Selective Serotonin Reuptake Inhibitor (SSRI) Add-On Therapy for the Negative Symptoms of Schizophrenia: A Meta-Analysis

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Background: Negative symptoms are among the most chronic symptoms of schizophrenia. Even with the advent of atypical antipsychotic drugs, negative symptoms remain mostly refractory to treatment. It has been proposed that selective serotonin reuptake inhibitor (SSRI) augmentation therapy in schizophrenia could provide a greater relief of these symptoms. Published studies, however promising, have produced conflicting results.

Objective: To overcome this discrepancy in results, we performed a meta-analysis of studies assessing SSRI add-on therapy for the negative symptoms of schizophrenia.

Data Sources and Study Selection: A search was performed using the computerized search engines PsycINFO, PubMed (MEDLINE), and Current Contents. Keywords used were *schizophrenia* and (for SSRI) *sertraline*, *citalopram*, *paroxetine*, *fluoxetine*, and *fluvoxamine*. Hand search of published review articles as well as cross-referencing were carried out, too. Pharmaceutical companies were also contacted. Studies were retained if (1) SSRI add-on therapy was compared with antipsychotic monotherapy among schizophrenia-spectrum disorder patients; (2) the clinical trial was randomized, double-blind, placebo-controlled with parallel-arm design; (3) negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms or the Positive and Negative Syndrome Scale-negative subscale.

Data Extraction: With a consensus, authors (A.A.S. and S.P.) extracted and checked the data independently on the basis of predetermined exclusion and inclusion criteria. Effect size estimates were calculated using Comprehensive Meta-Analysis software.

Data Synthesis: Eleven studies responded to our inclusion criteria. Within a random-effects model, a nonsignificant composite effect size estimate for (end point) negative symptoms was obtained (N = 393; adjusted Hedges' g = 0.178; p = .191). However, when studies were divided according to severity of illness, a moderate and significant effect size emerged for the studies involving so-called "chronic patients" (N = 274; adjusted Hedges' g = 0.386; p = .014).

Conclusion: The current meta-analysis provides no global support for an improvement in negative symptoms with SSRI augmentation therapy in schizophrenia.

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Since Bleuler,[1] negative symptoms (apathy, avolition, anergia, alogia, blunted affect, and social withdrawal) of schizophrenia have been reported to be the core features of the disease. Particularly difficult to treat, these symptoms represent significant obstacles for reaching better global functioning.[2,3]

First-generation antipsychotic drugs (typical) provide only minimal relief of these enduring symptoms.[4] Second-generation antipsychotic drugs have been developed in the hope of eliminating the side effects of typical neuroleptics and of improving negative and cognitive symptoms. Even after such developments, negative symptoms remain mostly refractory to treatment.[5] Meta-analytic studies have reported benefits of second-generation antipsychotics in the treatment of negative symptoms, but these benefits appeared to be modest.[6,7]

A role for antidepressant drugs as adjuvant treatment of negative symptoms has been discussed by Silver.[8] The rationale for the use of antidepressant add-on therapy is based on the primary/secondary dichotomy. Negative symptoms are classified as primary or secondary.[9,10] In contrast with primary negative symptoms, which are directly related to the schizophrenia pathophysiology, secondary negative symptoms result from other psychiatric symptoms (e.g., positive symptoms), medication side effects (e.g., extrapyramidal symptoms), or medical conditions (e.g., mental retardation).[9,10] In particular, negative symptoms may be secondary to depressive symptoms, which share common key symptoms such as anhedonia, asociality, avolition, and apathy.[11,12] In this context, the use

of antidepressants has been thought to be of potential interest in schizophrenia, as the treatment of depressive symptoms would eventually lead to a relief of secondary negative symptoms. In clinical practice, it has been estimated that antidepressants are prescribed as adjunctive treatment in approximately one third of schizophrenia patients.[13] However, add-on therapy with antidepressants such as monoamine oxidase inhibitors (MAOIs)[14] or tricyclics[15] in schizophrenia has produced limited results.[16]

