Citalopram Augmentation for Subsyndromal Symptoms of Depression in Middle-Aged and Older Outpatients With Schizophrenia and Schizoaffective Disorder: A Randomized Controlled Trial

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Background: Subsyndromal symptoms of depression (SSD) in older outpatients with schizophrenia are common and clinically important. While many physicians prescribe antidepressants to patients with schizophrenia and schizoaffective disorder who have SSD, evidence for their effectiveness and safety has been meager. We describe a randomized placebo-controlled trial of citalopram in 198 patients.

Method: Participants in this 2-site study, conducted from September 1, 2001, to August 31, 2007, were men and women with DSM-IV schizophrenia or schizoaffective disorder who were 40 years of age or older and who met study criteria for SSD. Patients were randomly assigned to flexible-dose treatment with citalopram or placebo augmentation of their current antipsychotic medication. Analysis of covariance was used to compare improvement in scores on the Hamilton Rating Scale for Depression and Calgary Depression Rating Scale between treatment groups; secondary efficacy analyses compared improvement in several other dimensions of schizophrenia.

Results: Augmentation with citalopram was significantly more effective than with placebo in improving depressive ($p = .002$) and negative ($p = .049$) symptoms, mental functioning ($p = .000$), and quality of life ($p = .046$). There were no significant differences between citalopram and placebo in suicidal ideation, positive symptoms, cognition, general medical health, physical functioning, or symptoms of movement disorders. No adverse events were more frequent in participants receiving citalopram than in those receiving placebo, and only 4 participants from each treatment group terminated early because of side effects.

Conclusions: Subsyndromal symptoms of depression in middle aged and older patients with schizophrenia responded to treatment with citalopram with lessening of depressive symptoms and improved functioning and quality of life. It may be important for clinicians to identify and treat SSD in middle-aged and older patients with chronic schizophrenia.

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Depressive symptoms in patients with chronic schizophrenia add a heavy burden to the already considerable challenges of living with this serious mental illness and are associated with disability, recurrence of illness, demoralization, poor motivation, and an increased risk for suicide.[1–4] These phenomena occur in a majority of patients with chronic schizophrenia and with regularity in all patients with schizoaffective disorder.

Patients with schizophrenia are 29 times more likely than the general population to have a lifetime diagnosis of major depressive episode (MDE),[5] and 59% of patients with schizophrenia meet DSM-III criteria for major or minor depression.[6] Comorbid MDEs markedly decrease quality of life,[7] increase relapse rate, and increase the risk

for suicide.[8] American Psychiatric Association guidelines for the treatment of patients with schizophrenia recommend antidepressant medications for syndromal major depression, especially when the depression is severe, causes significant distress, or interferes with functioning.[9] Yet, there have been only a few randomized controlled trials of antidepressant medications in patients with schizophrenia and MDE or schizoaffective disorder, and these do not provide conclusive evidence in favor of their overall effectiveness.[10]

Although substantially less well studied and understood than comorbid MDE, clinically significant depressive symptoms are much more prevalent than full MDE in patients with schizophrenia.[11] Indeed, they are so prevalent that some investigators have argued that depression is a core component of schizophrenia, similar to positive, negative, and disorganized symptom clusters.[12,13] A prospective study assessing depression during the longitudinal course of schizophrenia found that only 24% of subjects remained free of depressive symptoms. While slightly over one third (36%) met criteria for MDE, many more (40%) experienced only 2 to 4 symptoms of depression.[14] Zisook et al.[4] have previously reported that more than two thirds of schizophrenia patients who do not have MDEs have at least mild depressive symptoms and over 30% of patients had depressed mood, feelings of guilt, and/or feelings of hopelessness. Other studies have also reported high rates of depressive symptoms in older patients with psychotic disorders.[15]

In community samples of nonschizophrenia patients, subsyndromal symptoms of depression (SSD), defined as a depressive state having 2 to 4 symptoms of depression for more than 2 weeks and associated with social dysfunction, are even more prevalent than major depressive disorder (MDD), dysthymic disorder, or minor depression; are associated with significant psychosocial dysfunction; and are a significant risk factor for suicide and future MDE.[16,17] Although the concept of SSD has not been systematically applied to patients with schizophrenia, clinicians and researchers alike attest to the clinical importance of subthreshold symptoms of depression in patients with schizophrenia.[3,18] For example, an international survey of depression in schizophrenia[3] reported that a majority of American psychiatrists felt depression was a common problem throughout the course of schizophrenia, added to overall morbidity, and negatively impacted family adjustment; 14% of the respondents reported that a patient committed suicide in the previous year and most felt that depression was a significant factor in those patients. These clinical impressions have been validated with hard data from growing literature that posits that SSD in patients with schizophrenia is associated with social and financial distress,[1] diminished quality of life,[2] increased health service utilization,[2] greater overall symptom severity,[4] demoralization,[7] early relapse,[13] and possibly elevated risk of suicide.[19,20]

