Augmentation With Citalopram for Suicidal Ideation in Middle-Aged and Older Outpatients With Schizophrenia and Schizoaffective Disorder Who Have Subthreshold Depressive Symptoms: A Randomized Controlled Trial

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Objective: To examine the effects of citalopram augmentation of antipsychotics on suicidal ideation in middle-aged and older people with schizophrenia and subthreshold depressive symptoms.

Method: In this placebo-controlled trial conducted from September 1, 2001, to August 31, 2007, 198 outpatients ≥ 40 years old with *DSM-IV*–diagnosed schizophrenia or schizoaffective disorder and subthreshold depressive symptoms were randomly assigned to flexible-dose citalopram (n = 104) or placebo (n = 94) augmentation of their antipsychotic for 12 weeks. Depression was measured with the Hamilton Depression Rating Scale (HDRS) and Calgary Depression Rating Scale (CDRS). Primary suicidal ideation measures were the Clinical Global Impressions–Severity of Suicide scale (CGI-SS) and the InterSePT Scale for Suicidal Thinking (ISST); secondary outcomes were the Scale for Suicidal Ideation (SSI), Beck Hopelessness Scale (BHS), HDRS item 3, and CDRS item 8.

Results: Compared to placebo, at the final visit, citalopram was associated with lower BHS scores (4.21 vs 4.98; $P < .05$) and lower likelihood of having suicidal ideation on the ISST (17.7% vs 38.7%; $P < .005$) and HDRS item 3 (14.4% vs 22.6%; $P < .05$). Among the 114 participants with no baseline suicidal ideation, there were no significant differences between citalopram and placebo regarding "emergent" ideation on either primary outcome. Among the 55 participants with baseline suicidal ideation, fewer treated with citalopram had endpoint ideation on the ISST (28.6% vs 66.7%; $P < .05$). Significantly more depression responders than nonresponders went from having baseline suicidal ideation to no suicidal ideation on both the ISST (75.0% vs 31.4%; $P < .05$) and CGI-SS (84.6% vs 31.3%; $P < .05$).

Conclusions: Treatment-emergent suicidal ideation was no more common with citalopram than placebo. In participants with baseline suicidal ideation, citalopram reduced suicidal ideation, especially in those whose depressive symptoms responded to treatment.

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On average, patients with schizophrenia live about 15 fewer years than the general population,[1] and suicide stands out as the primary cause for premature death.[2,3] More than half of people with schizophrenia report suicide attempts or serious ideation at some point in their lives.[4] Overall, 4.9%–13% of patients with schizophrenia or schizoaffective disorder die by suicide, and rates of completed suicide among patients with schizophrenia are about 8–13 times higher than that of the general population in the United States.[5] Although many studies suggest that the risk is greatest in younger persons, especially in the first several years after the diagnosis is made,[6] suicide can occur at any time. An assessment of suicides among patients with schizophrenia in Finland indicated that one-third of suicide victims were over age 45 years, and the majority of the suicides (64%) occurred while patients experienced depressive symptoms.[7] More recently, Montross et al[8] also reported suicidal ideation and behavior to be prevalent in middle-aged and older patients with schizophrenia and depressive symptoms.

Depressive symptoms are so prevalent in patients with schizophrenia that some have argued that depression should be considered a core component of schizophrenia, similar to positive, negative, and disorganized symptom clusters.[9,10] A prospective study assessing depression during the longitudinal course of schizophrenia found that only 24% of subjects remained free of depressive symptoms. A significant proportion (40%) had 2 to 4 symptoms of depression, while almost as many (36%) met criteria for major depressive episodes (MDEs).[11] We have previously reported[12] that more than two-thirds of patients with schizophrenia who do not have MDEs have at least mild depressive symptoms, most often depressed mood, feelings of guilt, and/or feelings of hopelessness. Having ≥ 2 of such symptoms was associated with fewer years of formal education; greater overall psychopathology and more positive and negative symptoms; higher severity of general medical conditions and psychiatric illness; impaired physical and mental functioning; more severe akathisia; more anxiety and suicidality; and possibly greater likelihood of treatment with atypical antipsychotics and/or combinations of typical and atypical antipsychotics.[13] Thus, it is no surprise that many patients with schizophrenia receive antidepressant medications, even in the absence of full MDEs.[14]

While there is some evidence that antidepressant augmentation of antipsychotics helps relieve depressive and

negative symptoms in patients with schizophrenia and schizoaffective disorders,[15,16] little is yet known about the effects of such treatment on suicidality. The large and growing concern about the potential for antidepressants to "induce" or worsen suicidal thoughts[17] indicates this as an important gap in our clinical knowledge base.

