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Treatment of Subsyndromal Depressive Symptoms in Middle-Age and Older Patients With Schizophrenia: Effect of Age on Response

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Abstract

Objective—The authors hypothesized that age would moderate the response of patients with schizophrenia and subsyndromal depression (SSD) treated citalopram with depressive symptoms and other outcomes. Also, older patients would exhibit more side effects with citalopram.

Methods—Participants of 40 years or older had schizophrenia or schizoaffective disorder with SSD. Patients randomly received flexible dosing of citalopram or placebo augmentation of their antipsychotic medication. Linear regression determined whether age had any moderating effect on depressive symptoms, global psychopathology, negative symptoms, mental functioning, and quality of life. Age-related side effects were examined.

Results—There were no significant drug group by age interaction in depressive or psychotic symptoms, mental Short Form-12, or quality of life scores. Similarly, there were few age-related side effect differences.

Conclusion—Symptoms in younger and older patients with schizophrenia and SSD treated with citalopram seem to respond similarly. Adverse events do not seem to differ with age.

Keywords

Schizophrenia; age differences; citalopram; depression; psychopathology; quality of life

Depressive symptoms in patients with chronic schizophrenia are associated with disability, demoralization, and an increased risk for suicide.[1] A recent randomized controlled trial by our group using antidepressants to treat middle-aged and older patients with schizophrenia and subsyndromal depression (SSD) indicated that the selective serotonin reuptake inhibitor (SSRI) citalopram was more effective than placebo in relieving depression, negative symptoms, mental functioning, and quality of life.[2]

Previous findings in patients with depression demonstrated a weaker response in older persons with antidepressants.[3] Thus, we suspected that the improvement of depressive

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symptoms of older patients with schizophrenia in an acute treatment trial would not be as robust as in younger patients. To examine these questions, we conducted a secondary analysis of our dataset[2] and tested the following hypotheses: 1) age would moderate the response of patients with schizophrenia and SSD to citalopram with regards to depressive symptoms, positive and negative symptoms, mental functioning, and quality of life and also 2) older patients would exhibit more side effects with citalopram treatment.

METHODS

The study reported previously[2] was a 12-week, double- blinded, randomized, placebo-controlled two-site study of citalopram augmentation of antipsychotic medication in middle-aged and older outpatients with schizophrenia or schizoaffective disorder and SSD. Patients were randomly assigned to treatment with flexibly dosed citalopram or placebo augmentation of their current antipsychotic medication.

Participants ≥40 with schizophrenia or schizoaffective disorder had ≥2 of the nine items required for major depression and 17-item Hamilton Depression (HAMD) scores ≥8.[4] Exclusions were major depression or mania within 2 months, active substance abuse/ dependence for the past month, and dementia. Assessments were described previously[2]; they included the positive and negative syndrome scale for schizophrenia,[5] Calgary Depression Rating Scale (CDRS[6]), the HAMD,[4] Clinical Global Impressions Scale,[2] Heinrichs Quality of Life Scale,[7] and the Mental Component of the Medical Outcome Studies– Short Form-12 (short form-12[8]). Although the CDRS is more specific for depression in this population, the HAMD scale was also included because it is widely used in studies with this population. Major study visits occurred at baseline and at Week 12 or earlier with premature discontinuation.

Statistical Analysis

Linear regression assessed baseline differences in continuous variables with a term for site, treatment group, age, and treatment group by age interaction. Categorical variables were examined using logistic regressions with corresponding terms. Missing values were handled using last observation carried forward methodology. All statistical tests were two-tailed ($\alpha = 0.05$) using SPSS, version 17. There were differences between the two sites on marital status ($\chi^2 = 13.8$, $df = 5$, $p = 0.011$); living situation ($\chi^2 = 16.3$, $df = 8$, $p = 0.026$); gender ($\chi^2 = 7.6$, $df = 1$, $p = 0.009$); race ($\chi^2 = 24.1$, $df = 7$, $p = 0.001$); and age ($t = 174.0$, $df = 174$, $p = 0.001$); as a result, the site factor was added for hypothesis testing.