A part of the difficulty in studying SSD in patients with schizophrenia has been the confusion of whether depressive symptoms are a core component of schizophrenia, an understandable reaction to having this chronic and debilitating disorder, a prodromal or residual symptom of psychosis, an antipsychotic drug effect, a part of an akinetic syndrome or of the negative syndrome complex, or perhaps all of the above. However, regardless of the etiology of SSD in patients with schizophrenia, such symptoms are common and clinically important. But should they be treated? While it is clear that most physicians commonly prescribe antidepressants to patients with schizophrenia and schizoaffective disorder,[3] documented evidence for the effectiveness of medications is meager, and evidence for the potential harm of (ineffective) polypharmacy is mounting.[21]

In this randomized controlled trial of citalopram versus placebo in older outpatients with SSD, we hypothesized that, compared to placebo, treatment with citalopram would be associated with a significantly greater improvement in depressive symptoms. Secondary outcome measures included suicidality, everyday functioning, quality of life, symptoms of psychosis, and neurological function. The target population, middle-aged and older individuals with schizophrenia and schizoaffective disorder, was selected because of the growing number of individuals with severe and chronic mental illness in this age group coupled with the frequency of subthreshold depressive symptoms in older patients with schizophrenia and the paucity of information to guide treatment and prognostic decisions.[20,22]

METHOD

This was a 12-week, double-blind, randomized, placebo-controlled 2-site study (University of California, San Diego and University of Cincinnati) of citalopram augmentation of antipsychotic medication in middle-aged and older outpatients with schizophrenia or schizoaffective disorder and subsyndromal depression. The study was conducted from September 1, 2001, to August 31, 2007.

Study Population

At the University of California, San Diego site, participants were recruited from the National Institute of Mental Health–funded Intervention Research Center focusing on middle-aged and older persons with schizophrenia. At both sites, participants were recruited from board-and-care facilities, Veterans Affairs Health Care Centers, and general outpatient settings. The study was done in accordance with the principles of Helsinki and good clinical practice. Study approval was obtained from each site's

institutional review board, and a written informed consent was obtained from participants or their legally authorized representatives prior to the initiation of study procedures.

Consenting outpatients 40 years of age or older were eligible for the study if they met DSM-IV criteria for schizophrenia or schizoaffective disorder; met study criteria for subsyndromal depression, defined as having 2 to 4 of the 9 DSM-IV symptoms of MDE present most of the time for at least 2 weeks; had a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 8[23]; and were on a stable dose of an antipsychotic medication. Potential participants were excluded if they met clinical diagnosis of a dementing disorder (such as vascular dementia); had a recent (within 2 months) diagnosis of major depression or mania; had active substance abuse or dependence that, in the research physician's opinion, would impact on diagnostic decisions, safety, or anticipated adherence; were judged (clinically) to be a serious suicide risk, for whom the possibility of being treated with placebo rather than citalopram augmentation was considered unsafe; had previously experienced allergic reaction or significant adverse events while taking citalopram; or were advised (on the basis of the treating or study physicians' judgment) not to take selective serotonin reuptake inhibitors (SSRIs). Female participants of childbearing potential were required to use a medically acceptable form of contraception. In order to "optimize" antipsychotic treatment, the study physician could recommend antipsychotic dose adjustment to the treating physician prior to randomization if the study physician felt it was warranted. When changes were made, we waited until doses were stable for at least 4 weeks before completing baseline assessments and randomization.

Study Treatments

Patients were randomly assigned to treatment with citalopram (20 mg/day) or placebo augmentation of their current antipsychotic medication. After the first week, study dose could be reduced to 10 mg/day or increased, based on clinical response and/or side effects (minimum dose 10 mg/day, maximum dose 40 mg/day) at the blinded study physician's discretion. Subjects were instructed to take their study medication at the same time each day. Potential participants who otherwise met study criteria but were taking antidepressants could have their antidepressants tapered and discontinued; if they continued to meet study entrance criteria 4 or more weeks after antidepressant discontinuation, they could enter the study. Post-tapering assessments were used as baseline data. On a case-by-case basis, study participants were allowed to continue with low-dose antidepressant medications that had been prescribed by their treating physicians for insomnia or chronic pain. The study physician did not change antipsychotic medications or doses during the study, but if they noticed anything of concern, they were encouraged to contact the treating physician. Any medication adjustments made by the study physician were noted on case report forms. Psychotic exacerbations were considered serious adverse events, triggering reports to the treating physician and the University Internal Review Board. When participants were dropped from the study, the treating physician was invited to request information about the study medication from the research pharmacist.

Assessments

Training of raters was done prior to the enrollment of subjects at both sites on both the protocol and administration of assessments. With regards to interrater reliability, an intraclass correlation coefficient of ≥ 0.90 was established. All raters who were hired after the study had been initiated were trained and deemed reliable by previously trained raters from each site prior to rating subjects for the study.