The studies that led to the recently expanded black box warning regarding antidepressants' risk of suicidality found an increase in suicidal thoughts and behaviors in children and young adults treated with antidepressants relative to placebo, no increase in suicidal thoughts in adults 25–60 years old, and a decrease in suicidal thoughts in older adults over age 65 years.[18–20] However, these studies were limited by the exclusion of many individuals who might be at particular risk for suicidal thoughts and behaviors, such as those with schizophrenia or schizoaffective disorder, or individuals with past suicide attempts and/or present suicidal ideation.

We recently completed a randomized, placebo-controlled clinical trial examining whether selective serotonin reuptake inhibitor (SSRI) augmentation in middle-aged and older outpatients with schizophrenia and schizoaffective disorder helps improve depressive symptoms in patients with schizophrenia.[16] The initial publication of that study reported improvement in depressive and negative symptoms with citalopram but no overall changes in suicidal ideation based on suicide items of the Hamilton Depression Rating Scale (HDRS) or Calgary Depression Rating Scale (CDRS).[16] Using much broader and more comprehensive suicide rating scales, this current secondary analysis of that trial allows us to answer the following clinically important questions: (1) in patients with no suicidal ideation before augmentation, is treatment-emergent suicidal ideation more prevalent with citalopram than with placebo? (2) in patients with suicidal ideation at baseline, does citalopram augmentation increase or decrease suicidal ideation relative to placebo augmentation in this high-risk population? and (3) what is the relationship between depression response and changes in suicidal ideation during citalopram augmentation? Our working hypotheses were (1) treatment-emergent suicidal ideation will be less likely to occur with citalopram than placebo augmentation, (2) citalopram augmentation will decrease suicidal ideation to a greater extent than placebo augmentation, and (3) participants whose depression responds favorably to acute treatment will be more likely than nonresponders to experience decreases in suicidal ideation.

METHOD

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

Study Population

At both the San Diego and Cincinnati sites, participants were recruited from board-and-care facilities, Veterans Affairs health care centers, and general outpatient settings. Additionally, at the San Diego site, participants were recruited from the National Institute of Mental Health–funded Advanced Center for Innovation in Services and Intervention Research focusing on middle-aged and older persons with schizophrenia. Study approval was obtained from each site's institutional review board, and 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 (1) met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[21] criteria for schizophrenia or schizoaffective disorder; (2) met study criteria for subthreshold depression defined by having 2 to 4 of the 9 *DSM-IV* symptoms of MDE, present most of the time for at least 2 weeks; (3) had a 17-item Hamilton Depression Rating Scale (HDRS-17)[22] score ≥ 8; and (4) were taking a stable dose of an antipsychotic medication. Potential participants were excluded if they (1) met clinical diagnostic criteria for a dementing disorder (such as vascular dementia); (2) had a recent (within 2 months) diagnosis of major depression or mania; (3) had active substance abuse or dependence that, in the research physician's opinion, would impact on diagnostic decisions, safety, or anticipated adherence; (4) were judged (clinically) to be of sufficient imminent suicide risk that either outpatient care or the possibility of not being treated with antidepressant augmentation were considered potentially unsafe; (5) were taking citalopram or had taken it for the present episode of subthreshold depression; or (6) had previously experienced allergic reactions or significant adverse events while taking citalopram. Also excluded were individuals in whom SSRIs would be inadvisable (based on the treating or study physicians' judgment). Female participants of childbearing potential were required to use a medically acceptable form of contraception. At the San Diego site, persons on conservatorship were not enrolled because of local county mental health restrictions. 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

Potential participants who otherwise met study criteria but were taking antidepressants were given the opportunity to have their antidepressants tapered and discontinued. If these participants continued to meet study entrance criteria for 4 or more weeks after antidepressant discontinuation, they were permitted to enter the study. Posttapering assessments were used as baseline data. On a case-by-case basis, study participants were allowed to continue with low-dose antidepressant medications (eg, trazodone ≤ 100 mg qhs or

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tricyclic antidepressants, such as amitriptyline ≤ 75 mg or its equivalent) that had been prescribed by their treating physicians for insomnia or chronic pain.

