Adding antidepressants to antipsychotics for treatment of subsyndromal depressive symptoms in schizophrenia: Impact on positive and negative symptoms

Ipsit V. Vahia1,2, Nicole M. Lanouette1, Shahrokh Golshan1, Ian Fellows1, Somaia Mohamed3, John W. Kasckow4,5, Sidney Zisook1,6

1Department of Psychiatry, 2Stein Institute for Research on Aging, University of California San Diego, California, 3Department of Psychiatry, Yale School of Medicine, 4VA Pittsburgh Health Care System MIRECC and Behavioral Health Service, 5Department of Psychiatry, Western Psychiatric Institute and Clinics, University of Pittsburgh Medical Center, 6Department of Psychiatry, VA San Diego Healthcare System, USA

ABSTRACT

Objectives: It remains unclear how augmenting anti-psychotic medications with anti-depressants impacts primary positive and negative symptoms of schizophrenia. In this study, we used data collected from a randomized trial comparing citalopram to placebo for management of subsyndromal depression (SSD) in schizophrenia and schizoaffective disorder, to assess the effects of antidepressant augmentation on positive and negative symptoms.

Materials and Methods: Participants in this study conducted at the University of California, San Diego and the University of Cincinnati, were persons with schizophrenia or schizoaffective disorder aged 40 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 anti-psychotic medication. Analysis of covariance was used to compare changes in positive and negative syndrome scale (PANSS) scores between treatment groups. We also assessed mediating effects of improvement in depression and moderating effects of multiple factors on positive and negative symptoms.

Results: There was significant improvement in PANSS negative symptoms scores in the citalopram group, which was partially mediated by improvement in depressive symptoms. There was no effect on PANSS positive scores.

Conclusions: In patients with schizophrenia/schizoaffective disorder, treating depressive symptoms with citalopram appears to carry the added benefit of improving negative symptoms.

Key words: Citalopram, depression, negative symptom, schizophrenia

INTRODUCTION

Approximately one in three patients with schizophrenia in out-patient settings are treated with anti-depressants. Anti-depressants are prescribed for treatment of comorbid depression in schizophrenia as well as mood symptoms that may be part of the core illness. Augmentation of anti-psychotic medication with tricyclic anti-depressants has been reported for treatment of depressive symptoms and more recently, mirtazapine has been shown to have an additive effect on the anti-psychotic action of first generation anti-psychotics. These findings point to multiple roles for anti-depressants as a class in management of schizophrenia. Yet, limited evidence exists to provide clinical guidance for use of anti-depressant medications.
especially selective serotonin reuptake inhibitors (SSRIs).

Meta-analyses exploring use of anti-depressants for people with depression and schizophrenia have been largely inconclusive or have provided limited evidence at least in part because studies in this area have been limited by samples of fewer than 50.

The heterogeneous nature of schizophrenia symptoms complicates the process of determining relative risks and benefits of using antidepressants in schizophrenia management. Affective symptoms are the least defined of the schizophrenia domains, and may represent various combinations of primary mood symptoms, demoralization, or secondary symptoms related to medication effects, neurological symptoms or comorbid conditions. Overlap between negative symptoms of schizophrenia and vegetative symptoms of depression, (e.g., apathy, amotivation) further complicates clinical decision-making. When negative symptoms improve with anti-depressants, it often is unclear whether the attenuation in negative symptoms is a consequence of improvement in depression.

The need for evidence-based treatments is especially urgent in older patients with schizophrenia. Polypharmacy is common in older adults due to higher rates of medical comorbidity and this population is especially susceptible to medication side-effects. All current evidence is limited by small populations of entirely or predominantly younger age groups. There are no data derived from randomized controlled trials that focus on the impact of anti-depressants on positive and negative symptoms of schizophrenia in older adults.

In a large two-site, randomized, double blinded, placebo controlled trial studying citalopram augmentation of antipsychotic medications for treatment of subsyndromal symptoms of depression (SSD) in middle-aged and older adults with schizophrenia, we noted that citalopram improved depressive symptoms compared to placebo treatment. We also found that citalopram appeared to improve negative symptoms while showing no impact on positive symptoms. In this report from the same parent study, we examine in greater detail the impact of citalopram augmentation on positive and negative symptoms. We hypothesize that effects of citalopram treatment on negative symptoms partly reflect improvement in depression. In addition, we explore whether demographics or diagnosis (schizophrenia versus schizoaffective disorder) serve as moderators.