Screening evaluations included the Mini-Structured Clinical Interview for DSM-IV Axis I Disorders[24] and HAM-D-17.[23] After informed consent was signed, a psychiatric and medical history, vital signs, laboratory tests, and physical examination were performed. Additional baseline ratings included Calgary Depression Rating Scale (CDRS),[25] Positive And Negative Syndrome Scale (PANSS),[26] Clinical Global Impressions Scale (CGI),[27] Clinical Global Impressions-Severity of Suicide scale (CGI-SS),[27] Cumulative Illness Rating Scale for geriatric subjects (CIRS-G),[28] Quality of Life Scale (QLS),[29] 12-item Short-Form Health Survey (SF-12),[30] Systematic Assessment for Treatment Emergent Events (SAFTEE),[31] Simpson-Angus Extrapyramidal Side Effect Scale (SAEPS),[32] Barnes Akathisia Scale (BAS),[33] Abnormal Involuntary Movement Scale (AIMS),[27] and Mini-Mental State Examination (MMSE).[34]

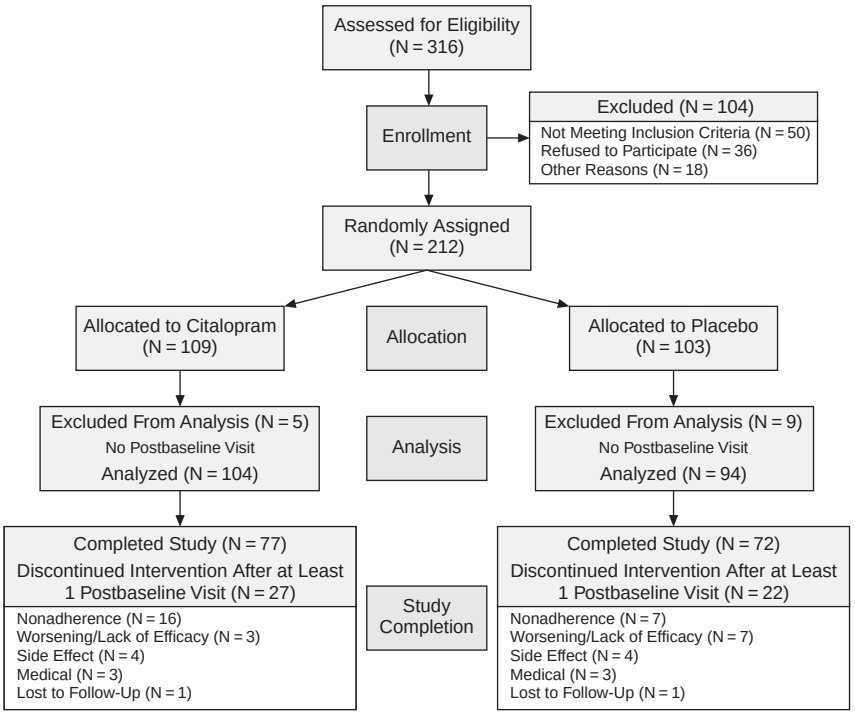
Major study visits occurred at baseline and at week 12 (end of double-blind treatment) or at the final visit if the subject discontinued the study prior to week 12. At these sessions, evaluations included vital signs and results on the HAM-D-17, CDRS, CGI, CGI-SS, PANSS, SF-12, QLS, SAEPS, BAS, AIMS, SAFTEE, and MMSE.

A shorter battery of tests was done at all other study visits (weeks 1, 2, 3, 4, 6, and 8). The assessment battery at these visits included the HAM-D-17, CDRS, CGI-SS, and SAFTEE, and the PANSS was repeated at weeks 4 and 8.

Statistical Analysis

For summary statistics, means and SDs were computed for continuous variables, and counts and percentages for discrete variables. We initially considered using a mixed-model regression analysis, but, because the hypothesis of primary interest was outcome at endpoint and the shape of the response trajectory was different between the sites, we chose to use endpoint analysis. Two-way analyses of

Figure 1. Participant Flow (CONSORT chart) for the Treatment of Subsyndromal Depression in Patients With Schizophrenia and Schizoaffective Disorder Study



Abbreviation: CONSORT = Consolidated Standards for Reporting Trials.

