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Citalopram in first episode schizophrenia: The DECIFER trial

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ABSTRACT

Antidepressants are frequently prescribed in first episode schizophrenia (FES) patients for negative symptoms or for subsyndromal depressive symptoms, but therapeutic benefit has not been established, despite evidence of efficacy in later-stage schizophrenia. We conducted a 52 week, placebo-controlled add-on trial of citalopram in patients with FES who did not meet criteria for major depression to determine whether maintenance therapy with citalopram would improve outcomes by preventing or improving negative and depressive symptoms. Primary outcomes were negative symptoms measured by the Scale for Assessment of Negative Symptoms and depressive symptoms measured by the Calgary Depression Scale for Schizophrenia; both were analyzed by an intent-to-treat, mixed effects, area-under-the-curve analysis to assess the cumulative effects of symptom improvement and symptom prevention over a one-year period. Ninety-five patients were randomized and 52 (54%) completed the trial. Negative symptoms were reduced with citalopram compared to placebo ($p = .04$); the effect size of citalopram versus placebo was 0.32 for participants with a duration of untreated psychosis (DUP) of <18 weeks (median split) and 0.52 with a DUP >18 weeks. Rates of new-onset depression did not differ between groups; improvement in depressive symptoms was greater with placebo than citalopram ($p = .02$). Sexual side effects were more common with citalopram, but overall treatment-emergent side effects were not increased compared to placebo. In conclusion, citalopram may reduce levels of negative symptoms, particularly in patients with longer DUP, but we found no evidence of benefit for subsyndromal depressive symptoms.

1. Introduction

Specialized treatment programs that integrate psychosocial interventions with optimal medication management have improved outcomes in first episode schizophrenia (FES) (Correll et al., 2018; Dixon et al., 2018) although negative symptoms, subsyndromal depressive symptoms, and functional impairment often persist. Antidepressants are not recommended for maintenance treatment of FES patients in the absence of major depression (Robinson et al., 2015), despite evidence of benefit for negative symptoms in people with later-stage illness (Helfer et al., 2016). However, antidepressants are commonly prescribed in non-depressed patients with FES; for example, of FES patients who were taking medication at the time of enrollment in the Recovery after an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) study, 36% were prescribed an antidepressant in the absence of a recent history of major depression (Robinson et al., 2015). To our knowledge, only three placebo-controlled studies of antidepressants have been reported in FES patients; all 3 studies were conducted in non-depressed patients and were designed to examine whether antidepressants might reverse antipsychotic-associated weight gain. In the first study, an 8 week trial of fluoxetine added to olanzapine in 30 FES participants, fluoxetine provided no benefit for negative or depressive symptoms compared to the addition of placebo and was associated with less improvement of psychotic symptoms (Poyurovsky et al.,

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2002), whereas in 2 trials of 6 weeks duration in which reboxetine was added to olanzapine (n = 20 and n = 59), reboxetine was associated with improvement in depressive symptoms but had no effect on positive or negative symptoms compared to placebo (Poyurovsky et al., 2003; Poyurovsky et al., 2007).

Duration of untreated psychosis (DUP) may be an important moderator of therapeutic outcome in FES. In the RAISE-ETP trial, only FES patients with shorter DUP (identified by a median split) benefited from enhanced psychosocial and pharmacologic treatment compared to treatment as usual (Kane et al., 2016). We recently found that DUP interacted with several biomarkers, including brain-derived neurotrophic factor (BDNF) genotype, to predict hippocampal atrophy in FES patients, which in turn predicted poor response of negative symptoms to treatment with second generation antipsychotics (Goff et al., 2018). This finding suggests that BDNF may play a protective role against the adverse effects of DUP on hippocampal integrity and on associated negative symptoms. Antidepressants increase levels of BDNF (De Foubert et al., 2004) and hippocampal neurogenesis (Malberg et al., 2000) and hence may play a neuroprotective role in FES. The BDNF Val66Met polymorphism, which modulates BDNF release, was found to predict response of depressive symptoms to citalopram (Choi et al., 2006). We therefore predicted that citalopram would exert a neuroprotective effect over the first 12 months of illness that would be associated with improved negative and depressive symptoms.

