.29 (14.62)	46.63 (15.84)	61.56 (19.72)	51.78 (21.10)	46.75 (26.12)	62.30 (19.24)	54.80 (21.47)	54.61 (19.13)	0.78	.588	0.16	.852
Affective flattening or blunting	18.30 (6.71)	15.71 (5.31)	13.88 (5.84)	17.5 (8.68)	15.04 (7.74)	13.58 (9.45)	18.36 (7.95)	15.44 (8.08)	15.52 (6.62)	1.39	.227	0.34	.711
Alogia	9.86 (5.47)	7.56 (5.25)	7.07 (4.20)	10.17 (5.39)	8.78 (5.30)	7.42 (5.27)	9.39 (4.66)	8.20 (4.66)	8.22 (4.04)	0.69	.658	0.27	.765
Avolition/apathy	10.47 (4.64)	8.29 (4.25)	7.75 (4.14)	11.38 (3.45)	8.56 (4.37)	8.00 (5.02)	11.18 (3.75)	10.24 (4.58)	9.83 (4.69)	0.98	.441	0.49	.613
Anhedonia/asociality	17.00 (5.34)	14.94 (3.45)	13.82 (3.05)	17.02 (5.13)	14.74 (5.50)	13.58 (6.83)	17.54 (5.44)	16.44 (5.14)	16.26 (4.99)	1.30	.267	0.72	.490
Attentional impairment	5.52 (2.57)	4.24 (3.17)	4.56 (3.12)	5.47 (2.99)	4.67 (2.92)	4.17 (3.28)	5.81 (3.92)	4.48 (4.20)	4.78 (4.13)	0.87	.517	0.07	.934
PANSS													
Total	73.13 (10.31)	62.18 (10.21)	59.41 (11.72)	72.06 (15.15)	63.89 (16.82)	59.96 (17.89)	75.06 (18.62)	66.16 (15.71)	62.04 (19.90)	0.70	.651	0.15	.864
Positive	12.78 (3.89)	11.47 (4.21)	10.71 (3.58)	12.79 (5.18)	12.19 (4.98)	11.46 (4.14)	13.57 (6.29)	12.44 (5.74)	12.00 (5.68)	1.55	.172	0.39	.678
General	34.43 (7.73)	29.12 (5.01)	28.88 (5.32)	33.76 (8.28)	30.26 (8.23)	28.83 (8.10)	35.27 (11.13)	30.80 (9.15)	30.09 (7.93)	1.44	.208	0.40	.671

[a]Values expressed as mean (SD).
[b]Model without interaction term.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

This negative result is consistent with that of a recent meta-analysis that was published after the onset of our trial.[16] The meta-analysis reviewed 23 trials with a total of 819 patients. The antidepressants involved were SSRIs, mirtazapine, reboxetine, mianserin, trazodone, and ritanserin. Antidepressants were overall superior to placebo, but when every antidepressant was studied separately, only fluoxetine, trazodone, and ritanserin showed greater efficacy than placebo. In agreement with our results, the meta-analysis did not find a beneficial effect of citalopram and reboxetine on negative symptoms. However, none of the included studies were longer than 3 months.

This meta-analysis hints that not all the groups of antidepressants, nor all antidepressants within the same group (such as SSRIs), may have the same efficacy; thus, more individualized studies with each antidepressant should be conducted.

As regards the efficacy of SSRIs, a meta-analysis by Sepehry et al[23] that included 11 clinical trials controlling for depression at onset of the study concluded that there was no convincing support for the addition of an SSRI antidepressant for the treatment of negative symptoms that had shown a poor response to antipsychotics alone.

In that analysis and in Singh and colleagues' meta-analysis,[16] only 1 trial with citalopram was included.[24] This trial studied a large sample of 90 patients (45 placebo, 45 citalopram) with a 3-month follow-up. Although their sample was larger than ours (we had 23 citalopram-treated patients), their results were also negative. Our follow-up was longer, which could suggest that the lack of efficacy seen in their study was not due to a short duration of follow-up. The authors comment that the lack of efficacy of citalopram in comparison with other SSRIs that have shown efficacy, such as fluoxetine,[22] may be attributed to its well-known higher selectivity on serotonin reuptake.[40]

Along the same lines, a more recent trial[17] assessed the efficacy of escitalopram on negative symptoms in a sample of 40 patients followed during 10 weeks and failed to find any positive results.