Patients were randomly assigned to treatment with citalopram (20 mg/d) or placebo augmentation of their current antipsychotic medication. After the first week, the study dose could be reduced to 10 mg/d or increased, based on clinical response and/or side effects (minimum dose 10 mg/d, maximum dose 40 mg/d), at the blinded study physician's discretion. Subjects were instructed to take their study medication at the same time each day. The study physicians 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, relapse of substance abuse, or worsening suicidality were considered serious adverse events, triggering reports to the treating physician and the instructional review boards. When participants were dropped from the study, the treating physician was invited to request information about the study medication from the research pharmacist.

Assessments

Raters were trained on the protocol and administration of assessments prior to the enrollment of subjects. With regard to interrater reliability, an intraclass correlation coefficient of ≥ 0.90 was established. Screening evaluations included the Mini-Structured Clinical Interview for *DSM-IV* Axis I Disorders[23] and HDRS-17.[24] After participants signed informed consent statements, we obtained psychiatric and medical histories, vital signs, and laboratory tests and conducted physical examinations. Additional baseline ratings included the CDRS, a 9-item scale designed to measure depression in psychotic patients that is scored from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) on each item.[25]

To conduct a comprehensive assessment of suicidality, we administered 6 suicide measures, including both self-report and clinician-rated instruments. The first of these were the clinician-rated item 3 of the HDRS-17 (rated 0 = absent; 1 = life not worth living; 2 = death wishes; 3 = ideas or gestures; 4 = attempts) and item 8 of the CDRS (rated 0 = absent; 1 = mild; 2 = moderate; 3 = severe). The other scales included:

Beck Hopelessness Scale. The Beck Hopelessness Scale (BHS)[26] is a 20-item self-report inventory originally designed to predict who would and who would not complete suicide. It measures 3 major aspects of hopelessness: feelings about the future, loss of motivation, and expectations. Each item is scored 0 = false or 1 = true for a total score ranging from 0 to 20, with higher scores indicating greater likelihood of suicide.

Beck Scale of Suicidal Ideation. The Beck Scale of Suicidal Ideation (BSSI)[27] is a widely used self-report instrument that measures the intensity and pervasiveness of suicidal ideation or intent during the previous week. It has been shown to be suitable for assessing suicidal risk in persons with schizophrenia.[28,29] Each of the 21 items is based on a 3-point scale (0, 1, 2), with high scores indicating stronger suicidal ideation. The BSSI includes 2 screening items that measure any active or passive desire to commit suicide. If patients endorse having such ideation, they are required to complete the full 21-item measure, thereby assessing the frequency and intensity of such thoughts as well as any preparation for suicide.

Clinical Global Impressions-Severity of Suicide scale. The Clinical Global Impressions-Severity of Suicide scale (CGI-SS)[30] is a global assessment of suicidality that was developed specifically for the International Suicide Prevention Trial (InterSePT) study. Raters choose the most severe level of suicidality experienced by the patient over the previous 7 days on a 5-point scale, ranging from 1 (not at all suicidal) to 5 (attempted suicide).

InterSePT Scale for Suicidal Thinking. The InterSePT Scale for Suicidal Thinking (ISST)[31] is a 12-item scale that was adapted for the InterSePT study to assess suicidality in patients with schizophrenia and schizoaffective disorder. Information on this scale is obtained during a semistructured interview examining suicidal behaviors in the previous 7 days. Each item is scored on a scale from 0 to 2. Total scores are calculated by summing the 12 items. As a categorical measure, a total scale score of 0 = no suicidality and ≥ 1 = suicidal.[30]

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, HDRS, CDRS, Clinical Global Impressions-Improvement scale, CGI-SS, BHS, BSSI, and ISST. 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 HDRS, CDRS, and CGI-SS.