2. Methods

2.1.1. Study design

We conducted a four-site, 52 week, randomized placebo-controlled trial of citalopram added to clinician-determined second generation antipsychotic medication in individuals with FES who did not meet criteria for major depression to determine whether citalopram would improve clinical course over a 12 month period by improving or preventing depressive and negative symptoms. The primary outcome at the time of initial protocol development was depression measured by the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1996). Based on the results of our work and others since then (Goff et al., 2018; Helfer et al., 2016), negative symptoms measured by the Scale for the Assessment of Negative Symptoms (SANS) modified by elimination of items measuring inattention and inappropriate affect (Blanchard and Cohen, 2006) was elevated from a secondary outcome to a co-primary outcome and DUP was added as a potential predictor of response. Because the study was not powered for two co-primary outcomes, we maintained the threshold for significance at p = .05 and hence each primary outcome is exploratory. Because the withholding of antidepressant from FES patients with major depression in a placebo-controlled design was considered unethical, individuals with greater than moderate depression at screening were excluded and the focus was on response of mild-to-moderate depressive symptoms and on the prevention of new or worsening depressive symptoms using an area-under-the-curve (AUC) analysis. Other outcomes included prevention of relapse defined by hospitalization, increased frequency of visits, or a 25% increase in Brief Psychiatric Rating Scale (BPRS) total score, suicidal ideation measured by the International Suicide Prevention Trial Scale for Suicidal Ideation (ISSI) (Alphs et al., 2004), cognition measured by the MATRICS Consensus Cognitive Battery (MCCB) composite score (Nuechterlein and Green, 2006), and quality of life measured by the Henrichs Carpenter Quality of LifeScale (QLS) (Heinrichs et al., 1984).

2.1.2. Study setting and participants

The protocol for the Depression and Citalopram in First Episode Recovery (DECIFER) Study (ClinicalTrials.gov: NCT01041274), was approved by IRBs at the four participating sites: New York University Medical Center, the Massachusetts General Hospital, Shanghai Mental Health Center, and the Second Xiangya Hospital of Central South University, Changsha; all participants provided written informed consent. A sample size of 100 participants was estimated to provide 80% power to detect a clinically-significant effect size of 0.6 for citalopram versus placebo with a 10% attrition rate and 76% power with a 40% attrition rate assuming a constant hazard of loss to follow-up and 80% of treatment efficacy achieved by week 8. Enrollment began in January 2010 and was completed in December 2014. Eligibility criteria included a first episode of schizophrenia or schizophreniform disorder based on the Structured Clinical Interview for DSM IV-TR (SCID) (First, 1994), ages 15–40, onset of psychosis before age 35, cumulative antipsychotic treatment for at least 4 weeks and fewer than 24 weeks, no antidepressant treatment within four weeks, a score <7 on the CDSS, (6 is a threshold for probable major depression) (Addington et al., 2014), and a score <3 (moderate) on the Clinical Global Impression Scale for Severity of Suicidality (CGI-SS) (Lindenmayer et al., 2003). In addition, participants had to have been free of substance abuse (except cannabis) for 3 months, not have unstable medical illness, and have a QTC <500 msec.

2.1.3. Screening and assessments

A research psychiatrist reviewed psychiatric and medical history and performed a physical exam, including EKG, routine screening labs, urine toxicology screen and pregnancy test. DUP was estimated based on history provided by the participant and by family members and was defined as the number of weeks elapsed since the onset of at least one persistent psychotic symptom of moderate or greater severity prior to initiation of antipsychotic medication. Symptoms and side effects were assessed weekly for the first 4 weeks, then every 4 weeks, with the BPRS, SANS, CDSS, ISS, QLS, and the Systematic Assessment for Treatment-Emergent Events (SAFTEE) (Levine and Schooler, 1986). Cognition was assessed at baseline and weeks 26 and 48 with the MCCB. Medication adherence was rated at every visit according to participant self-report using the Brief Adherence Rating Scale (BARS) (Byerly et al., 2008). Raters at all sites were trained in-person on all rating scales and in the administration of the MCCB and met inter-rater reliability criteria on three videotaped interviews for the BPRS, SANS and CDSS. Raters were required to score within one point on each item and to maintain an inter-rater correlation of $r > 0.8$ with the "gold standard" total scores. Ratings of videotaped interviews with the BPRS, SANS and CDSS were reviewed by conference call every 3 months and in-person trainings were repeated annually to maintain inter-rater reliability and proficiency in the administration of the MCCB. In addition, structural MRI scans were acquired at baseline, 24 weeks and 48 weeks; results will be reported separately.