variance, adjusting for site, were used to compare continuous baseline clinical and demographic characteristics and percentage change in depression scores. Cochran-Mantel-Haenszel tests were used to compare discrete characteristics across treatments, adjusting for site. The data were analyzed using an intent-to-treat analysis as well as a modified intent-to-treat basis in which participants who underwent randomized assignment, who took at least 1 dose of the study medication, and who completed at least 1 postbaseline visit were included. Since the results were consistent either way, we choose to report the modified intent-to-treat analysis. The primary efficacy criteria were treatment differences at end of treatment (last value) in HAM-D-17 and CDRS total scores. Missing values were handled using last-observation-carried-forward (LOCF) methodology. All statistical tests were 2 tailed and the level of statistical significance was set at $p \leq .05$. Analysis of covariance (ANCOVA) was used to compare improvement in HAM-D-17 and CDRS scores between treatment groups (antipsychotic plus citalopram vs. antipsychotic plus placebo), and, for secondary efficacy analyses, to compare changes in other dimensions of schizophrenia: suicidal ideation (CGI-SS and HAM-D-17 item 3), global psychopathology (CGI), positive and negative symptoms (PANSS), cognitive functioning (MMSE), functional status (SF-12), general medical health (CIRS-G), quality of life (QLS), and symptoms of movement disorders (AIMS, SAEPS, and BAS). The ANCOVA model was formulated with outcome at the study endpoint as the dependent variable. Treatment group, site, baseline severity, and treatment group–by-site interaction were included as independent variables. Site was centered around 0. A treatment-by-site interaction term was added to the primary and key secondary analysis models to explore the possibility of treatment-by-site interactions. Response rates, defined as ≥ 50% improvement in HAM-D-17 and CDRS scores, were analyzed using Mantel-Haenszel tests, stratified by site. The treatment effect for time to response was examined with a Cox regression model, with separate baseline hazard functions for each site.

RESULTS

Overall and Group Baseline Characteristics

One hundred ninety-eight men and women between the ages of 41 and 75 years comprised the modified intent-to-treat sample (Figure 1). Table 1 summarizes participants' demographic characteristics and relevant elements of participants' pretreatment clinical history, along with results of the statistical tests used to compare the 2 augmentation treatment groups. No significant differences

Table 1. Demographic and Baseline Clinical Characteristics of Participants With SSD Receiving Antipsychotic Augmentation With Either Citalopram or Placebo by Treatment (N = 198)

	Citalopram (N = 104)		Placebo (N = 94)				
Characteristic	Mean	SD	Mean	SD	F[a]	df	p
Age, y	53.14	7.68	51.70	6.33	2.032	1,192	.156
Age at onset of first psychotic episode, y	28.44	10.67	27.30	10.29	0.484	1,167	.488
Education level, y	12.09	2.14	11.78	2.31	0.938	1,194	.334
	N[b]	%	N[b]	%	χ^2	df	p
Female gender	23	22.1	20	21.3	0.015	1	.903
Race					3.029	3	.387
White	54	51.9	54	57.4			
Black	40	38.5	26	27.7			
Hispanic	5	4.8	9	5.3			
Other	5	4.8	5	9.6			
Marital status					15.169	3	.002
Never married (single)	32	30.8	48	51.1			
Married or cohabiting	18	17.3	10	10.6			
Divorced or separated	41	39.4	35	37.2			
Widowed	13	12.5	1	1.1			
Age < 18 years at onset of first psychotic episode	9	10.1	12	14.6	0.409	1	.522
Ever attempted suicide	48	47.5	41	46.6	1.891	2	.389
Diagnosed schizoaffective	48	46.2	33	35.1	1.521	1	.218
Medications					0.036	2	.982
First-generation antipsychotics	10	10.2	9	9.9			
Second-generation antipsychotics	69	70.4	65	71.4			
Both first- and second-generation antipsychotics	19	19.4	17	18.7			
Anticholinergics/antihistamines	30	30.6	26	28.6	0.035	1	.853
Tapered from antidepressant ≥ 4 weeks prior to study	19	18.3	15	16.0	0.386	1	.534

[a]Derived from analysis of covariance, adjusting for baseline values, site, and site-by-treatment interactions.
[b]Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.
Abbreviation: SSD = subsyndromal symptoms of depression.

were observed between the 2 groups except that the citalopram group had a greater proportion of participants who were widowed. None of the site-by-group interactions were significant. About 90% of participants in both treatment groups were either taking second-generation antipsychotics alone (71%) or in combination with first-generation antipsychotics (19%). Not shown in the table, 3 participants were taking lithium and 9 were taking anticonvulsants, with no differences between groups.