The primary measures of suicidal ideation were the ISST and the CGI-SS because they were developed specifically to assess suicidal ideation in patients with schizophrenia[30] and have been found sensitive to pharmacologic effects.[31] Secondary measures included the BHS, BSSI, CDRS item 8, and HDRS-17 item 3. All of the scales except the BHS showed a large proportion of subjects with no suicidality, leading to highly skewed, zero-inflated distributions. For this reason, we chose to dichotomize the scales.

Statistical Analysis

For summary statistics, means and standard deviations were computed for continuous variables, and counts and percentages were computed for discrete variables. Two-way analyses of variance, adjusting for site, and baseline clinical and demographic characteristics were used to compare continuous baseline clinical and demographic characteristics mean scores on suicide outcome measures. Cochran-Mantel-Haenszel tests were used to compare discrete characteristics across treatments, adjusting for site. The data were analyzed using a modified intent-to-treat basis in which participants who underwent randomized assignment, took at least 1 dose of the study medication, and completed at least 1 postbaseline

visit were included. All statistical tests were 2-tailed, and the level of statistical significance was set at $P \leq .05$. For continuous outcomes, analysis of covariance (ANCOVA), adjusting for site and baseline severity, was used to compare improvement in suicidal ideation between treatment groups (antipsychotic plus citalopram vs antipsychotic plus placebo). The ANCOVA model was formulated with suicide ideation outcome at the study end point as the dependent variable. Treatment group, site, and baseline severity were included as independent variables. For binary outcomes, logistic regression was used. Similar to the continuous case, the logistic models were formulated with treatment group, site, and baseline severity as independent variables and outcome at endpoint as the dependant variable. We also compared the rates of suicidality in the drug groups at endpoint among those who had no suicidality at baseline, as well as the rates among those who did have suicidality at baseline. These were analyzed using Mantel-Haenszel tests stratifying by site.

RESULTS

Overall and Group Baseline Characteristics

As described elsewhere,[16] 198 men and women between the ages of 41 and 75 years comprised the modified intent-to-treat sample. The mean age was 53 years, and the mean number of years since first experiencing psychotic symptoms of schizophrenia was 25 years. Twenty-two percent were female, 54% white, 33% black, and 5% Latino. Forty percent had never married, while 14% were married and 46% were divorced, separated, or widowed. Forty-one percent were diagnosed with schizoaffective disorder. Ten percent were taking first-generation antipsychotics, 71% second-generation antipsychotics, and 19% both. No significant differences were observed between the two augmentation treatment groups on any of these baseline demographic or clinical features except that the citalopram group had a greater proportion of participants who were widowed. Site-by-group interactions were investigated, and none were statistically significant.

Baseline and Past Suicidality

Almost half of the participants (47%) had made previous suicide attempts, and between 21% and 37%, depending on the scale used, expressed at least mild suicidal ideation at baseline (Table 1).

Table 1. Baseline Suicidality (N = 198)

Suicide Measure	%	Total N
Past attempts	47	189
Current suicidal ideation		
BSSI (item 4 or 5 > 0)	21	190
CDRS item 8 ≥ 1	22	198
HDRS item 3 ≥ 1	32	198
CGI-SS ≥ 2	21	182
ISST ≥ 1	37	191

Abbreviations: BSSI = Beck Scale of Suicidal Ideation, CDRS = Calgary Depression Rating Scale, CGI-SS = Clinical Global Impressions–Severity of Suicide scale, HDRS = Hamilton Depression Rating Scale, ISST = InterSePT Scale for Suicidal Thinking.

Suicidal Ideation Outcomes During Treatment With Citalopram and Placebo Augmentation

Table 2 summarizes differences between treatment groups on the suicidal ideation outcome measures. Because mean scores on the CDRS item 8, CGI-SS, HDRS item 3, and ISST are too skewed to meet normality assumptions for ANCOVAs, only dichotomous measures are provided for these scales. On the continuous rating scales, the BHS revealed less severe hopelessness at the end of treatment with citalopram than placebo (4.21 vs 6.03, $F = 4.77$, $P = .031$). On the categorical ratings, the citalopram group had fewer participants with suicidal ideation at the end of treatment compared to the placebo group on both the ISST (17.7% vs 38.7%, $\chi^2 = 8.489$, $P = .004$) and the HDRS item 3 (14.4 vs 22.6, $\chi^2 = 4.20$, $P = .040$).