2.1.4. Randomization and masking

Participants remained on their clinician-determined second generation antipsychotic and were randomized to add-on citalopram or placebo in a 1:1 ratio stratified by site. Within each stratum, the sequence of treatment assignments was constructed by a statistician using permuted random blocks with variable block sizes and study drug and placebo were prepared in identical capsules and labelled by a research pharmacist. All other research personnel remained blinded until the end of the study.

2.1.5. Study drug

Citalopram was initiated at a dose of 20 mg once daily and increased after one week to a target dose of 40 mg if tolerated. Dose adjustment within a range of 10–40 mg daily was allowed during the trial based on clinical assessment of side effects. Subjects were assessed by a psychiatrist every week for the first four weeks and then every two weeks thereafter.

2.1.6. Psychoeducation

All participants received 16 sessions of weekly, individual psychoeducation and relapse prevention planning followed by 8 monthly sessions. The intervention was provided by a doctoral level

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clinician with extensive experience treating individuals with first episode psychosis.

2.1.7. Cognitive–behavioral therapy (CBT)

Participants who scored 3 (moderate suicidality) on the CGI-SS or 7 or greater on the CDSS at any point during the trial were treated with a standard 12 session CBT approach to depression (Padesky and Greenberger, 1995). Participants who continued to meet these criteria after 4 weeks or who scored a 4 (severe) or higher on the CGI-SS or 10 or greater (severe) on the CDSS were dropped from double-blind treatment and could be openly prescribed an antidepressant.

2.1.8. Statistical analysis

The primary analyses tested the differential effect of citalopram versus placebo on depressive and negative symptoms using an intent-to-treat linear mixed model of CDSS and SANS with AUC as the primary outcome measures (eAppendix 1). The model included fixed terms for the treatment × visit interaction, with visit treated as a categorical variable. A spatial-power covariance structure indexed by time between visits was used to account for intra-subject correlations. The model was fitted using data from all available visits, and AUC was estimated and tested by the trapezoidal rule, using a linear contrast and Wald test. The same modeling strategy was applied to secondary outcomes, when applicable.

In order to address the large, nonrandom attrition rate, the linear mixed model with AUC analysis of observed data was repeated with multiple imputation for the SANS total score. The sequence of information used for imputation was: country (CHINA/USA), baseline results, DUP, treatment arm and all post-baseline visit results sorted by visit. Fifteen imputed data sets were used for multiple imputation analyses. Multiple imputation could not be used for analysis of the CDSS due to a highly skewed distribution bounded by 0.

In order to explore potential effect modifiers (predictors of response), a mixed effect model incorporating time trajectory was developed (eAppendix 2). Log scale of time (visit in weeks) was used in addition to linear time scale in order to capture the non-linear time trajectory. Linear scale time, log scale time, and three-way interaction between treatment arm, log scaled time and effect modifier was included as a predictor, which captures the effect modification activities. Subject-level random linear time and log scale time were included in the model, and the two random effects were assumed to be correlated. The same spatial-power covariance structure used in the AUC analysis was applied to allow additional correlations in residuals. To estimate effect sizes, a last observation carried forward imputation was carried out for all subjects with at least one post-baseline SANS measurement and the change from baseline between treatment groups compared by a two-sample *t*-test. All analyses were performed using SAS version 9.3.

3. Results

One hundred twenty-nine participants were screened, 95 were randomized (49 to citalopram and 46 to placebo), 73 completed assessments at 6 months and 52 completed 12 month assessments (Fig. 1). Completion rates did not differ between placebo (59%) and citalopram (51%) groups. The mean daily dose of citalopram was 35.8 [8.2] mg and of placebo was 36.3 [7.9] mg; adherence rates were 89.3% and 92.4% respectively. The mean antipsychotic dose in chlorpromazine equivalents was 374 [179] mg/d (eTables 1 & 2). Participants assigned to citalopram did not differ at baseline from participants assigned to placebo (Table 1), whereas completers had lower baseline total scores on the SANS and BPRS and scored higher on the MCCS compared to non-completers (Table 1).