More recently, selective serotonin reuptake inhibitors (SSRIs) have been investigated as augmentation therapies for the negative symptoms of schizophrenia. On the basis of preliminary results, Silver[8] has proposed the usage of SSRI augmentation therapy for these enduring symptoms. However, other studies published so far have produced conflicting results.[17,18] A Cochrane registered systematic review by Whitehead et al.[19] showed that add-on antidepressant for persons with schizophrenia and comorbid depression may be of therapeutic value; yet, Whitehead et al. reviewed a small number of trials, which may have led to a possible study bias, so the interpretation of their result should be done with care. A new quantitative review of 7 trials (N = 202) by Rummel and colleagues,[20] showed that combination of antipsychotics with antidepressants may perhaps be effective in controlling predominant negative symptoms. However, they report only 3 studies with SSRI (also included in our meta-analysis), and so to draw a conclusion on SSRI add-on therapy would be limited. Nevertheless, the authors assert that their finding needs to be substantiated by further larger-sized trials.[20]

Also it is noteworthy that the number of participants in these studies has been small, ranging from 20 patients[21] to 75 patients.[22] These studies did not include enough patients to detect a 20% difference between groups in symptom improvement, which is the clinical standard for the pharmacologic studies in schizophrenia.[23] To detect such a difference between groups, it is required that a trial include 131 participants per study arm ($\alpha = .05$; power, 80%).[24]

To reach the sample size required for detecting a 20% difference between groups (power, 80%), we conducted a meta-analysis of studies assessing SSRI add-on therapy for the negative symptoms of schizophrenia. This meta-analysis raised the sample size in each study arm to more than 131 participants. The results of this meta-analysis are of therapeutic importance, considering the chronic nature of negative symptoms. They could also shed light on the potential role of serotonin in the pathophysiology of negative symptoms.

METHOD

Data Sources

Systematic review of the literature on SSRI add-on therapy for the negative symptoms of schizophrenia was performed. Keywords used for the search were *schizophrenia* and (for SSRI) *sertraline*, *citalopram*, *paroxetine*, *fluoxetine*, and *fluvoxamine*. The search engines were PsycINFO, PubMed (MEDLINE) (1967–2005), and Current Contents (1993–2005). Hand search of published review articles, as well as cross-referencing, have been carried out to gather further data. When relevant, authors were contacted for missing data. Pharmaceutical companies were also contacted to retrieve unpublished data (no further records were found).

Study Selection

A consensus was reached among authors on the studies retained or discarded, on the basis of the following inclusion and exclusion criteria.

Inclusion Criteria

Studies were retained if (1) SSRI add-on therapy was compared with antipsychotic treatment; (2) patients had a diagnosis of a schizophrenia-spectrum disorder; (3) the clinical trial was randomized, double-blind, placebo-controlled with parallel-arm design; and (4) negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS)[25] or the Positive and Negative Syndrome Scale-negative subscale (PANSS-N),[26,27] before (baseline) and after follow-up (end point). Overall, these scales have been demonstrated to have high internal consistency and external validity for the population group.[27] Further, these scales have been reported to be relatively comparable.[15,28–31]

Exclusion Criteria

Studies were discarded if (1) schizophrenia patients had been diagnosed with comorbid obsessive-compulsive disorder (DSM criteria); (2) the study assessed the efficacy of MAOI, tricyclic, dual-action, or atypical antidepressants (e.g., bupropion); (3) the study had incomplete or unavailable data; or (4) a crossover study design was employed.

Data Extraction and Quantitative Data Synthesis

Two reviewers (A.A.S. and S.P.) independently extracted data; disagreements were resolved by consensus. Using Comprehensive Meta-Analysis,[32] effect size estimates were derived from the differences in negative symptoms between schizophrenia patients treated with add-on SSRI (SSRI group) and patients on placebo (placebo group), both before (baseline) and after treatment (end point). Effect size estimates were calculated from sample size, means, and standard deviations (PANSS-N score or SANS total score) for each group of patients: SSRI and placebo. When available, full data without attrition were preferred to intention-to-treat or last-observation-carried-forward data. Within a random-