Reboxetine did not demonstrate efficacy in the only controlled clinical trial published before ours, despite an open trial[27] in which it was shown to be effective. Schutz and Berk[28] conducted a 6-week double-blind placebo-controlled trial in 30 patients with schizophrenia treated with haloperidol and did not find positive results. We believe that this lack of efficacy could be mainly attributed to methodological issues, since the sample size was small, the duration of the trial was short, and the sample was clinically heterogeneous, in that it included both patients with an acute exacerbation and patients who were stabilized. Although in our study we tried to improve upon these 3 methodological limitations, we did not find efficacy for negative symptoms in patients on reboxetine. Another trial with reboxetine,[41] also included in Singh and colleagues' meta-analysis, did not have as a primary objective the assessment of negative symptoms, but rather the attenuation of olanzapine-induced weight gain. The findings were that reboxetine was useful for reducing weight but did not improve psychotic symptomatology at 6 weeks.

Recent basic research suggests that reboxetine may be useful when combined with mirtazapine (an alfa-2 noradrenergic antagonist) for the treatment of negative symptoms in schizophrenia, because although each drug individually does not increase cortical dopamine, they do achieve this increase when acting in combination.[42]

For the assessment of negative symptoms, we used SANS as well as the negative subscale of PANSS. These 2 scales are the most employed in clinical trials to assess treatments in schizophrenia. PANSS has good reliability and validity when compared with SANS.[43] Most of the trials

Table 3. Effect Size Estimation (Cohen *d*) for Treatment Group and Time × Treatment Group

			SANS Subdomains					Other PANSS Subdomains		
	PANSS Negative	SANS Total	Affective Flattening or Blunting	Alogia	Avolition/ Apathy	Anhedonia/ Asociality	Attentional Impairment	Total	Positive	General
Treatment group										
Citalopram vs reboxetine	0.02	−0.06	−0.08	−0.17	−0.20	0.02	−0.03	−0.06	−0.23	−0.24
Citalopram vs placebo	−0.19	−0.13	−0.19	−0.12	−0.21	−0.21	−0.08	−0.14	−0.20	−0.16
Placebo vs reboxetine	0.21	0.07	0.10	−0.05	0.01	0.23	0.05	0.08	−0.03	−0.08
Time × treatment group										
Citalopram vs reboxetine										
Visit 0	0.06	−0.02	0.10	−0.06	−0.23	−0.01	0.02	0.07	0.00	0.07
Visit 3	−0.09	−0.16	−0.14	−0.29	−0.15	−0.02	−0.18	−0.22	−0.18	−0.24
Visit 6	−0.10	−0.15	−0.25	−0.29	−0.03	−0.06	−0.01	−0.27	−0.33	−0.23
Citalopram vs placebo										
Visit 0	−0.05	−0.06	−0.01	0.09	−0.18	−0.10	−0.09	−0.12	−0.15	−0.09
Visit 3	−0.31	−0.28	−0.14	−0.23	−0.43	−0.32	−0.10	−0.13	−0.08	−0.15
Visit 6	−0.45	−0.37	−0.39	−0.29	−0.33	−0.41	−0.10	−0.15	−0.24	−0.12
Placebo vs reboxetine										
Visit 0	0.11	0.04	0.11	−0.15	−0.05	0.10	0.11	0.19	0.15	0.16
Visit 3	0.22	0.11	0.00	−0.06	0.29	0.31	−0.08	−0.10	−0.11	−0.09
Visit 6	0.36	0.22	0.14	0.00	0.30	0.36	0.08	−0.11	−0.09	−0.10

Abbreviations: PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

on which we have commented used only 1 of the scales; trials with citalopram and reboxetine used only the PANSS. For rating these symptoms, SANS is preferred to PANSS, in that several negative symptoms constructs are ascertained, with multiple items related to each. Related to this, use of a detailed scale like the SANS facilitates the separation of negative and cognitive symptoms.[44]

Although it was not a primary objective of our clinical trial, we also assessed psychotic positive and general symptoms. We failed to find any improvement. This result may be influenced by the fact that our patients were clinically stabilized, with predominant negative symptomatology and only mild positive and general symptomatology. In contrast to our study, Salokangas et al[24] performed secondary analyses and found that citalopram alleviated symptoms in the depression/anxiety dimension of PANSS.[45]

We did not find differences in side effects among the 3 groups as measured with the UKU and Simpson-Angus Scale. The 3 subjects who experienced an acute exacerbation of symptoms were receiving antidepressants (2 receiving reboxetine and 1 receiving citalopram), but considering the lack of statistically significant differences, the clinical significance of this finding is difficult to interpret.