Emergent Suicidal Ideation Outcomes for Participants Without Suicidal Ideation at Baseline

Most of the participants who entered the study without suicidal ideation continued without suicidal ideation throughout the study (85 of 99 based on an ISST = 0 and 108 of 119 based on CGI-SS = 1). Figure 1 illustrates the rates of "emergent" suicidal ideation for participants treated with citalopram and placebo on the 2 primary suicide outcome measures, the ISST and the CGI-SS. Although numerically lower rates of "emergent" suicidal ideation were found for citalopram augmentation than for placebo augmentation on both measures, differences did not reach statistically significant levels (9.6% vs 19.1% on the ISST and 6.5% vs 12.3% on the CGI-SS).

Improvement in Suicidal Ideation for Participants With Suicidal Ideation at Baseline

Two-thirds of the 55 participants (66.7%) who entered the study with suicidal ideation on the ISST (baseline ISST ≥ 1) and were treated with citalopram ended treatment without suicidal ideation (endpoint ISST = 0) compared to 28.6% of those given placebo augmentation (Mantel-Haenszel $\chi^2 = 6.42$, $P = .011$). The CGI-SS also showed a large effect in the same direction for the 29 participants who started with suicidal ideation, but the trend was not statistically significant, possibly due to low power (78.6% for citalopram vs 40% for placebo, Mantel-Haenszel $\chi^2 = 2.75$, $P = .097$; observed power = 29%; Figure 2).

Relationship Between Depression Response and Suicidal Ideation at the End of Treatment

As Figure 3 shows, the depression responders (based on ≥ 50% improvement on CDRS) were much less likely to endorse suicidal ideation at the last treatment visit (based on ISST ≥ 1 or CGI-SS ≥ 2) than nonresponders. Of those who started with baseline suicidal ideation on the ISST (n = 55), 75% of responders compared to 31.4% of nonresponders no longer had suicidal ideation at the final visit (Mantel-Haenszel $\chi^2 = 5.686$, $P = .017$). Similarly, of the 29 participants

Table 2. Change in Suicidal Ideation Ratings Among Participants Receiving Antipsychotic Augmentation With Either Citalopram or Placebo by Treatment

Measure	Treatment: Citalopram	Treatment: Placebo	F[a]	*df*	P[b]
Continuous ratings—mean (SD)					
Outcomes (n Citalopram, n Placebo)					
BHS (66, 63)					
Baseline	5.88 (5.32)	6.48 (4.91)			
End of treatment	4.21 (4.27)	6.03 (4.98)	4.77	1,125	**.031**
BSSI sum 1–5 (80, 74)					
Baseline	0.84 (1.44)	1.09 (1.74)			
End of treatment	0.50 (1.53)	1.00 (1.74)	2.61	1,150	.108
			χ^2[d]	*df*	P[b]
Categorical ratings—Percentage with suicidal ideation (mild or greater)[c]					
Primary outcomes (n Citalopram, n Placebo)					
ISST total score ≥ 1 (79, 75)					
Baseline	34.2	37.3			
End of treatment	17.7	38.7	8.489	1	**.004**
CGI-SS score ≥ 2 (76, 72)					
Baseline	18.4	20.8			
End of treatment	10.5	22.2	3.634	1	.057
Other outcomes					
BSSI item 4 or 5 > 0 (80, 74)					
Baseline	17.5	27.0			
End of treatment	10.0	17.6	1.00	1	.317
CDRS item 8 ≥ 1 (104, 93)					
Baseline	22.1	22.6			
End of treatment	10.6	18.3	2.62	1	.105
HDRS item 3 ≥ 1 (104, 93)					
Baseline	36.5	26.9			
End of treatment	14.4	22.6	4.20	1	**.040**

[a]Derived from analysis of covariance adjusting for baseline value and site.
[b]Bolded *P* values denote significance.
[c]Sums do not always equal N because of missing data; percentages are based on number of subjects for whom both baseline and endpoint data were available.
[d]Logistic regression adjusting for baseline value and site.
Abbreviations: BHS = Beck Hopelessness Scale, BSSI = Beck Scale of Suicidal Ideation, CDRS = Calgary Depression Rating Scale, CGI-SS = Clinical Global Impressions-Severity of Suicide scale, HDRS = Hamilton Depression Rating Scale, ISST = InterSePT Scale for Suicidal Thinking.

with baseline suicidal ideation on the CGI-SS, 84.6% of the responders compared to 31.3% of nonresponders became free of suicidal ideation by the end of treatment (Mantel-Haenszel $\chi^2 = 4.218$, $P = .040$).