Table 1. Study Characteristics of Randomized, Double-Blind, Placebo-Controlled Trials of SSRI Add-On Therapy for the Negative Symptoms of Schizophrenia

Study	N[a]	SSRI	SSRI Dosage (mg/d)	Antipsychotic	Scale	Patient Description	EPS/Depression Controlled	Treatment Duration, wk
Silver and Nassar[22]	30	Fluvoxamine	50–100	Unspecified	SANS	Chronic/Inpatient	Yes/Yes	5
Buchanan et al[21]	33	Fluoxetine	20–80	Clozapine	SANS	Nonresponder/Outpatient	No/Yes	8
Spina et al[18]	30	Fluoxetine	20	Typical	SANS	Chronic/Inpatient	**/Yes	12
Arango et al[35]	32	Fluoxetine	20	Typical	SANS	Outpatient	Yes/Yes	8
Silver et al[36]	52	Fluvoxamine	50–100	Typical	SANS	Chronic/Inpatient	Yes/Yes	6
Lee et al[17]	36	Sertraline	50	Typical	PANSS-N	Chronic/Inpatient	Yes/Yes	8
Poyurovsky et al[37]	24	Fluoxetine	20	Olanzapine	SANS	1st episode/Inpatient	No/Yes	8
Bustillo et al[38]	20	Fluoxetine	20–60	Olanzapine	PANSS-N	Outpatient	Yes/Yes	16
Salokangas et al[39b]	75	Citalopram	20–40	Typical	PANSS-N	Chronic/Outpatient	**/No	12
Mulholland et al[40]	20	Sertraline	50–100	Mixed	SANS	Chronic/Outpatient	**/Yes	4
Jockers-Scherubl et al[41]	25	Paroxetine	20–30	Mixed	PANSS-N	Chronic/Outpatient	**/Yes	12

[a]Number of patients who completed the trial.
[b]Data for this particular study were provided by the author.
Abbreviations: EPS = extrapyramidal symptoms, PANSS-N = Positive and Negative Syndrome Scale-negative subscale, SANS = Scale for the Assessment of Negative Symptoms, SSRI = selective serotonin reuptake inhibitor.
Symbol: ** = no data.

effects model, effect size estimates were derived using Hedges' g,[33] which provides effect sizes adjusted for sample size. Random-effects models, being more stringent than fixed-effects models, allow population-level inferences.[34]

In order to control for baseline clinical characteristics, effect size estimates were performed with available data (see Table 1). For age (7 studies), positive symptoms (10 studies), depressive symptoms (9 studies), and extrapyramidal symptoms (6 studies), effect estimates were calculated on the basis of mean scores and SDs for both comparison groups. In the case of sex (9 studies), the effect size estimate was computed as a nonparametric "rate difference," using male/female ratios. In addition, end point data were used to calculate effect size estimates for positive, depressive, and extrapyramidal symptoms. For some studies, extrapyramidal symptom total scores were not available, only extrapyramidal symptom subscale scores. These subscores were collapsed using D-STAT[42] to generate a total extrapyramidal symptom score (mean differences).

Homogeneity of Effect Size Estimates

It is more legitimate to aggregate effect size estimates when effect sizes are homogeneous. A universal mean to indicate the extent of heterogeneity (variability due to chance, due to scale used, etc.) is the application of statistical test, frequently portrayed as Cochran χ^2 test or the Q test/statistic. The Q statistic is similar to χ^2 statistics but uses meta-analytic data to examine the homogeneity of the effect sizes included in the studies.[43] Thus, we have calculated the Q statistic for the effect size estimates of the studies included in the meta-analysis (baseline and end point, separately). Significance was defined a priori as $p < .1$. A significant result is an indication of the presence of moderating variables within the dataset.