3.1. Outcomes

The mixed effects AUC analysis revealed a significant reduction in ratings of depression (CDSS) in the placebo group compared to the citalopram group ($p = .02$) (Table 2, Fig. 2). "Remission" rates defined as a week 24 CDSS score ≤ 1 did not differ between citalopram (27/37; 73%) and placebo (25/35; 71%) ($p = .88$). Three (6.1%) of the citalopram group and 4 (8.7%) of the placebo group scored ≥7 on the CDSS during the course of the trial ($p = .63$).

The mixed effects AUC analysis using observed data revealed a trend for greater reduction in the SANS with citalopram compared to placebo ($p = .05$) (Fig. 3) and a significant reduction when multiple imputed values were used for missing data ($p = .04$). Among the four SANS subscales, only the avolition subscale was significantly improved with citalopram versus placebo ($p = .002$). Change from baseline in total score on the QLS, the BPRS total score, the BPRS psychosis subscale and the composite score of the MCCB did not differ between treatments (Table 2). Eight relapse events occurred in 6 (12.2%) of the citalopram group and 2 events occurred in 2 (4.3%) of the placebo group ($p = .27$) (eTable 3).

3.2. Moderators of response

Based on the mixed effect model incorporating time trajectory, DUP was significantly associated with response of SANS at 52 weeks in the placebo group ($p = .03$) but not in the citalopram group ($p = .65$) such that shorter DUP predicted greater placebo response. The estimated effect size of citalopram versus placebo on response of SANS total was 0.32 for participants with a DUP of <18 weeks (median split) and 0.52 for participants with a DUP >18 weeks. Higher baseline SANS total scores based on a median split were associated with a greater difference in SANS response between treatment groups, favoring citalopram (eTable 4). Baseline antipsychotic dose was negatively correlated with the reduction in the CDSS but was not significantly associated with reduction in SANS scores (eTable 5).

3.3. Tolerability

Three participants withdrew from study due to side effects; two placebo-treated participants due to weight gain and one citalopram-treated participant due to blurry vision. The mean total number of treatment-emergent side effects per participant rated as mild or greater was 2.3 [1.8] in the citalopram group vs. 4.8 [3.4] in the placebo group ($p = .05$). Side effects that were reported by >5% of participants and that occurred more frequently in citalopram-treated participants included loss of sexual interest, problems with sexual arousal, and delayed or absent orgasm (eTable 6).

4. Discussion

The citalopram group exhibited less improvement in depressive symptoms compared to placebo, but the difference was small and decreased over time and the mean level of depressive symptoms at baseline was mild. In addition, because only 9% of the placebo group developed clinically-significant depression over the course of the 52 week trial, statistical power to assess efficacy for the prevention of depressive episodes was very limited. Studies of individuals with later-stage schizophrenia suggest that antidepressants are more effective for prominent and persistent depression than for mild or recent-onset depressive symptoms (Helfer et al., 2016) and in a recent meta-analysis only negative symptoms and not depression in individuals with schizophrenia improved with antidepressant (Galling et al., 2018). Two studies in FES patients found antidepressant benefit for the norepinephrine reuptake inhibitor, reboxetine (Poyurovsky et al., 2007; Poyurovsky et al., 2003), raising the question of whether noradrenergic agents might be more effective than citalopram. Superiority