**MATERIALS AND METHODS**

The data for this study were collected as part of a broader 12-week, double-blind, randomized, placebo-controlled two-site study of citalopram augmentation of anti-psychotic medication in middle-aged and older patients with schizophrenia or schizoaffective disorder and SSD. The study was conducted simultaneously at the University of California, San Diego, and the University of Cincinnati. Details of the parent study are described elsewhere.

**Study population**

In San Diego, participants were recruited from the National Institute Mental Health (NIMH)-funded Intervention Research Center at University of California, San Diego, focusing on middle-aged and older persons with schizophrenia, board- and -care facilities, and general outpatient settings. Cincinnati participants were recruited from University of Cincinnati outpatient clinics, clinics from the Cincinnati metropolitan area, and the Cincinnati and Chillicothe VA Medical Centers. 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 patients 40 years of age or older were eligible for the study if they: (a) Met Diagnostic and Statistical Manual – 4th Edition (DSM-IV) criteria for schizophrenia or schizoaffective disorder; (b) met study criteria for SSD defined by having two to four of the nine DSM-IV symptoms of major depressive episode, present most of the time for at least 2 weeks; (c) had a Hamilton depression rating scale (HAM-D) 17-item score >8; and (d) 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 diagnosis (within 2 months) of major depression or mania; had active substance abuse or dependence which, in the research physician’s opinion, would impact 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 reactions or significant adverse events while taking citalopram; or if 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. 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 flexible-dose treatment with citalopram (20 mg/day) or placebo augmentation of their current antipsychotic medication. After the 1st 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 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 anti-depressant medications that had been prescribed by their treating physicians for insomnia or chronic pain.

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 inter-rater reliability, an intra-class correlation 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 the new raters’ administering the study protocol.

Screening evaluations included the Mini-Structured Clinical Interview for DSM-IV Axis 1 Disorders (Mini-SCID).[19] and HAM-D).[20] After informed consent was signed, we obtained psychiatric and medical history, documented vital signs and conducted laboratory tests and physical examination. Depression symptoms were assessed using the Calgary depression rating scale (CDRS)[20] and HAM-D.[21] Positive and negative symptoms were assessed using the positive and negative syndrome scale (PANSS).[22] HAM-D and CDRS assessments were done during study visits at weeks 1, 2, 3, 4, 6, 8 and 12 and PANSS was administered at weeks 1, 4, 8 and 12. To assess the degree to which depressive symptoms and negative symptoms overlap, we used the PANSS factor structure described by Lykouras et al.[23] This factor structure consisted of a positive symptoms component (5 items), negative symptoms component (6 items), excitement component (5 items), cognitive component (5 items), and depression component (3 items). Six items did not load onto any of the 5 factors

Statistical analysis
For summary statistics, means and standard deviations were computed for continuous variables, and counts and percentages for discrete variables. We initially considered using a mixed model analysis, but because our hypotheses of primary interest focused on outcome at endpoint, and the shape of the response trajectory for intermediate time points was different between the sites, we chose to use endpoint analysis similar to the parent study. Two-way ANOVAs (with drug group and site as factors) 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 on a modified intent-to-treat basis. All analyses included participants who underwent randomized assignment, took at least one dose of the study medication, and completed at least one post-baseline visit. All statistical tests were two-tailed and the level of statistical significance was set at $P<0.05$. Analysis of co-variance (ANCOVA) was used to assess whether treatment had any effect on the outcome measures. Similar to the parent study,[17] our ANCOVAs included terms for drug group, site (centered around zero), drug group by site interaction, and the positive or negative subscales of PANSS measure at baseline. As a secondary analysis, we performed a mediator analysis to determine if the observed drug group differences on positive and negative subscales of PANSS could be explained by changes in CDRS following the methodology described by Baron and Kenny.[24] We chose CDRS for this analysis since it was designed specifically to assess severity of depressive symptoms in schizophrenia.[25]

We also investigated whether the treatment effect was moderated by gender, diagnosis, and type of anti-psychotic by using the ANCOVA model.[24] The drug group by site interaction term was dropped from the ANCOVA for the mediator/moderator analyses, as it was non-significant for all outcomes.