RESULTS

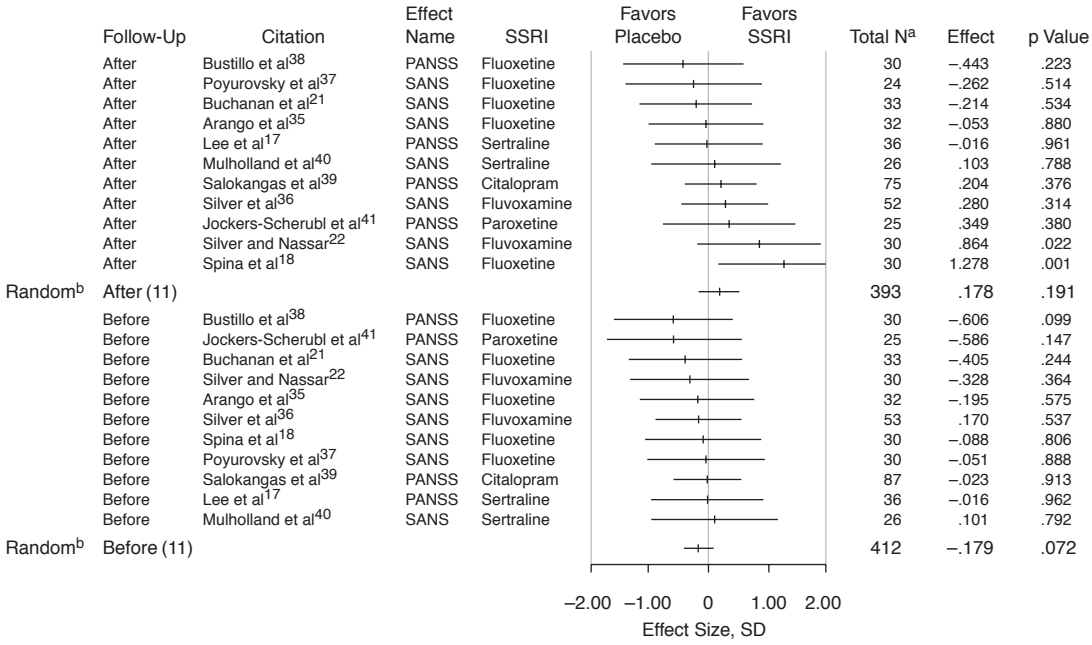
Study Characteristics

Five hundred ninety-one possible articles emerged. Of these, 552 studies were discarded on the basis of the evaluation of the abstract and 28 studies on the basis of the evaluation of the article, according to the following reasons: (1) type of article/study (e.g., review, case study, challenge study, survey, retrospective study, open-label trial, postmortem study, molecular study, letter to the editor, book chapter, and crossover study), (2) type of population (e.g., nonhuman subjects, patients with comorbid conditions, nonschizophrenia patients), (3) treatment type (e.g., non-SSRI antidepressants, nonpharmacologic therapy), and (4) incomplete or unavailable data.[44–46] The remaining 11 studies responded to our inclusion criteria (data were available for each study).

The 11 studies included in the meta-analysis were clinically heterogeneous (Table 1), in the following areas:

- SSRI medication: fluoxetine (5 studies), fluvoxamine (2 studies), sertraline (2 studies), citalopram (1 study), and paroxetine (1 study);
- antipsychotic drug: atypical (3 studies), typical (5 studies), not specified (1 study), and mixed (2 studies);
- psychiatric assessment: SANS (7 studies) and PANSS-N (4 studies);
- patient type (Note: Studies were classified according to population description explicitly stated by authors): chronic (7 studies) and nonchronic (4 studies);
- psychiatric setting: inpatient (5 studies) and outpatient (6 studies);
- treatment duration: from 4 weeks to 4 months;

Figure 1. Effect Sizes of Randomized Trials of SSRI Add-On Therapy for Negative Symptoms of Schizophrenia



[a]Ns in this figure pertain both to last-observation-carried-forward (LOCF) and intention-to-treat (ITT) data, as is the case for Bustillo et al. (LOCF) and Mulholland et al. (ITT).
[b]Analysis based on random-effects model.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SSRI = selective serotonin reuptake inhibitor.

- type of data: last-observation-carried-forward or intention-to-treat (4 studies) versus study completers (7 studies).