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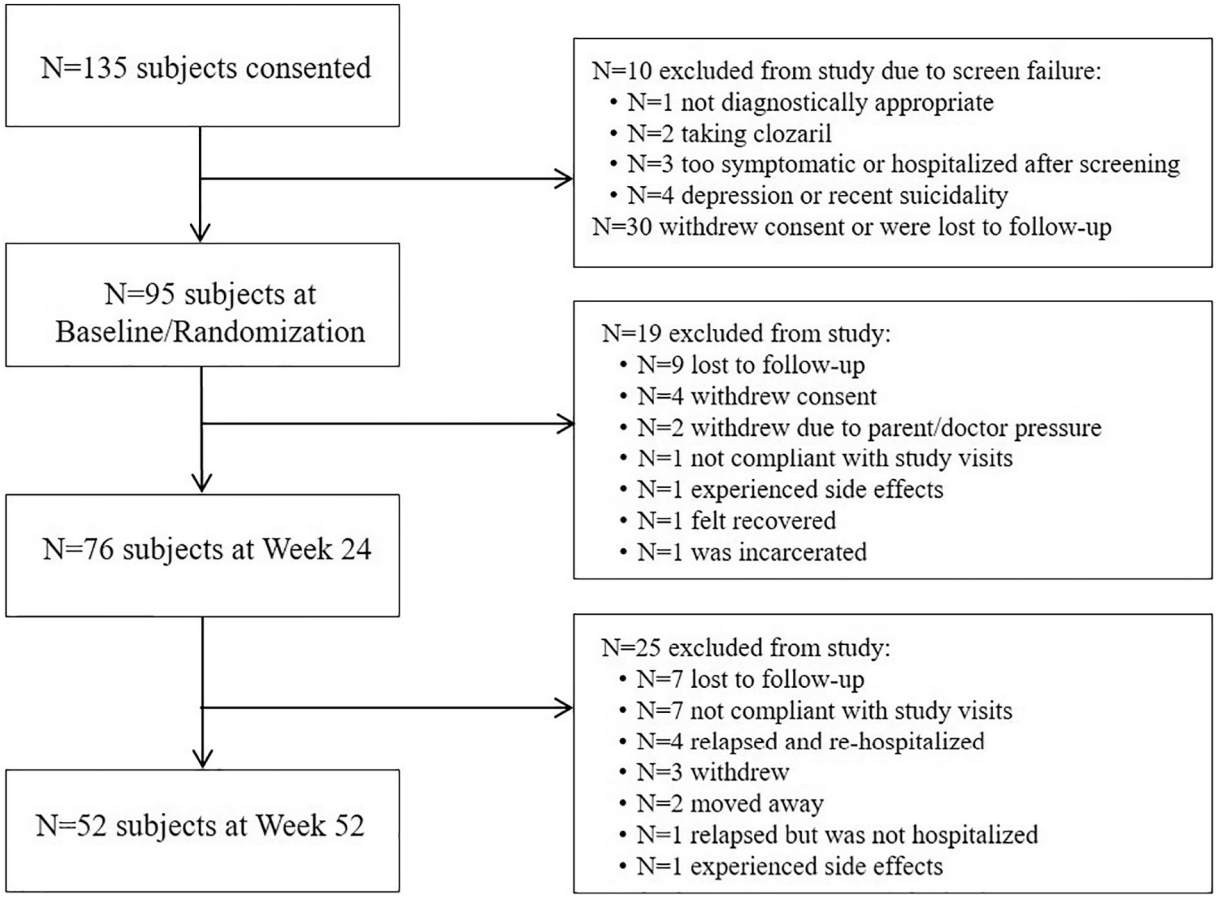

Fig. 1. Consort diagram.

of reboxetine over SSRIs for depression was not found, however, in a meta-analysis of antidepressant trials that included both FES and chronic schizophrenia patients (Helfer et al., 2016). In the RAISE-ETP study, antidepressants were not prescribed for subsyndromal depressive symptoms in the enhanced treatment group. The enhanced treatment group thus received fewer antidepressants than the treatment-as-usual group, yet the enhanced treatment group had a greater reduction in depressive symptoms (Kane et al., 2016). While our results do not support a role for citalopram for mild or moderate depressive symptoms in FES or for the prevention of more severe depressive episodes, the role of antidepressants for more severe depression in FES requires further study.

We did detect a therapeutic benefit of citalopam for negative symptoms; this effect was on the cusp of significance ($p = .05$) with the prespecified AUC analysis and achieved significance ($p = .04$) when we repeated the AUC analysis with multiple imputation, which may better model missing data due to the nonrandom, high rate of attrition (Rubin, 1996). However, because we did not correct for multiple comparisons, this finding must be considered exploratory. The improvement in negative symptoms was restricted to the avolition/apathy subscale of the SANS. Avolition previously has been found to be the

Table 1
Baseline characteristic of participants.