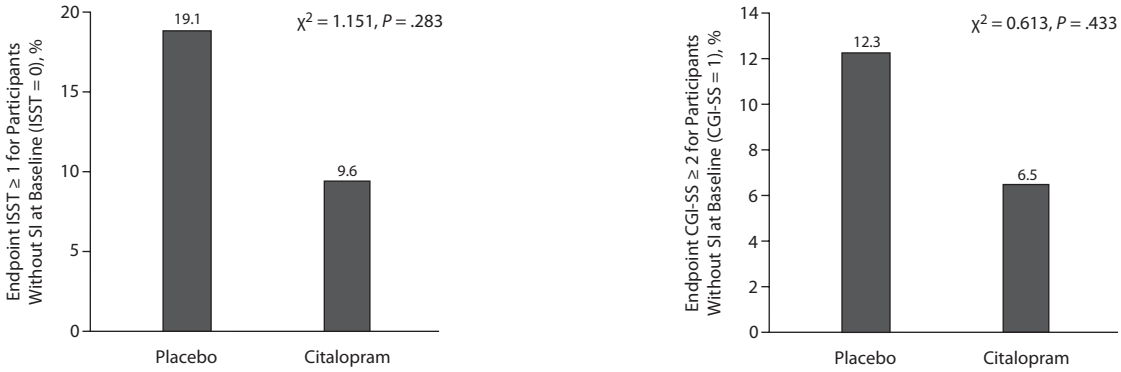
DISCUSSION

In this sample of middle-aged and older patients with schizophrenia and schizoaffective disorder and co-occurring subsyndromal depressive symptoms, augmentation with the SSRI citalopram, aimed at relieving depressive symptoms, appeared to also reduce suicidal ideation. All 3 study hypotheses were at least partially confirmed: (1) treatment-emergent suicidal ideation was no more likely to occur with citalopram than placebo augmentation in participants without suicidal ideation at baseline; (2) on some measures of suicidal ideation (BHS mean scores and percentage participants with no suicidal ideation on the ISST and HDRS-17 item 3), citalopram augmentation improved suicidal ideation relative to placebo augmentation; and (3) responders were less likely than nonresponders to experience suicidal ideation by the end of treatment.

At the onset of the study, true clinical equipoise was a reasonable assumption. That is, it was not clear whether we would find that treatment with an SSRI would decrease suicidal ideation (our hypothesis), have minimal impact on ideation, or actually increase suicidal thoughts relative to placebo. Although the literature on treatment of depression suggested that SSRIs might play a protective role against suicidal ideation in older patients (that is, those over 65),[19] most of the patients in this study were middle-aged, all were diagnosed with schizophrenia or schizoaffective disorder, and many had additional risk factors such as past attempts and suicidal ideation at baseline. While our previous publication from this study[16] showed that citalopram was an effective antidepressant in this population, it did not answer the question of whether such treatment reduced suicidal ideation or, in contrast, induced or worsened suicidal ideation. This is the first large, controlled study of which we are aware that shows that SSRIs might also play a role in suicide prevention, by reducing suicidal ideation, in patients with schizophrenia and schizoaffective disorder.