Linear regression examined whether age as a continuous variable had any moderating effect on treatment efficacy. The models included outcome at baseline, age, drug (citalopram versus placebo), and age group by drug group interaction. Baseline treatment by drug interaction was assessed by a regression with site, age group, drug group, and age by drug group interaction. Response rates of HAMD and CDRS scores, defined as a >50% improvement relative to baseline, as well as side-effect rates were analyzed by logistic regression with terms for site, age, drug group, and age by drug-group interaction. Nondichotomous categorical demographics were analyzed using a multinomial logistic regression model with similar terms.

Diagnostic tests and visualizations were performed on the regressions. The residuals were determined to be sufficiently normal; heteroskedasticity and nonlinearity were also investigated and the necessary assumptions for using parametric approaches for continuous variables were met. For testing differences in side effects between citalopram and placebo groups, we divided our sample into two groups based on the age, such as aged 40–49 years and 50 years or older, because it allowed for a nearly equal division of the sample. We tested

whether there was an interaction between age and treatment using methods similar to those used in our first hypothesis.

RESULTS

There were a total of 198 participants. The average age of participants was 52.5 ± 7.1 years (N = 196; range = 40–75). The average age of onset of psychosis was 27.94 ± 10.5 years (N = 171; range = 10–59). The average years of education was 11.94 ± 2.2 years (N = 198; range = 6–18). Forty three (22%) were women; 108 (56%) were Caucasian; 64 (33%) were African American; 10 (5%) were Hispanic; and 14 (7%) were other. In terms of marital status, 28 (14%) were married/cohabitating and 81 (41%) were diagnosed with schizoaffective disorder (versus schizophrenia). The Mini-Mental Status score at baseline was 27.0 ± 2.6 (N = 197; range = 18–30).

Table 1 summarizes linear regression interaction effects (drug group by age) on the primary outcome measures, HAMD and CDRS. At baseline, adjusting for site there were no significant drug group by age effects with regard to HAMD or CDRS scores. The main effects have been presented in a previous article.[2] At endpoint, adjusting for site and baseline, there were no significant drug group by age effects with regard to either HAMD or CDRS scores. In addition, there was no significant logistic interaction effect for percentage response on HAMD or CDRS. For illustrative purposes, we dichotomized the baseline and endpoint total HAMD and total CDRS scores as well as percentage HAMD and CDRS responders.

Secondary Outcomes

Table 1 also summarizes differences between treatments at baseline and at the last observation in several other dimensions of schizophrenia: global psychopathology, positive and negative symptoms, mental component of Short Form-12 scores, and quality of life. The main effects have been presented in a previous article.[2] At baseline, adjusting for site there were no significant drug group by age effects with regard to these measures. At endpoint, adjusting for site and baseline, there were also no significant drug group by age effects. For illustrative purposes, we also present baseline and endpoint values for these secondary measures with our group dichotomized at ages 40–49 years and 50 years or older.

Dose, Side Effects, and Tolerability

Although a majority of participants experienced adverse events, most were mild and transient. As reported[2] in the citalopram group, the following adverse events occurred in at least 10% of the patients: anxiety, decreased libido, difficulty falling asleep, dry mouth, faintness/dizziness, headache, nausea, vomiting, stomach/abdominal discomfort, diarrhea, pain (muscle, joint, bone), tiredness/fatigue, and upper respiratory infection. There were two significant main effects with age: 1) the 40–49 years old group had more “dry mouth” and 2) the 50-year-old group had higher levels of “tiredness/fatigue.” When we dichotomized our participants into our four groups, there were no statistically significant differences in terms of age, age of onset of illness, education, gender, or race. Older patients did exhibit lower mini-mental state examination scores (40–49 years group: citalopram 27.8 ± 1.9, N = 39; placebo 27.3 ± 2.2, N = 41, and ≥50 years group: citalopram 26.9 ± 2.5, N = 64; placebo 26.3 ± 3.2, N = 51; p = 0.02). In addition, we detected no significant interactions at baseline on any of the other observed variables. Finally, there were no significant age-by-treatment interactions with regards to any of these side effects.