Primary Outcomes for Citalopram and Placebo Augmentation

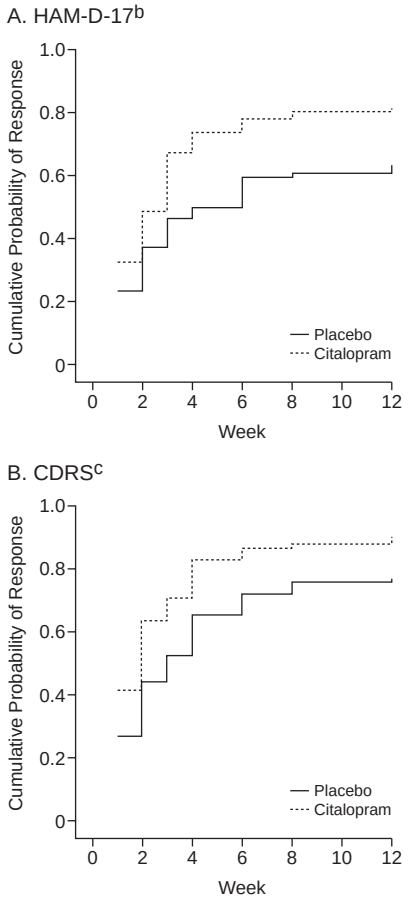
Table 2 summarizes differences between treatment groups on the primary outcome measures, HAM-D-17 and CDRS, and provides differences in endpoint response rates based on the number of participants in each group with ≥ 50% improvement from baseline. None of the site-by-group interactions were significant. At the last observation period, participants treated with citalopram had lower HAM-D-17 (F = 4.410, df = 1,193; p = .037) and CDRS (F = 9.430, df = 1,193; p = .002) total scores, greater percentage improvement on the CDRS (F = 6.091, df = 1,193; p = .014), and higher response rates on the HAM-D-17 (χ^2 = 5.81, df = 1, p = .016) and CDRS (χ^2 = 6.56, df = 1, p = .011) than participants treated with placebo. The number needed to treat (NNT) was 5.6 and

Table 2. Improvement and Response in Depression Measures Among Participants With SSD Receiving Antipsychotic Augmentation With Either Citalopram or Placebo by Treatment

	Citalopram (N = 104)[a]		Placebo (N = 94)[a]				
Measure	Mean	SD	Mean	SD	F[b]	df	p
HAM-D-17							
Baseline	13.590	4.390	13.380	4.080	0.057	1,194	.812
End of treatment	8.365	5.686	9.957	5.895	4.413	1,193	.037
% Change	36.200	42.600	24.500	41.000	3.429	1,194	.066
Responders[c]	43[d]	41.3[e]	22[d]	23.4[e]	5.813[f]	1	.016
CDRS							
Baseline	6.462	3.170	7.021	3.070	1.957	1,194	.163
End of treatment	3.820	3.380	5.650	4.510	9.434	1,193	.002
% Change	36.400	57.500	16.700	58.400	6.091	1,194	.014
Responders[g]	52[d]	50[e]	34[d]	30.9[e]	6.566[h]	1	.011

[a]Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.
[b]Derived from analysis of covariance, adjusting for baseline values at end of treatment, site, and site-by-treatment interactions.
[c]Response defined as ≥ 50% reduction from baseline score on HAM-D-17.
[d]N.
[e]%.
[f]Mantel-Haenszel χ^2; number needed to treat = 5.587.
[g]Response defined as ≥ 50% reduction from baseline score on CDRS.
[h]Mantel-Haenszel χ^2; number needed to treat = 5.236.
Abbreviations: CDRS = Calgary Depression Rating Scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSD = subsyndromal symptoms of depression.

Figure 2. Cumulative Probability of Response[a] for Participants With SSD Receiving Citalopram or Placebo Augmentation Treatment by Time in Treatment (Kaplan-Meier survival estimates)



[a]Response measured by ≥ 50% improvement from baseline.
[b]$\chi^2 = 6.630$, df = 1, p = .010.
[c]$\chi^2 = 6.412$, df = 1, p = .011.
Abbreviations: CDRS = Calgary Depression Rating Scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSD = subsyndromal symptoms of depression.

the Cohen's d effect size was 0.273 with the HAM-D-17; with the CDRS, the NNT was 5.2 and the Cohen's d effect size was 0.452.

Differences between completers and noncompleters were minimal. One hundred forty-nine participants completed the study up to the last blinded visit (77 citalopram; 72 placebo). For HAM-D-17, the means were similar to the LOCF analysis, although in the completer-only analysis, the endpoint means (8.48 vs. 9.10; F = 1.611, df = 1, p = .206) and percentage responders (41% vs. 25%; $\chi^2 = 0.162$, p = .052) were no longer significant. For the CDRS, the endpoint means (3.72 vs. 5.00; F = 6.148, df = 1, p = .014) and percentage responders (54% vs. 35%; $\chi^2 = 0.217$, p = .022) remained significant. Similarly, after eliminating the subsample of 36 participants (16 in placebo, and 20 in citalopram) who had been tapered from antidepressants prior to study entry, results were similar. On the HAM-D-17, endpoint means were 8.13 vs. 9.64; F = 3.397, df = 1, p = .067. On the CDRS, endpoint means were 3.55 vs. 5.68; F = 9.420, df = 1, p = .003.

The internal reliabilities (alpha) of the HAM-D-17 ($\alpha = .386$) and CDRS ($\alpha = .551$) were low, likely reflecting the nature of the sample, excluding individuals with < 4 symptoms of major depression and including those with low HAM-D-17 scores (≥ 8). As expected, the 2 primary outcome measures, HAM-D-17 and CDRS, were highly correlated (r = 0.547. p < .001).