	All randomized participants - baseline						All completers vs. non-completers - baseline					
		Placebo		Citalopram	Test statistic			Non-completers		Completers	Test statistic	
	N	M (SD)	N	M (SD)	$t/\chi^2(df)$	p value	N	M (SD)	N	M (SD)	$t/\chi^2(df)$	p value
Age	45	23.69 (4.63)	49	23.2 (5.09)	$t(92) = 0.482$	*.63*	43	23.65 (5.08)	51	23.25 (4.69)	$t(92) = 0.393$	*.67*
Race												
White (%)	46	13 (28.3)	49	16 (32.7)	$\chi^2(8) = 1.87$	*.60*	44	13 (29.5)	51	16 (31.4)	$\chi^2(8) = 8.05$	*.04*
Black		8 (17.4)		4 (8.2)				10 (22.7)		2 (3.9)		
Asian		23 (50.0)		27 (55.1)				19 (43.2)		31 (60.8)		
Other		2 (4.3)		2 (4.1)				2 (4.5)		2 (3.9)		
Women, no. (%)	46	18 (39.1)	49	17 (34.7)	$\chi^2(4) = 3.149$	*.53*	44	14 (31.8)	51	21 (41.2)	$\chi^2(4) = 3.85$	*.43*
Education	45	12.44 (2.50)	49	12.71 (2.43)	$t(92) = -0.53$	*.60*	43	12.51 (2.41)	51	12.65 (2.51)	$t(93) = -0.92$	*.36*
Parental education	37	12.00 (3.34)	42	11.55 (3.65)	$t(77) = 0.572$	*.57*	32	11.38 (3.49)	47	12.02 (3.50)	$t(77) = -0.806$	*.42*
DUP (weeks)	42	29.36 (39.79)	45	53.71 (90.06)	$t(61.4) = -1.65$	*.10*	38	40.50 (69.80)	49	43.08 (72.78)	$t(71) = -0.167$	*.87*
BPRS total score	45	37.96 (9.26)	46	39.0 (11.49)	$t(89) = -0.477$	*.64*	40	41.12 (11.62)	51	36.41 (8.92)	$t(89) = 2.19$	*.03*
SANS total score	45	18.91 (12.08)	46	21.37 (14.25)	$t(89) = -0.887$	*.38*	40	23.40 (14.36)	51	17.61 (11.74)	$t(89) = 2.12$	*.04*
CDSS total score	45	2.58 (2.99)	46	1.83 (1.79)	$t(89) = 1.46$	*.15*	40	2.37 (2.44)	51	2.06 (2.52)	$t(89) = 0.60$	*.55*
QLS total score	46	75.85 (23.19)	49	71.53 (25.95)	$t(93) = 0.853$	*.40*	44	68.41 (25.46)	51	78.12 (23.17)	$t(93) = -1.95$	*.06*
MCCB composite	44	32.14 (16.26)	48	34.23 (12.97)	$t(90) = -0.685$	*.50*	43	29.09 (14.01)	49	36.86 (14.25)	$t(90) = -2.63$	*.01*

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Table 2
Change from baseline in efficacy outcomes.

	Difference[a]	Standard error	t (df)	p-Value
Outcome				
Calgary Depression Scale (CDSS)	−0.7048	0.3027	−2.33 (912)	*.02*
Quality of Life Scale (QLS)	−4.0537	3.3806	−1.20 (520)	*.23*
MCCB Composite Score	0.4960	1.5647	0.32 (31)	*.75*
BPRS Total Score	0.7894	1.6042	0.49 (640)	*.62*
BPRS Psychosis Subscale Score	0.0754	0.8161	0.09 (641)	*.93*
SANS total score	3.3046	1.7042	1.94 (704)	*.05*
SANS subscales				
SANS Affective Flattening Subscale	0.6464	0.8762	0.74 (706)	*.46*
SANS Alogia Subscale	0.3436	0.3838	0.90 (706)	*.37*
SANS Avolition Subscale	1.6873	0.4542	3.71 (706)	*.002*
SANS Anhedonia Subscale	0.4925	0.5655	0.87 (706)	*.38*

[a] Difference is calculated as placebo group mean – citalopram group mean. The difference is estimated using the AUC under a mixed effect model. The estimate of each difference is a weekly average over the 52 weeks of study period. Negative values indicate decrease from baseline.

strongest predictor of functional outcomes in first episode schizophrenia patients at 12 month follow-up (Chang et al., 2016). Because depressive symptom ratings were low at baseline and improved more with placebo than citalopram, it is likely that citalopram's benefit for negative symptoms was a primary effect and not secondary to an antidepressant response. Response of negative symptoms did correlate at a trend level ($p = .09$) with response of psychotic symptoms at week 52, although response of psychotic symptoms did not differ between treatment groups (Table 2; eTable 7).