RESULTS
There were 98 patients in the citalopram group and 89 in the placebo group from both sites [Table 1]. The groups did not differ at baseline in demographic characteristics, scores on HAM-D, CDRS, or positive and negative subscales of PANSS. However, the groups were significantly different on the PANSS total score ($F=5.24, df=1,183; P=0.023$). There were no significant differences between the two groups or between the two sites in drop-out rates.

We compared PANSS scores at the last available visit [Table 2] using baseline values as covariates. The PANSS positive subscale scores did not show a statistically significant difference between groups. However, the patients in the citalopram group had significantly lower scores on the PANSS negative symptoms scale. To examine the overlap between negative symptoms and depressive symptoms, we separated PANSS items into 5 factors and compared the treatment and placebo groups on total scores for each factor. All factors had Cronbach’s alpha of 0.6 or higher, indicating acceptable internal consistency in these subjects. The results, described in Table 2, show that only the PANSS negative component (composed of items measuring blunted affect, emotional withdrawal, poor rapport, passive/apathetic/social withdrawal, lack of spontaneity and motor retardation) was significantly lower, (i.e., – significantly improved) in the citalopram
Table 1: Baseline characteristics of sample

| Variable                          | Placebo group | Citalopram group | df | F/χ² | P value |
|----------------------------------|---------------|------------------|----|------|---------|
| Total N                          | 89            | 98               |    |      |         |
| Gender (male) (%)                | 70 (79)       | 75 (77)          | 1  | 0.29 | 0.593   |
| Marital status (married/cohabitating) (%) | 9 (10)       | 17 (17)          | 1  | 0.86 | 0.354   |
| Race (caucasian) (%)             | 51 (57)       | 49 (50)          | 1  | 0.58 | 0.445   |
| Living status (living alone) (%) | 26 (30)       | 30 (31)          | 1  | 0.01 | 0.945   |
| Mean age at enrollment (years)   | 51.6 (6.4)    | 53.4 (7.7)       | 1  | 2.98 | 0.086   |
| Mean age of onset (years)        | 27.3 (10.3)   | 28.6 (10.9)      | 1  | 0.56 | 0.454   |
| Mean education level (years)     | 11.8 (2.3)    | 12.1 (2.1)       | 1  | 0.89 | 0.346   |
| Baseline diagnosis of schizophrenia* (%) | 57 (64)   | 54 (55)          | 1  | 0.99 | 0.319   |
| Atypical antipsychotics (%)      | 10 (17.5)     | 9 (15.5)         | 1  | 0.002| 0.962   |
| HAM-D (mean score)               | 13.4 (4.1)    | 13.6 (4.4)       | 1  | 0.04 | 0.839   |
| CDRS (mean score)                | 6.8 (2.8)     | 6.4 (3.2)        | 1  | 0.98 | 0.323   |
| PANSS positive (mean score)      | 16.3 (4.5)    | 14.9 (6.1)       | 1  | 2.96 | 0.087   |
| PANSS negative (mean score)      | 16.4 (5.3)    | 15.5 (4.9)       | 1  | 1.72 | 0.190   |

Table 2: Differences in positive and negative syndrome scale factor scores* at the time of last visit

| Variable                          | Placebo group | Citalopram group | df | F | P value |
|----------------------------------|---------------|------------------|----|---|---------|
| PANSS positive total             | 14.8 (4.9)    | 14.4 (6.0)       | 1  | 2.57 | 0.111   |
| PANSS negative total             | 16.4 (5.7)    | 14.5 (4.7)       | 1  | 3.93 | 0.049   |
| PANSS positive factor cluster    | 11.5 (0.3)    | 11.9 (0.3)       | 1  | 0.86 | 0.343   |
| PANSS negative factor cluster    | 13.0 (0.47)   | 11.4 (0.44)      | 1  | 0.68 | 0.010   |
| PANSS depression factor cluster  | 7.3 (0.3)     | 6.9 (0.3)        | 1  | 0.05 | 0.330   |
| PANSS cognition factor cluster   | 10.13 (0.3)   | 10.44 (0.3)      | 1  | 0.64 | 0.424   |
| PANSS excitement factor structure| 6.8 (0.2)     | 6.9 (0.2)        | 1  | 0.11 | 0.740   |