Time to Response

As shown in Figure 2, Kaplan-Meier survival estimates showed that time to response was different between the 2 groups with the HAM-D-17 ($\chi^2 = 6.630$, df = 1, p = .010) and the CDRS ($\chi^2 = 6.412$, df = 1, p = .011). Among participants who responded, on the basis of HAM-D-17 results, the median time to response was 3 weeks (SE = 0.273) for participants receiving citalopram augmentation and 6 weeks (SE = 0.946) for those receiving placebo augmentation. Among participants who responded, on the basis of CDRS results, the median time to response was 2 weeks (SE = 0.215) for participants receiving citalopram augmentation and 3 weeks (SE = 0.492) for those receiving placebo augmentation.

Secondary Outcomes

Table 3 summarizes differences between treatments at baseline and at the last observation in several other dimensions of schizophrenia: suicidal ideation, global psychopathology, positive and negative symptoms, cognitive functioning, functional status and general medical health, quality of life, and symptoms of movement disorders. The assumptions of the ANCOVA models were checked and satisfied. All residuals were unimodal and roughly symmetrical, so, given our sample size and the central limit theorem, the normality assumption is sufficiently met. Levine's test of equality of error variances was performed on each ANCOVA. One of 14 tests was marginally significant (AIMS, p = .034). This is well within the range of what would be expected of homogeneous variances.

None of the site-by-group interactions was significant. The only pretreatment variable that was different between groups was lower mean PANSS total score in the citalopram group. After correcting for site and baseline severity, the citalopram group had more improvement in PANSS negative symptoms, mental functioning (SF-12-mental), and quality of life (QLS). There were no significant treatment-related differences in suicidal ideation,

Table 3. Improvement in Secondary Outcomes Among Participants With SSD Receiving Antipsychotic Augmentation With Either Citalopram or Placebo by Treatment

	Citalopram (N = 98)		Placebo (N = 90)				
Measure	Mean	SD	Mean	SD	F[a]	df	p
Suicidality							
HAM-D, item 3 score							
Baseline	0.490	0.737	0.404	0.738	0.572	1,194	.450
End of treatment	0.231	0.611	0.308	0.640	1.224	1,193	.270
CGI-SS							
Baseline	1.200	0.518	1.220	0.492	0.087	1,178	.768
End of treatment	1.105	0.419	1.191	0.496	0.819	1,131	.367
Psychopathology							
PANSS-negative							
Baseline	15.330	4.830	16.510	5.470	3.870	1,193	.510
End of treatment	14.541	4.670	16.467	5.710	3.927	1,182	.049
PANSS-positive							
Baseline	14.880	5.990	16.450	4.550	2.492	1,194	.116
End of treatment	14.480	6.040	14.844	4.900	2.170	1,183	.142
Cognition							
MMSE							
Baseline	27.200	2.300	26.720	2.810	1.727	1,193	.190
End of treatment	27.680	2.070	27.040	2.880	0.664	1,152	.417
Quality of Life, Functioning, and Health							
SF-12-physical							
Baseline	44.660	10.200	42.090	11.060	2.874	1,190	.092
End of treatment	42.921	10.280	43.643	10.570	0.411	1,149	.552
SF-12-mental							
Baseline	40.560	10.430	41.230	10.690	0.109	1,190	.742
End of treatment	47.946	10.190	43.442	9.970	13.245	1,149	.000
CIRS-G-total							
Baseline	6.430	3.490	6.510	3.290	0.306	1,184	.581
End of treatment	6.897	3.740	6.110	3.650	0.852	1,139	.358
AIMS							
Baseline	1.860	3.088	2.320	3.849	0.436	1,183	.510
End of treatment	1.260	2.100	1.990	3.740	0.806	1,142	.371
SAEPS							
Baseline	9.402	4.966	9.952	5.326	0.021	1,176	.804
End of treatment	10.093	5.200	9.789	4.600	0.216	1,131	.643
BAS							
Baseline	0.294	1.870	0.033	2.241	0.754	1,190	.386
End of treatment	0.494	0.882	0.417	0.818	0.133	1,140	.716
QLS[b]							
Baseline	60.960	22.280	56.410	22.270	1.400	1,167	.238
End of treatment	64.859	24.420	57.472	22.350	4.038	1,135	.046

[a]Derived from analysis of covariance, adjusting for baseline values at end of treatment, site, and site-by-treatment interactions.
[b]Significant drug-by-site interaction: F = 4.214, df = 1,135; p = .042.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, CGI-SS = Clinical Global Impressions-Severity of Suicide scale, CIRS-G = Cumulative Illness Rating Scale for geriatric subjects, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale, SAEPS = Simpson-Angus Extrapyramidal Side Effect Scale, SF-12 = 12-item Short-Form Health Survey, SSD = subsyndromal symptoms of depression.