The benefit of citalopram over placebo for negative symptoms was greater in participants with long DUP. The effect size of response to citalopram versus placebo in participants with a DUP less than the median split of 18 weeks was 0.32 versus an effect size of 0.52 in participants with a longer DUP. This finding reflects a DUP effect on placebo response and not on citalopram response; participants with long DUPs did not respond to placebo but did respond to citalopram, whereas participants with short DUPs responded similarly to both placebo and citalopram. In the RAISE-ETP study, superior response to the NAVIGATE treatment program compared to treatment as usual was observed in participants with a shorter DUP only (Kane et al., 2016). Like the psychosocial interventions in NAVIGATE, the frequent staff interactions and weekly individualized psychoeducational sessions in the DECIFER trial created a relatively enhanced psychosocial experience for some participants that may have contributed to the placebo response. Recent evidence suggests that antidepressants may act in part by increasing plasticity, thereby facilitating brain reorganization in response to enriched environmental stimulation (Castren, 2013). It is possible that patients with longer DUP may lack the plasticity to respond to enhanced environmental stimulation and may benefit from a combination of an antidepressant and a rehabilitation program.

Citalopram was well tolerated, with side effects limited to sexual complaints. Sexual dysfunction is common in schizophrenia, possibly related to both the illness and to antipsychotic medication, and can adversely affect quality of life and treatment adherence (de Boer et al., 2015; Drake et al., 2015) and so the increased risk of sexual side effects with supplemental SSRI treatment should be closely monitored. The addition of antidepressants to antipsychotics in individuals with schizophrenia has been well tolerated in previous controlled add-on trials (Galling et al., 2018; Helfer et al., 2016) and was associated with reduced mortality by suicide in a large registry-based case linkage study (Tiihonen et al., 2012). However, two previous studies reported an apparent inhibition of antipsychotic response associated with early antidepressant treatment (Kramer et al., 1989; Poyurovsky et al., 2002). We did not observe a worsening in psychosis, although participants in the DECIFER trial had been stabilized on antipsychotic prior to initiating citalopram. Citalopram was associated with an increase in relapse (odds ratio = 3.0) but, due to the low frequencies of this event (12% vs 4.3%), the confidence intervals for the odds ratio were quite wide [0.51–32.4] and the difference was not statistically significant. It should be noted that citalopram was selected for the DECIFER trial because it does not affect metabolism of antipsychotic drugs and participants were carefully screened to minimize the risk of adverse cardiac effects. Citalopram has been linked to cardiac arrhythmia at daily doses above 40 mg, although the clinical risk remains uncertain (Vieweg et al., 2012).

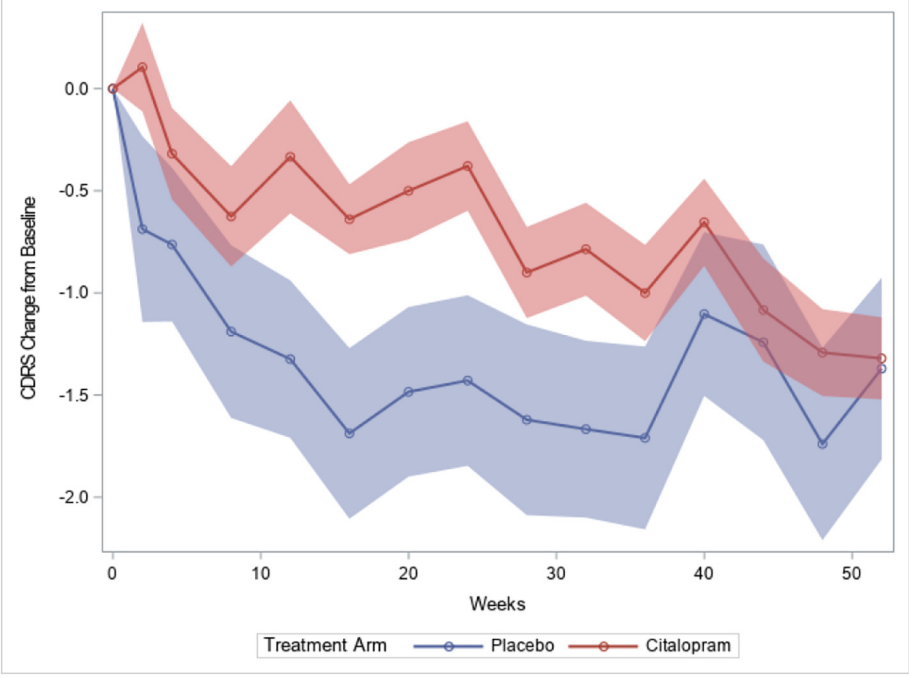

Fig. 2. Effect of citalopram vs. placebo on depression (CDSS) in observed cases.