DISCUSSION

In order to study how augmenting anti-psychotic medications with anti-depressants impacts positive and negative symptoms of schizophrenia in the middle-aged and elderly, we analyzed data from a large two-site, placebo controlled, randomized double blind clinical trial comparing patients treated with citalopram and an anti-psychotic agent to those treated with antipsychotic agents alone for SSD. To our knowledge, this is the first large double blind study in middle aged and older patients with schizophrenia and schizoaffective disorder assessing effects of adding SSRIs to anti-psychotic medications on schizophrenia symptoms.

We noted that citalopram augmentation appears to improve negative symptoms that may impair social functioning – rapport, flow of conversation, spontaneity, apathy and social withdrawal. It also appears to improve motor retardation. We noted that the effect of citalopram on negative symptoms was partly mediated by improvements in symptoms of depression, even though depression and negative symptoms have been demonstrated as distinct clinical dimensions of schizophrenia.[26] This finding is consistent with observations of a degree of overlap between negative and depressive symptom domains,[14] and is encouraging in suggesting that improvement in both domains may be seen with citalopram treatment. Since negative symptoms have been associated with worse functioning[27] and quality of life,[28] improving this important dimension of schizophrenia with anti-depressants may produce a cascading chain of benefits resulting in improved functioning and quality of life. It is noteworthy that these benefits were obtained without simultaneous worsening of positive symptoms.

Our finding that citalopram augmentation did not worsen positive symptoms is consistent with recent reports.[10] The contrast between this finding and previous reports of worsening of positive symptoms with tricyclics is possibly explained by selective action of citalopram on serotonin reuptake. It may be that SSRIs are the preferred class of medications for treating depressive symptoms in patients with schizophrenia, but further comparative studies are needed before this conjecture can be stated with certainty.
The findings of this study must be interpreted in light of its limitations. The parent clinical trial was not designed to assess the impact of anti-depressant medications on negative symptoms and the sample was not selected for this study specifically. The power of the study design was based on estimation of depressive symptoms response and not negative symptom response. Since this study was designed to study middle-aged and older patients with schizophrenia, applicability of these findings to younger populations remains unclear. We did not standardize the treatment of the primary disorder, though we did attempt to ‘optimize’ anti-psychotic treatment prior to randomization and starting citalopram or placebo.

This study also has several strengths. It addresses a major gap in the evidence for co-prescribing anti-depressants for older patients with schizophrenia – a rapidly growing population.[29] Additionally, both the groups in the sample were randomized and sample sizes were large.

For future research in this area, we recommend further study of issues of medication adherence, impact on quality of life, and improvements in global indices of outcome like insight and social functioning.

ACKNOWLEDGMENTS

The authors wish to thank the San Diego VA Healthcare System; Advanced Center for Innovations in Services and Interventions Research (ACISIR) at the Division of Geriatric Psychiatry, University of California, San Diego (UCSD); Stein Institute for Research on Aging at UCSD; Cincinnati VA Medical Center and the University of Cincinnati, for their support.

The views do not represent the views of the US Department of Veterans Affairs or that of the US government. This study was supported in part by NIMH grants MH063931 and MH6398.