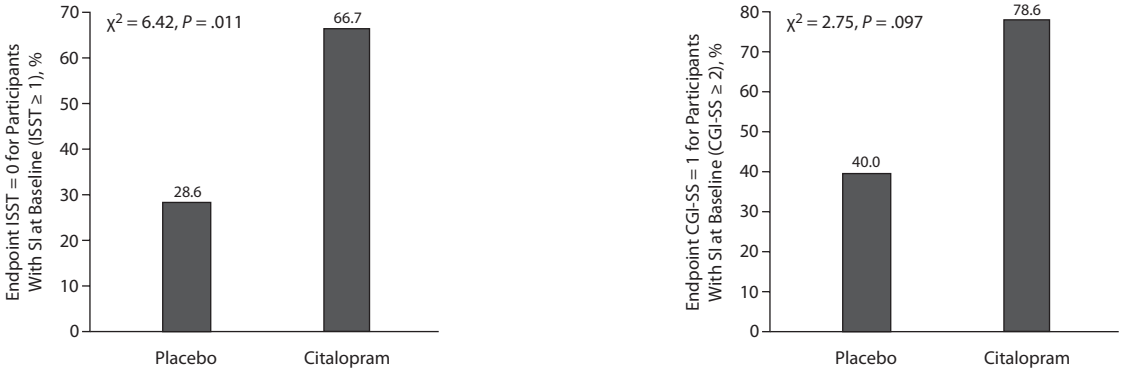
Historically, the introduction of the first-generation antipsychotics had little net effect on overall suicide rates.[32,33] Similarly, most first- or second-generation antipsychotics and psychosocial treatments have not demonstrated an appreciable effect on suicidal ideation.[34–36] Also, there is no evidence to support that first-generation antipsychotics

Figure 1. Emergent Suicidal Ideation for Participants Without Suicidal Ideation at Baseline



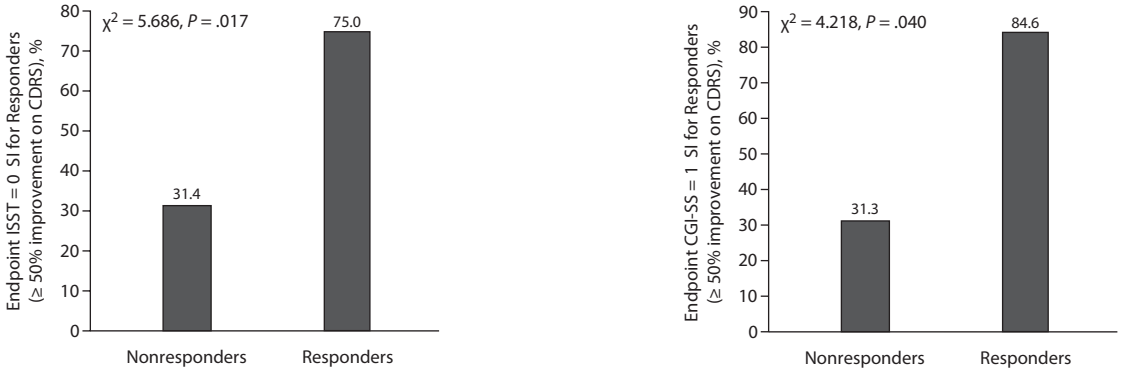
Abbreviations: CGI-SS = Clinical Global Impressions-Severity of Suicide scale, ISST = InterSePT Scale for Suicidal Thinking.

Figure 2. Improvement in Suicidal Ideation for Participants With Suicidal Ideation at Baseline



Abbreviations: CGI-SS = Clinical Global Impressions-Severity of Suicide scale, ISST = InterSePT Scale for Suicidal Thinking.

Figure 3. Relationship Between Improvement in Suicidal Ideation and CDRS Antidepressant Response



Abbreviations: CDRS = Calgary Depression Rating Scale, CGI-SS = Clinical Global Impressions-Severity of Suicide scale, ISST = InterSePT Scale for Suicidal Thinking.

decrease suicidality in patients with schizophrenia. In fact, many suspect that first-generation antipsychotics may actually increase the risk of suicidality, particularly early in the course of treatment, perhaps due to anxiety or akathisia.[37,38] Although the second- and third-generation antipsychotics may have a better profile than the older medications in this regard, akathisia remains a concern when prescribing the newer antipsychotics as well.[39] The only medication that has been found to decrease suicidal ideation or behaviors in patients with schizophrenia is clozapine.[31,40]