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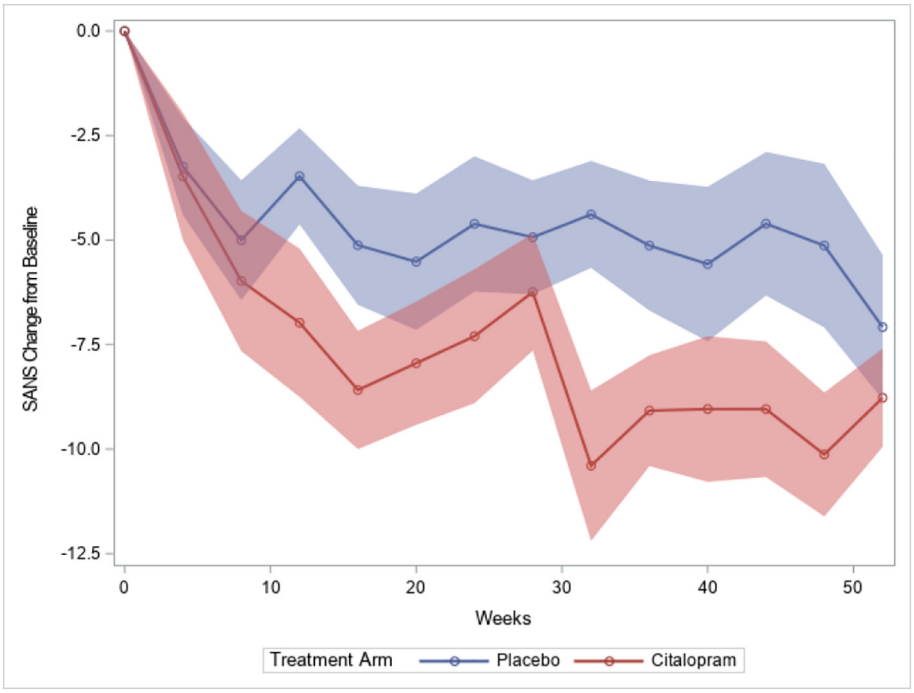

Fig. 3. Effect of citalopram versus placebo on negative symptoms (SANS) in observed cases.

4.1. Limitations

High attrition rates limited our statistical power to assess efficacy and safety and to identify moderators of response. The observed therapeutic benefit of citalopram for negative symptoms is exploratory since we did not correct the threshold of significance for the addition of a second primary outcome. It is also of uncertain clinical significance since we did not observe a change in global outcome measures. Our assessment of antidepressant efficacy was limited to the treatment of mild-to-moderate symptoms at baseline and our assessment of citalopram's efficacy in the prevention of clinically significant depression was limited by the low incidence of new onset depression during the 52 week trial. The small but statistically significant greater improvement in depression associated with placebo is unlikely to be of clinical significance. Finally, replication with a larger sample is needed to establish safety and efficacy of citalopram in FES.

5. Conclusion

In FES patients stabilized on antipsychotic medication for 4–24 weeks and no greater than moderate depressive symptoms at baseline, add-on citalopram was associated with greater improvement of negative symptoms, especially in participants with long DUP. Placebo was associated with greater improvement in depression but this effect was small and of uncertain clinical significance. Rates of new-onset depression were too low to assess a role for citalopram in the prevention of depressive episodes. Citalopram was well-tolerated, except for sexual side effects.

Conflict of interest

All authors report no conflict of interest in the past three years.

Contributors

Dr. Donald Goff designed the study, obtained funding and wrote the initial draft of the paper. Dr. Oliver Freudenreich, Dr. Jijun Wang & Dr. Jingping Zhao were site principle investigators. Chenxiang Li and Dr. Andrea Troxel provided statistical analysis. All authors have contributed to and approved the final manuscript.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.01.028.

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