It is noteworthy that 2 studies were not primarily designed to assess negative symptoms.[37,38] Studies reporting previously used data were withdrawn from analysis.[47–49]

Quantitative Data Synthesis

A total of 11 randomized, double-blind, placebo-controlled trials, with parallel-arm design (N = 393 patients at end point) were identified in which add-on SSRI therapy was compared with antipsychotic monotherapy. No significant differences were found between the treatment groups for negative symptoms using end point data (adjusted Hedges' g = 0.178; p = .191; random-effects model) (Note: An overall 5% attrition has been calculated.) (Figure 1). Interestingly, for baseline data, a composite effect size estimate for negative symptoms was obtained that bordered on significance (N = 412; adjusted Hedges' g = –0.179; p = .072), suggesting a potential study bias. For age, sex, and positive, depressive, and extrapyramidal symptoms, no significant differences between the SSRI and placebo groups were detected at baseline.

In order to control for masked effects, secondary analyses were performed. Effect size estimates for negative symptoms were calculated according to the following categories: antipsychotic type (typical, atypical, or mixed), SSRI medication (fluoxetine vs. others), psychiatric setting (inpatient/outpatient), psychiatric assessment (PANSS-N and SANS), and treatment duration (less than 12 weeks or longer than or equal to 12 weeks) (Note: In add-on SSRI for treatment of negative symptoms, a long-term duration of treatment of no less than 12 weeks is recommended[15]). These secondary analyses all provided nonsignificant composite effect size estimates for negative symptoms. A run was also performed excluding the studies by Bustillo and colleagues[38] and Poyurovsky et al.[37] A low and significant effect size estimate for negative symptoms was reached (N = 339; adjusted Hedges' g = 0.277; 95% CI = –0.087 to 0.640; p = .049). In addition, when studies were divided according to severity of illness (chronic/nonchronic), a moderate effect size for negative symptoms was obtained for the chronic group of studies (N = 274; adjusted Hedges' g = 0.386; 95% CI = –0.018 to 0.791; p = .014). Additionally, when studies were separated into last-observation-carried-forward or intention-to-treat versus study completers, similar results were yielded. Both effect estimates were nonsignificant and small: last-observation-carried-forward or

Table 2. Z Scores Obtained for Each Study

	Baseline		End Point	
Study	Placebo	Add-On SSRI	Placebo	Add-On SSRI
Buchanan et al[21]	–0.2465	0.1661	–0.0991	0.1219
Spina et al[18]	0.4650	0.5421	0.1908	–1.2916
Arango et al[35]	–0.1817	0.0260	0.0519	0.1038
Silver et al[36]	–0.0622	0.0895	0.1513	–0.1632
Silver and Nassar[22]	0.6276	1.0015	–0.4254	–1.2037
Poyurovsky et al[37]	0.7726	0.8178	–1.1366	–0.8255
Mulholland et al[40]	0.0880	–0.0176	0.0176	–0.0880
Salokangas et al[39]	0.3939	0.4166	–0.3676	–0.5802
Lee et al[17]	–0.0246	–0.0082	0.0082	0.0246
Bustillo et al[38]	–0.2367	0.3836	–0.3020	0.1551
Jockers-Scherubl et al[41]	0.3811	0.8675	–0.4104	–0.8302

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

intention-to-treat (effect size = 0.093; p value = .594) and study completers (effect size = 0.240; p value = .225).

The set of 11 studies (end point data) included in the meta-analysis was slightly heterogeneous (Q = 16.830; p = .078). They were no longer heterogeneous when the studies were divided according to severity of illness (so called "chronic patients") (Q = 9.060; p = .170). Also, when the 2 studies not designed to primarily assess negative symptoms were excluded, effect size estimates of negative symptoms were no longer heterogeneous (Q = 12.312; p = .138).