DISCUSSION

Siris[9] reported that practitioners prescribe antidepressants to 30% of inpatients and 43% of outpatients with schizophrenia and depression at all ages. SSRIs are the most commonly prescribed antidepressants in patients with schizophrenia and depressive symptoms. [9] Our results did not support the premise that there would be age-related differences in efficacy or side effects with this common clinical practice approach. There were inconsistent main effects of age depending on the outcome measures. The older group had significantly higher percentages of responders based on HAMD scores relative to the young group (old responders (41%) versus young responders (20%); Wald = 5.2, *df* = 1; p = 0.022). However, for CDRS scores, the differences were not significantly different (old 46% versus young 33%; Wald = 3.6, *df* = 1, p = 0.058). It is not clear whether this finding has clinical significance.

As one of the study limitations, there was a paucity of geriatric individuals. Despite our best efforts to target this age range for this study, the preponderance of participants was between the ages of 40 and 55 years. The decrease in community prevalence that may be due to early mortality associated with the illness creates challenges in recruiting from this population.[10] It is entirely possible that we would have found different responses to citalopram in a truly geriatric cohort. Furthermore, two of our exclusion criteria could have underestimated the likelihood of side effects. The first one excluded participants who had a previous reaction to any SSRIs. The second one excluded individuals based on whether the treating or study physician judged that SSRIs were inadvisable for the individual.

In addition, another limitation of our study was that our group was heterogeneous, comprising individuals with and without histories of major depression, schizoaffective disorder, and schizophrenia. Furthermore, our sample possibly included patients with residual or prodromal symptoms of major depression, and even some with prominent negative symptoms or extrapyramidal side effects.

There was also variability in the adequacy and type of treatment of the underlying disorder. We always attempted to “optimize” antipsychotic treatment by observing the patient before randomization and often recommended antipsychotic dose adjustment to the treating physician if the study physician felt that it was warranted. When changes were made, we waited until doses were stable for at least 4 weeks before completing baseline assessments.

In conclusion, SSD in middle-aged and older patients with schizophrenia is an important clinical entity that may be underappreciated, underrecognized, and associated with substantial morbidity and distress. This study supports the premise that age does not seem to have a moderating effect on subsyndromal depressive symptoms on treatment with the SSRI citalopram. Citalopram seems to provide similar levels of improvement in a variety of psychological outcomes with patients of variable ages, including functioning and quality of life.