PANSS total or positive symptoms, cognition (MMSE), physical functioning (SF-12-physical), or symptoms of movement disorders. In general, baseline HAM-D-17 and CDRS total scores were mildly to moderately correlated with the outcome measures that were different between treatment groups. The partial correlations (controlling for site) between HAM-D-17 and PANSS negative symptoms were low and not significant (r = 0.041, p = .567) but reached significance for the CDRS and PANSS negative symptoms (r = 0.155, p = .030). After controlling for site, we found that the SF-12-mental was related to both HAM-D-17 and CDRS (r = –0.389, p < .001; and r = –0.584, p < .001; respectively). The QLS was not associated with the HAM-D-17 but was moderately associated with the CDRS (r = 0.042, p = .558; and r = –0.226, p = .003; respectively).

Side Effects and Tolerability

Although a majority of participants experienced adverse events, these tended to be mild and transient. Nine citalopram and 13 placebo participants experienced serious adverse events, including substance use problems

Table 4. Adverse Events Reported by ≥ 5 Participants

Adverse Event	Citalopram (N = 104), N (%)	Placebo (N = 94), N (%)	χ^{2a}	p
Gastrointestinal				
Diarrhea	19 (18)	18 (19)	0.025	.874
Stomach/abdominal discomfort	23 (22)	12 (13)	2.965	.085
Nausea	18 (17)	11 (12)	1.241	.265
Vomiting	10 (10)	7 (7)	0.296	.587
Flatulence	7 (7)	8 (9)	0.223	.637
Constipation	6 (6)	6 (6)	0.033	.857
Appetite increase	8 (8)	8 (9)	0.045	.833
Appetite decrease	4 (4)	7 (7)	1.220	.269
Increased thirst	6 (6)	3 (3)	0.756	.385
Behavioral				
Difficulty falling asleep	24 (23)	12 (13)	3.529	.060
Anxiety	8 (8)	11 (12)	0.915	.339
Irritability	8 (8)	6 (6)	0.129	.720
Sexual				
Decreased libido	11 (11)	5 (5)	1.837	.175
Ejaculatory disorder	3 (3)	2 (2)	0.115	.735
Erectile disorder	4 (4)	1 (1)	1.553	.213
General				
Tiredness/fatigue	16 (15)	24 (26)	3.154	.076
Headache	12 (12)	12 (13)	0.700	.792
Flu	8 (8)	5 (5)	0.453	.501
Weight gain	5 (5)	5 (5)	0.027	.870
Rash	3 (3)	3 (3)	0.016	.900
Musculoskeletal				
Pain (muscle/bone/joint)	22 (21)	24 (26)	0.531	.466
Neurological				
Faintness/dizziness	14 (13)	8 (9)	1.225	.268
Tremor	4 (4)	5 (5)	0.247	.619
Other				
Upper respiratory infection	16 (15)	18 (19)	0.492	.485
Dry mouth	14 (13)	16 (17)	0.487	.485
Chest pain	7 (7)	7 (7)	0.039	.844
Nasal congestion	8 (8)	5 (5)	0.453	.501
Injury, accidental	2 (2)	6 (6)	2.533	.112
Urination, increased frequency	5 (5)	4 (4)	0.035	.852
Blurred vision	1 (1)	6 (6)	4.255	.039
Cramps	3 (3)	4 (4)	0.272	.602
Tinnitus	4 (4)	2 (2)	0.496	.481
Heartbeat (rapid)	2 (2)	4 (4)	0.914	.339
Shortness of breath	3 (3)	3 (3)	0.016	.900
Urination, difficulty	3 (3)	1 (1)	0.827	.363
Pharyngitis	3 (3)	2 (2)	0.115	.735

[a]Mantel-Haenszel χ^2; df = 1.

(N = 7), hospitalization for medical reasons (N = 7) or worsening of symptoms (N = 6), and suicidal ideation (N = 2). Four participants in each treatment group had to leave the study because of adverse events. Table 4 lists all adverse events experienced by ≥ 5 participants. The only significant difference was more blurred vision ($\chi^2 = 4.255$, df = 1, p = .039) with placebo than with citalopram.

DISCUSSION

In this sample of middle-aged and older patients with schizophrenia and schizoaffective disorder and co-occurring SSD, augmentation with the SSRI citalopram was more effective than augmentation with placebo in improving depressive and negative symptoms, mental functioning, and quality of life. There was no significant difference between augmentation with citalopram and placebo on suicidal ideation, positive symptoms, cognition, general medical health, physical functioning, and symptoms of movement disorders. Serious adverse events were seen in 9 patients taking citalopram and 13 taking placebo. This is by far the largest study we were able to locate examining the effectiveness and safety of the common but off-label practice of prescribing SSRIs to patients with schizophrenia who do not meet criteria for a co-occurring MDD.