REFERENCES

1. Tempier RP, Pawlik NH. Conventional, atypical, and combination antipsychotic prescriptions: A 2-year comparison. J Clin Psychiatry 2003;64:673-9.
2. Buckley PF, Miller BJ, Lehner DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull 2009;35:383-402.
3. Escamilla MA. Diagnosis and treatment of mood disorders that co-occur with schizophrenia. Psychiatr Serv 2001;52:911-9.
4. Chakos MH, Glick ID, Miller AL, Hamner MB, Miller DD, Patel JK, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. Psychiatr Serv 2006;57:1094-101.
5. Siris SG, Bermanzohn PC, Mason SE, Shuwall MA. Maintenance imipramine therapy for secondary depression in schizophrenia. A controlled trial. Arch Gen Psychiatry 1994;51:109-15.
6. Siris SG, Morgan V, Fagerstrom R, Rifkin A, Cooper TB. Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. Arch Gen Psychiatry 1987;44:533-9.
7. Joffe G, Terevnikov V, Joffe M, Stenberg JH, Burkin M, Tihonen J. Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: A double-blind, randomized, placebo-controlled trial. Schizophr Res 2009;108:245-51.
8. Kasckow JW, Zisook S. Co-occurring depressive symptoms in the older patient with schizophrenia. Drugs Aging 2008;25:631-47.
9. Whitehead A, Moss S, Cardno A, Lewis G. Antidepressants for people with both schizophrenia and depression. Cochrane Database Syst Rev 2002;CD002305.
10. Rummel C, Kissing L, Leucht S. Antidepressants for the negative symptoms of schizophrenia. Cochrane Database Syst Rev 2006;3:CD005581.
11. Mulholland C, Lynch G, King DJ, Cooper SJ. A double-blind, placebo-controlled trial of sertraline for depressive symptoms in patients with stable, chronic schizophrenia. J Psychopharmacol 2003;17:107-12.
12. Addington D, Addington J, Patel S, Rendeles A, Moaumi J, Labelle A, et al. Double-blind, placebo-controlled comparison of the efficacy of sertraline as treatment for a major depressive episode in patients with remitted schizophrenia. J Clin Psychopharmacol 2002;22:20-5.
13. Combblatt BA, Lenz T, Smith CW, Olsen R, Author AM, Nakayama E, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. J Clin Psychiatry 2007;68:546-57.
14. Lindenmayer JP, Kay SR. Depression, affect and negative symptoms in schizophrenia. Br J Psychiatry Suppl 1989:155:108-14.
15. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007;5:345-51.
16. Silver H, Nassar A. Fluvoxamine improves negative symptoms in treated chronic schizophrenia: An add-on double-blind, placebo-controlled study. Biol Psychiatry 1992;31:698-704.
17. Zisook S, Kasckow JW, Golshan S, Fellows I, Solorzano E, Lehman D, et al. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: A randomized controlled trial. J Clin Psychiatry 2008;69:562-71.
18. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278-96.
19. Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:22-33.
20. Addington D, Addington J, Mataica-Tyndale E. Assessing depression in schizophrenia: The Calgary depression scale. Br J Psychiatry Suppl 1993;163:39-44.
21. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
22. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-76.
23. Lykouras L, Oulis P, Psarros K, Daskalopoulou E, Botsis A, Christodoulou GN, et al. Five-factor model of schizophrenic psychopathology: How valid is it? Eur Arch Psychiatry Clin Neurosci 2000;250:93-100.
24. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-82.
25. Addington D, Addington J, Mataica-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res 1992;6:201-8.
26. Diwan S, Cohen CI, Bankole AO, Vahia I, Kehn M, Ramirez PM. Depression in older adults with schizophrenia spectrum disorders: Prevalence and associated factors. Am J Geriatr Psychiatry 2007;15:991-8.
27. Kasckow J, Patterson T, Fellows I, Golshan S, Solorzano E, Mohamed S, et al. Functioning in middle aged and older patients with schizophrenia and depressive symptoms: Relationship to psychopathology. Am J Geriatr Psychiatry 2008;16:660-3.
28. Bankole AO, Cohen CI, Vahia I, Diwan S, Kehn M, Ramirez PM. Factors affecting quality of life in a multicultural sample of older persons with schizophrenia. Am J Geriatr Psychiatry 2007;15:1015-23.
29. Vahia I, Bankole AO, Reyes P, Diwan S, Palekar N, Sapra M, et al. Schizophrenia in later life. Aging Health 2007;3:383-96.

Source of Support: NIMH grants MH063931 and MH6398, Conflict of Interest: None declared