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TABLE 1

Baseline and Endpoint Measures Among Participants

Measure	Total		Treatment				Linear Regression Interaction Effect $F_{[df,df]}$	Interaction Effect, p
			Citalopram		Placebo			
	Mean	SD	40–49 yr	≥50 yr	40–49 yr	≥50 yr		
HAM-D								
Baseline	13.5 (N = 196)	4.24	13.6 (4.2) (N = 39)	13.6 (4.5) (N = 64)	13.6 (5.0) (N = 41)	13.3 (3.2) (N = 52)	$0.092_{[1,191]}$	0.762
End of treatment	9.12 (N = 196)	5.83	9.7 (6.4) (N = 39)	7.5 (5.1) (N = 64)	10.6 (5.0) (N = 41)	9.6 (6.5) (N = 52)	$0.161_{[1,190]}$	0.688
							Wald (*df*)	p
% Responders[a]			26	52	15	29	0.201 (1)	0.654
CDRS							*F*	p
Baseline	6.73 (N = 196)	3.13	7.5 (3.3) (N = 39)	5.8 (2.9) (N = 64)	7.0 (2.9) (N = 41)	7.1 (3.2) (N = 52)	3.025 (1,191)	0.084
End of treatment	4.71 (N = 196)	4.06	4.59 (3.9) (N = 39)	3.34 (3.0) (N = 64)	6.15 (4.2) (N = 41)	5.37 (4.7) (N = 52)	0.056 (1,190)	0.813
							Wald	p
% Responders[b]			49	50	17	40	1.102 (1)	0.294
Psychopathology							*F*	p
CGI-S								
Baseline	4.0 (N = 195)	0.721	4.0 (0.78) (N = 39)	3.9 (0.72) (N = 63)	4.1 (0.65) (N = 41)	4.0 (0.74) (N = 52)	0.058 (1,190)	0.811
End of treatment	3.9 (N = 196)	0.747	4.0 (0.83) (N = 39)	3.7 (0.70) (N = 64)	4.1 (0.64) (N = 41)	3.9 (0.79) (N = 52)	0.124 (1,189)	0.726
PANSS—Total								
Baseline	63.6 (N = 195)	15.2	68.1 (16.1) (N = 39)	56.3 (12.6) (N = 64	67.0 (15.2) (N = 41)	66.6 (14.5) (N = 51)	.347 (1,190)	0.556
End of treatment	60.0 (N = 186)	15.1	63.6 (16.7) (N = 34)	53.2 (13.1) (N = 63)	62.1 (15.0) (N = 40)	60.7 (14.5) (N = 49)	0.285 (1,179)	0.594
PANSS—Negative								
Baseline	15.9 (N = 195)	5.2	16.7 (4.7) (N = 39)	14.5 (4.8) (N = 64)	16.9 (5.7) (N = 41)	16.3 (5.3) (N = 51)	.161 (1,190)	0.689
End of treatment	15.5 (N = 186)	5.3	14.9 (4.4) (N = 34)	14.4 (4.9) (N = 63)	16.6 (5.9) (N = 40)	16.4 (5.7) (N = 49)	0.701 (1,179)	0.404
PANSS—Positive								
Baseline	15.7 (N = 196)	5.4	17.8 (6.7) (N = 39)	13.1 (4.8) (N = 64)	16.9 (4.5) (N = 41)	16.2 (4.6) (N = 52)	1.349 (1,191)	0.247
End of treatment	14.7 (N = 186)	5.5	18.0 (6.6) (N = 34)	12.6 (4.8) (N = 63)	15.3 (5.3) (N = 40)	14.5 (4.6) (N = 49)	0.000 (1,180)	0.991
Quality of life, function and health								
MOS-12, mental component								

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	Total		Treatment					
			Citalopram		Placebo		Linear Regression Interaction Effect	
Measure	Mean	SD	40–49 yr	≥50 yr	40–49 yr	≥50 yr	$F_{[df,df]}$	Interaction Effect, p
Baseline	40.8 (N = 192)	10.5	40.0 (10.4) (N = 39)	41.0 (10.6) (N = 64)	41.8 (10.1) (N = 38)	40.5 (11.0) (N = 51)	0.515 (1,187)	0.474
End of treatment	45.9 (N = 155)	10.3	48.3 (9.1) (N = 29)	48.1 (10.6) (N = 51)	42.0 (10.7) (N = 34)	44.7 (9.4) (N = 41)	0.185 (1,146)	0.668
QLS								
Baseline	58.6 (19.8) (N = 169)	22.4	53.3 (19.8) (N = 34)	65.7 (22.7) (N = 55)	54.1 (21.8) (N = 36)	57.6 (22.6) (N = 44)	0.009 (1,164)	0.923
End of treatment	61.0 (N = 141)	23.7	59.8 (23.6) (N = 25)	67.6 (25.0) (N = 45)	59.1 (21.1) (N = 33)	55.6 (23.5) (N = 38)	0.251 (1,132)	0.617

Notes: The *F* and p values to the right of the Table for Linear Regression are based on ANCOVA; for main effects with descriptive statistics, see Ref [2]. Unless otherwise specified, values represent means (SD) or percent. QLS: Henrichs quality of life scale; MOS-12: medical outcome studies short form-12; PANSS: positive and negative syndrome scale; CGI-S: clinical global impressions scale.

[a] Response defined as ≥50% reduction from baseline score on 17-item Hamilton Rating Scale for Depression.

[b] Response defined as ≥50% reduction from baseline score on Calgary Depression Rating Scale.