Although the antipsychotics in this study (risperidone and olanzapine) have different mechanisms of action with regard to their dopamine D_2 receptor action (a potent versus a moderate D_2 receptor antagonist), our results cannot be generalized to the association of citalopram and reboxetine with other antipsychotics. Therefore, our results do not rule out the possibility that the combination of antidepressants with antipsychotics that have other receptor properties (serotonin, glutamate, etc) might be useful in the treatment of negative symptoms. For example, although methodological limitations should be considered, 2 trials with fluoxetine have shown contradictory results: fluoxetine was found to be useful in combination with a depot antipsychotic,[46] whereas in combination with clozapine, no improvement was reported.[47]

One of the main strengths of our study is that our clinical trial had a length of 6 months. Although there is growing consensus that trials should be about 6 months long[48] to establish treatment efficacy in negative symptoms, there are, to our knowledge, no published trials with a follow-up of this length. Another strength of the study is that our methodology took into account the guidelines of the Consensus Development Conference[44] that recommend a specific design to determine efficacy of treatment for true negative symptoms. Our patients were stable, with minimal positive psychotic and depression symptoms, and the experimental treatment was given as an adjunct to stable antipsychotic treatment. We used both the PANSS and the SANS subscales to assess negative symptoms. Finally, we included only patients with prominent negative symptoms.

The main limitations of the present study are the sample size and the dropout rate. Although our sample is quite large, the study did not have the power to capture a statistically significant difference of less than 3 points between treatment groups. Our dropout rate at 6 months was 29%, but at 3 months it was only 14%, which is similar to, for example, that of Salokangas and colleagues' trial[24] (13% at 3 months). We consider these rates to be typical of this kind of complex controlled trial. Finally, our results cannot be generalized to combinations with other antipsychotics.

In conclusion, our results do not support the combination of citalopram or reboxetine with risperidone or olanzapine for the treatment of negative symptoms in schizophrenia that had not previously responded to these antipsychotics.

Despite the aforementioned limitations, we believe that our results are of some interest, because they add valuable information to an issue that is still controversial and has relevant implications to clinical practice. More studies with larger samples are needed in order to assess antidepressant efficacy for negative symptoms.

Drug names: biperiden (Akineton), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), trazodone (Oleptro and others).