Sensitivity Analysis

To control for the methodological shortcomings aforementioned (end point heterogeneity and baseline differences in negative symptoms), mean values reported by different researchers were transformed into z scores using their standard deviations for assessing a pooled variance (Table 2). The new data attained were then analyzed for differences between the 2 study conditions (SSRI vs. placebo) and between initial scores and final appraisal with a 2 × 2 factorial analysis of variance. The critical level of significance was set at 5%. Patients improved in time (F = 21.94, df = 1,40; p < .001) but no differences were observed between the 2 medication regimens (F = 2.64, df = 1,40; p = .112 NS). The same method was replicated for the so-called "chronic patients," and again time-treatment interaction emerged to be nonsignificant (F = 0.88; df = 1,24; p = .357).

DISCUSSION

The objective of this meta-analysis was to determine if SSRI add-on therapy provides relief of negative symptoms among schizophrenia patients. Using search engines, 11 randomized, double-blind, placebo-controlled trials were identified, involving 393 patients. Using Comprehensive Meta-Analysis,[32] effect size estimates for differences in negative symptoms (end point data) between both groups (SSRI and placebo) were calculated. Within a random-effects model, a nonsignificant composite effect size estimate was obtained, suggesting that SSRI augmentation therapy does not relieve the negative symptoms of schizophrenia. Secondary analyses were performed to control for potential confounding factors, such as psychiatric setting (inpatient/outpatient), psychiatric assessment (PANSS-N/SANS), antipsychotic type (typical/atypical/mixed), specific SSRI (fluoxetine vs. others), and treatment duration (shorter than 12 weeks or longer than or equal to 12 weeks). Again, no significant differences emerged between the SSRI and the placebo groups on negative symptoms. However, a significant but low effect size estimate for negative symptoms was obtained when the 2 studies not primarily designed to assess changes in negative symptoms (Bustillo et al.[38] and Puyurovsky et al.[37]) were excluded. In addition, a moderate and significant effect size for negative symptoms was reached using end point data when a run was performed with studies involving chronic patients. Of interest, these patients are the most likely to benefit from SSRI add-on therapy since negative symptoms are among the most enduring signs of the disorder.[2] Nevertheless, after a factorial analysis using baseline and end point data, even the so-called "chronic" schizophrenia patient did not seem to profit from this treatment regimen. Moreover, it must be taken into consideration that no operational definition of "chronic schizophrenia"—a stigmatizing term—has been consensually established.[50]

This first set of analyses comprised 2 limitations. First, a trend toward significance was observed when the composite effect size estimate was calculated for differences in baseline negative symptoms. Patients in the placebo group tended to have fewer negative symptoms at baseline, suggesting a potential study bias. In addition, end point effect size estimates for negative symptoms appeared to be heterogeneous. However, in the current meta-analysis, the heterogeneity problem must not be overestimated, for 2 reasons: (1) the number of studies included was small (11), which limits the power of the Q statistic,[51] and (2) for our secondary analyses (e.g., severity of illness), effect size estimates for negative symptoms were no longer heterogeneous.

To control for these shortcomings, means and SDs on PANSS-N and SANS scores were transformed into z scores (SSRI and placebo groups; baseline and end point data), allowing for the calculation of a composite 2 × 2 factorial analysis of variance of negative symptoms, with group and time as independent variables. A nonsignificant result was obtained, further suggesting that SSRI augmentation therapy does not relieve the negative symptoms of schizophrenia.

The results of the current meta-analysis provide no clear evidence for the presumed efficacy of SSRI augmentation treatment of negative symptoms. Whereas previous studies

relied on samples too small to detect clinically significant differences, pooling of the published randomized, double-blind, placebo-controlled studies that were methodologically homogeneous provided a sample of more than 150 patients per arm; however, the global sample size for the 11 studies remained small (393 patients). In addition, the study provides evidence that this lack of efficacy can not be attributed to clinical differences in age, sex, positive symptoms, depressive symptoms, or extrapyramidal symptoms. However it is imperative to touch base with clinical and methodological issues in this debate. For discussion of clinical implications and methodological concerns related to primary and secondary negative symptoms, please refer to the studies by Moller[52] and Rummel and colleagues.[20]

In conclusion, our findings offer no support for polypharmacy—combining antipsychotics and SSRI—at least not for the treatment of negative symptoms of schizophrenia for which there was a poor response to antipsychotics alone.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft).

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