Similarly, the role of antidepressants in suicide prevention is unclear, at best.[41,42] As with antipsychotics, akathisia has been described in patients taking SSRIs,[43] and the intense dysphoria associated with this effect has been formulated as one of the key reasons SSRIs, like antipsychotics, may cause or increase suicidal thoughts, impulses, and behaviors.[39] To

that point, some studies have found SSRIs to induce suicidal ideation in patients without ideation before treatment[44] or to worsen suicide risk in those with preexisting ideation.[45] Contrary to those reports, we found that newly "emergent" suicide ideation was no more likely to occur with citalopram than with placebo, suggesting relative safety with SSRI treatment in this population. Furthermore, the decreased suicidal ideation seen more frequently with citalopram than placebo on some suicidality measures suggests the possibility of a preventive effect.

In patients with major depressive disorder who do not have schizophrenia, response or remission to antidepressant treatment is strongly associated with suicidal ideation reduction.[46] This report extends that finding to patients with schizophrenia and depressive symptoms, even without full-blown major depressive episodes. Thus, clinicians may be advised to treat depressive symptoms in patients with schizophrenia aggressively enough to promote a meaningful improvement in depressive symptom severity.

The results of this report must be interpreted in the context of several of the study's limitations. First, we were not able to compare actual suicides or attempts (there were none in this study). However, suicidal ideation is a well-documented predictor of suicide risk,[1] and it is likely that the treatments that decrease ideation may also decrease the risk for attempts and completions. In addition, this study used several self and observer ratings of ideation that are among the most valid and reliable for this population.[30,47] Second, the study tested only 1 SSRI, citalopram. We do not know if the findings are generalizable to other SSRIs, non-SSRI antidepressants, or other pharmacologic and nonpharmacologic treatments. Third, the patient population was heterogeneous, comprising individuals with and without past histories of major depression. The study was not adequately powered to test whether or not subgroups based on past history respond differently. Fourth, the study did not include participants under 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 been largely ignored in much of the treatment research. Fifth, since both sites relied heavily on Veterans Affairs populations for subject recruitment, the sample was predominantly male. Sixth, since this was an outpatient study and used a placebo augmentation control, we were not able to include participants judged to be in imminent suicide risk who required immediate inpatient care or for whom the study clinician felt antidepressant augmentation was clearly indicated. Thus, this study cannot answer the important question of whether antidepressant medication is effective in reducing suicidal ideation in patients judged to be imminently suicidal. Finally, 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 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.

It is important to note that one of the major limitations of the studies and meta-analyses reviewed by the US Food and Drug Administration (FDA) that informed the black box warnings was that the studies were placebo-controlled; thus, the studies enrolled predominantly moderately depressed outpatients with minimal suicide risk. Therefore, it was impossible to estimate any potential benefits of a reduction in baseline suicidal ideation.[48] Because this study included participants with active suicidal ideation, we were able to demonstrate an overall reduction in suicidal ideation for most patients, especially those treated with citalopram. Further, the studies enlisted by the FDA did not include patients with schizophrenia, a group who might be at particularly high risk for "emergent" or worsening suicidal ideation. By including participants with baseline suicide ideation and with schizophrenia, the study adds an important new piece to the "SSRI and suicidality" puzzle.

In conclusion, suicidal thoughts and behaviors are important clinical concerns in middle-aged and older patients with schizophrenia and schizoaffective disorder and are present throughout the course of the illness, including before, during, and after treatment. This study found that, compared to placebo augmentation, augmentation with the SSRI citalopram was associated with greater improvement in suicidal ideation overall and was no more likely than placebo to induce treatment-emergent suicidal ideation in those without ideation at the initiation of treatment. In addition, augmentation with citalopram resulted in improvement in suicidal ideation among those who started treatment with suicidal ideation. Perhaps most importantly, there was a strong relationship between response to treatment and reduction in suicidal ideation.

Our findings reinforce the complexity and frequency of suicidal ideation and behaviors in patients with schizophrenia and schizoaffective disorder. They also underscore the importance of maintaining careful surveillance and treating depressive symptoms as vigorously as necessary to attain meaningful response. Further work is needed investigating other treatments and focusing on specific subsets of patients to broaden our understanding of how to reduce suicide risk in schizophrenia.

Drug name: citalopram (Celexa and others).

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