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REFERENCES

1. Carpenter WT Jr, Arango C, Buchanan RW, et al. Deficit psychopathology and a paradigm shift in schizophrenia research. *Biol Psychiatry*. 1999;46(3):352–360.
2. Möller HJ, Bottlender R, Gross A, et al. The Kraepelinian dichotomy: preliminary results of a 15-year follow-up study on functional psychoses: focus on negative symptoms. *Schizophr Res*. 2002;56(1–2):87–94.
3. Ventura J, Hellemann GS, Thames AD, et al. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophr Res*. 2009;113(2–3):189–199.
4. Gråwe RW, Levander S. Neuropsychological impairments in patients with schizophrenia: stability and prediction of outcome. *Acta Psychiatr Scand Suppl*. 2001;104(408):60–64.
5. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia. *Schizophr Bull*. 1999;25(1):173–182.
6. Elvevåg B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol*. 2000;14(1):1–21.
7. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
8. Barnes TRE, Paton C. Do antidepressants improve negative symptoms in schizophrenia? *BMJ*. 2011;342:d3371.
9. Kane JM. Pharmacologic treatment of schizophrenia. *Biol Psychiatry*. 1999;46(10):1396–1408.
10. Arango C, Buchanan RW, Kirkpatrick B, et al. The deficit syndrome in schizophrenia: implications for the treatment of negative symptoms. *Eur Psychiatry*. 2004;19(1):21–26.
11. Buchanan RW, Kreyenbuhl J, Kelly DL, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71–93.
12. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts," 5: treatment and prevention: past, present, and future. *Schizophr Res*. 2010;122(1–3):1–23.
13. Möller HJ. Non-neuroleptic approaches to treating negative symptoms in schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(2):108–116.
14. Rummel C, Kissling W, Leucht S. Antidepressants as add-on treatment to antipsychotics for people with schizophrenia and pronounced negative symptoms: a systematic review of randomized trials. *Schizophr Res*. 2005;80(1):85–97.
15. Joffe G, Terevnikov V, Joffe M, et al. Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: a double-blind, randomized, placebo-controlled trial. *Schizophr Res*. 2009;108(1–3):245–251.
16. Singh SP, Singh V, Kar N, et al. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry*. 2010;197(3):174–179.
17. Iancu I, Tschernihovsky E, Bodner E, et al. Escitalopram in the treatment of negative symptoms in patients with chronic schizophrenia: a randomized double-blind placebo-controlled trial. *Psychiatry Res*. 2010;179(1):19–23.
18. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry*. 1996;153(4):466–476.
19. Ichikawa J, Ishii H, Bonaccorso S, et al. 5-HT_{2A} and D_2 receptor blockade increases cortical DA release via 5-HT_{1A} receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. *J Neurochem*. 2001;76(5):1521–1531.
20. Díaz-Mataix L, Scorza MC, Bortolozzi A, et al. Involvement of 5-HT1A receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. *J Neurosci*. 2005;25(47):10831–10843.
21. Lee MS, Kim YK, Lee SK, et al. A double-blind study of adjunctive sertraline in haloperidol-stabilized patients with chronic schizophrenia. *J Clin Psychopharmacol*. 1998;18(5):399–403.
22. Arango C, Kirkpatrick B, Buchanan RW. Fluoxetine as an adjunct to conventional antipsychotic treatment of schizophrenia patients with residual symptoms. *J Nerv Ment Dis*. 2000;188(1):50–53.
23. Sepehry AA, Potvin S, Elie R, et al. Selective serotonin reuptake inhibitor (SSRI) add-on therapy for the negative symptoms of schizophrenia: a meta-analysis. *J Clin Psychiatry*. 2007;68(4):604–610.
24. Salokangas RK, Saarijärvi S, Taiminen T, et al. Citalopram as an adjuvant in chronic schizophrenia: a double-blind placebo-controlled study. *Acta Psychiatr Scand*. 1996;94(3):175–180.
25. Wong EH, Sonders MS, Amara SG, et al. Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. *Biol Psychiatry*. 2000;47(9):818–829.
26. Devoto P, Flore G, Saba P, et al. Co-release of noradrenaline and dopamine in the cerebral cortex elicited by single train and repeated train stimulation of the locus coeruleus. *BMC Neurosci*. 2005;6(1):31.
27. Raedler TJ, Jahn H, Arlt J, et al. Adjunctive use of reboxetine in schizophrenia. *Eur Psychiatry*. 2004;19(6):366–369.
28. Schutz G, Berk M. Reboxetine add on therapy to haloperidol in the treatment of schizophrenia: a preliminary double-blind randomized placebo-controlled study. *Int Clin Psychopharmacol*. 2001;16(5):275–278.
29. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
30. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
31. Kay SR, Opler LA, Fiszbein A. *The Positive and Negative Syndrome Scale (PANSS) Rating Manual*. San Rafael, CA: Social and Behavioral Sciences Documents; 1986:28–29.
32. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry*. 1982;39(7):784–788.
33. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale. *Acta Psychiatr Scand*. 1987;334:81–94.
34. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand suppl*. 1970;45(S212):11–19.
35. Andreasen NC, Pressler M, Nopoulos P, et al. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry*. 2010;67(3):255–262.
36. Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. *J Biopharm Stat*. 2001;11(1–2):9–21.
37. Leon AC, Mallinckrodt CH, Chuang-Stein C, et al. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biol Psychiatry*. 2006;59(11):1001–1005.
38. Lane P. Handling drop-out in longitudinal clinical trials: a comparison of the

LOCF and MMRM approaches. *Pharm Stat*. 2008;7(2):93–106.
39. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry*. 2004;61(3):310–317.
40. Hyttel J. Citalopram—pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. *Prog Neuropsychopharmacol Biol Psychiatry*. 1982;6(3):277–295.
41. Poyurovsky M, Fuchs C, Pashinian A, et al. Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: a double-blind placebo-controlled study. *Psychopharmacology (Berl)*. 2007;192(3):441–448.
42. Masana M, Bortolozzi A, Artigas F. Selective enhancement of mesocortical dopaminergic transmission by noradrenergic drugs: therapeutic opportunities in schizophrenia. *Int J Neuropsychopharmacol*. 2011;14(1):53–68.
43. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenics. *Psychiatry Res*. 1988;23(1):99–110.
44. Kirkpatrick B, Fenton WS, Carpenter WT Jr, et al. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*. 2006;32(2):214–219.
45. Taiminen TJ, Syvälahti E, Saarijärvi S, et al. Citalopram as an adjuvant in schizophrenia: further evidence for a serotonergic dimension in schizophrenia. *Int Clin Psychopharmacol*. 1997;12(1):31–35.
46. Goff DC, Midha KK, Sarid-Segal O, et al. A placebo-controlled trial of fluoxetine added to neuroleptic in patients with schizophrenia. *Psychopharmacology (Berl)*. 1995;117(4):417–423.
47. Buchanan RW, Kirkpatrick B, Bryant N, et al. Fluoxetine augmentation of clozapine treatment in patients with schizophrenia. *Am J Psychiatry*. 1996;153(12):1625–1627.
48. Alphs L. An industry perspective on the NIMH consensus statement on negative symptoms. *Schizophr Bull*. 2006;32(2):225–230.