It is important to place this study's findings in the context of other clinical investigations that document the prevalence of depressive spectrum disturbance in schizophrenia, the misery it causes, and its response to treatment. Previous studies have documented the efficacy of tricyclic antidepressants as add-on acute treatment for postpsychotic depression,[35] for "affective distress,"[36] and for maintenance treatment,[37] in patients with schizophrenia. More recently, atypical antipsychotics have been shown to ameliorate depressive symptoms in some patients with schizophrenia.[38] While several double-blind placebo-controlled trials of SSRI augmentation of antipsychotics have been published,[10,39–47] none of these studies were designed specifically to treat SSD or depressive symptoms, most were limited by small sample sizes, and results on depressive symptoms, when provided, were mixed. Most of these studies involved SSRI augmentation of typical antipsychotics. In the 1 small study that reported a double-blind controlled trial of SSRI augmentation of atypical antipsychotics,[41] there was no significant improvement in depressive, positive, or negative symptoms with fluoxetine compared to placebo augmentation of clozapine. Thus, the present study provides the strongest endorsement available for SSRI augmentation of antipsychotics, particularly SSRI augmentation of atypical antipsychotics.

Although treatment of negative symptoms was not the primary goal of this study, it was not surprising that negative symptoms were significantly ameliorated with citalopram.[48] While there clearly is some overlap between negative symptoms and depressive symptoms (e.g., anhedonia, amotivation, anergia), other investigators have shown that these 2 symptom constructs are not identical,[14] and we,[4] and others[22] have previously reported that depressive symptoms actually are more closely associated with positive than negative symptoms. Likewise, as SSD has been linked with impaired functioning and quality of life, it was noteworthy that antidepressant treatment was associated with improvements in these important dimensions. We are not aware of other large-scale studies that have previously documented antidepressant effects

on functioning or quality of life in patients with schizophrenia or schizoaffective disorder.

There are a number of safety issues that are important to address when considering the risk-benefit ratio of adding antidepressants to antipsychotics in middle-aged and older patients with schizophrenia or schizoaffective disorder. Do antidepressants, as in some patients with mood and anxiety disorders,[49] increase suicidal ideation? Do they have a negative impact on psychotic symptoms, on general medical health, or on symptoms of movement disorders? In this study, citalopram augmentation was no more likely to increase suicidal ideation, psychotic symptoms, health problems, or movement disorders than placebo augmentation, and the adverse event profile was similar to that of other patient groups taking citalopram.

The results of this article must be interpreted in the context of several of the study's limitations. First, the SSD group was heterogeneous, comprising individuals with and without past histories of MDD, possibly others with residual or prodromal symptoms of depression, and, also, some participants with prominent negative symptoms or movement abnormalities. However, the etiology of depressive symptoms is often difficult to ascertain in clinical situations. Subsequent analyses will examine whether particular subgroups of individuals with SSD are particularly responsive to treatment. Second, the study did not include participants younger than age 40 years, potentially restricting our ability to generalize findings to all age groups. It was our intention to concentrate on middle-aged and older patients with schizophrenia and schizoaffective disorder as this group has high rates of SSD and has been largely ignored in much of the treatment research. Third, there was variation in the adequacy and type of treatment of the underlying disorder. However, we always attempted to "optimize" antipsychotic treatment by observing the patient before randomization and often recommending antipsychotic dose adjustment to the treating physician if the study physician felt it was warranted. When changes were made, we waited until doses were stable for at least 4 weeks before completing baseline assessments and randomization. Fourth, it is possible that including some participants who had been taking antidepressants 4 or more weeks prior to entering the study may have biased the sample against finding a drug versus placebo difference, as these participants had already not had a satisfactory outcome with an antidepressant trial. Despite that negative bias, outcome results supported the effectiveness of citalopram augmentation, perhaps lending even more credibility to the findings. Fifth, caution should always be applied when adding potent psychotropics to patients already taking antipsychotic medications. It is possible that certain antidepressants could have potentially dangerous drug-drug interactions with specific antipsychotics, such as fluoxetine with clozapine.[50] In this study, a majority of participants tolerated citalopram added to the antipsychotic agent they were already taking. We do not know, however, the longer-term risk-benefit ratio of citalopram in these patients. Finally, there is a possibility of type I error due to the number of statistical tests done.

In conclusion, SSD in middle-aged and older patients with schizophrenia is an important clinical dimension that may be underappreciated, underrecognized, and associated with substantial morbidity and distress. This study found that SSD in these patients responded to treatment with the SSRI citalopram and improved functioning and quality of life. When confronted with a patient with schizophrenia who has mild to moderate symptoms of depression, even when those symptoms do not add up to a full diagnosis of MDD, clinicians may consider augmenting antipsychotics with antidepressants. This study does not inform clinicians regarding the risks and benefits of other SSRIs, other classes of antidepressant medications, or nonpharmacologic antidepressant treatment strategies. Further work is needed to examine the effect of antidepressants and relative risks and benefits in specific subsets of patients.

Drug names: citalopram (Celexa and others), clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others).

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