



## PSYCHOPHARMACOLOGY

# A Pilot Study of Citalopram Treatment in Preventing Relapse of Depressive Episode after Acute Treatment

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## Abstract

**Purpose:** To examine the benefit of continuation treatment with citalopram in adolescents 13 to 18 years of age with major depression using a multi-site randomized placebo controlled discontinuation design. **Methods:** Subjects with depression who responded to open label treatment with citalopram in 12-week acute phase were randomized to continued treatment with citalopram or placebo for 24 weeks. **Results:** Twenty five subjects were randomized to either continued treatment with citalopram ( $n = 12$ ) versus placebo ( $n = 13$ ). Seventy-five percent of subjects on citalopram (75%) remained well as compared to placebo (62%). Time to relapse was compared between groups using the log rank test and was not found to be significantly different ( $\chi^2(1) = 0.35$ ,  $P = 0.55$ ). A Cox proportional hazards model including drug assignment (hazard ratio ( $HR = 0.51$ , 95% CI 0.11 to 2.36,  $P = 0.39$ ), gender ( $HR = 0.58$ , 95% CI 0.14 to 2.37,  $P = 0.44$ ), or HAM-score at entry to continuation phase ( $HR = 1.33$ , 95% CI 0.90 to 1.95,  $P = 0.95$ ) was not significant. **Conclusion:** Although we did not find statistically significant differences between citalopram and placebo, the findings suggest a possible benefit of continued treatment with citalopram over placebo. A larger clinical trial with adequate power is required to confirm or disconfirm these findings.

**Key Words:** adolescents, depression, antidepressants, citalopram

## Résumé

**Objectif:** Examiner l'avantage d'un traitement de stabilisation par citalopram chez des adolescents de 13 à 18 ans souffrant de dépression majeure au moyen d'un essai d'arrêt randomisé, multicentrique et contrôlé contre placebo. **Méthodes:** Les sujets souffrant de dépression qui ont répondu au traitement avec étiquetage en clair par citalopram durant une phase aiguë de 12 semaines ont été randomisés dans le traitement de stabilisation par citalopram ou placebo durant 24 semaines. **Résultats:** Vingt-cinq sujets ont été randomisés dans un traitement de stabilisation soit par citalopram ( $n = 12$ ), soit contre placebo ( $n = 13$ ). Soixante-quinze pour cent des sujets traités par citalopram (75%) sont demeurés sans rechute comparativement à ceux du placebo (62%). Le délai avant la rechute a été comparé entre les groupes à l'aide du test de Mantel-Haenzel et n'était pas significativement différent ( $\chi^2(1) = 0,35$ ;  $P = 0,55$ ). Un modèle de risques proportionnels de Cox incluant l'assignation des médicaments (rapport des risques ( $RR = 0,51$ ; IC à 95% 0,11 à 2,36;  $P = 0,39$ ), le sexe ( $RR = 0,58$ ; IC à 95% 0,14 à 2,37;  $P = 0,44$ ), ou le score à l'échelle HAM au départ jusqu'à la phase de stabilisation ( $RR = 1,33$ ; IC à 95% 0,90 à 1,95;  $P = 0,95$ ) n'était pas significatif. **Conclusion:** Bien que nous n'ayons pas observé de différences statistiquement significatives entre le citalopram et le placebo, les résultats suggèrent un avantage possible du traitement de stabilisation par citalopram plutôt que placebo. Il faut un essai clinique plus vaste de puissance adéquate pour confirmer ou infirmer ces résultats.

**Mots clés:** adolescents, dépression, antidépresseurs, citalopram

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Treatment for depression is often divided into three phases: the first eight to 12 weeks is considered acute therapy; treatment from acute recovery up until six months is considered continuation therapy; and, treatment beyond six months is considered maintenance therapy. Recent meta-analyses examining the efficacy of antidepressant treatment for adolescent depression suggest that treatment of depressed adolescents with antidepressants is an effective means of providing relief from acute symptomatology. Despite the growing literature on acute treatment of adolescent depression with antidepressants, there are little data from controlled trials on long-term treatment with antidepressants (Bridge, Salary, Birmaher, Asare, & Brent, 2005). The Practice Parameters published by the American Academy of Child and Adolescent Psychiatry suggests continuation therapy is necessary in all patients after the acute phase (Birmaher & Brent, 2007). Extrapolation from the adult literature also suggests that a significant proportion of depressed patients not continued on treatment beyond acute treatment are at greater risk of relapse/recurrence (Frank et al., 1991; Franchini, Zanardi, Gasperini, & Smeraldi, 1999). Although virtually all guidelines for the treatment of adolescent depression recommend that treatment continue beyond the acute phase, only one randomized trial has examined the efficacy of continuation antidepressant therapy for depression in adolescents. In 2008, Emslie et al. reported the results of the only continuation study in children and adolescents involving 168 depressed children and adolescents aged seven to 18 years. After 12 weeks of open treatment with fluoxetine, 102 participants were randomly assigned to continuation treatment with fluoxetine or placebo. Significantly fewer participants on fluoxetine relapsed (42%) compared with participants in the placebo group (69%). Time to relapse was also significantly shorter in the placebo group (Emslie et al., 2008). Emslie and colleagues also examined for possible influence of gender and residual symptoms on the likelihood of relapse during continuation phase. Males were more likely to remain well on fluoxetine compared to females. Furthermore, participants who had at least one residual symptom after acute treatment were more likely to relapse during the continuation phase (Emslie et al., 2008; Emslie, Mayes, & Ruberu, 2005).

Although this trial demonstrated superiority of continued antidepressant treatment, it is unclear whether the results can be generalized to other antidepressants in the same putative class or whether fluoxetine alone is effective in continuation treatment. Citalopram was used in this study because at the time the study commenced it had just been introduced and was quickly becoming the most widely prescribed antidepressant in Canada for this age group. This trial was designed as a randomized controlled trial of continuation treatment of citalopram in adolescents with depression.

## Methods

Subjects 13 to 18 years of age were recruited, over three years (2003 to 2006), at mood disorders clinics in four tertiary care centres across Canada. Informed consent was obtained from eligible and interested subjects and parents (if subject < 16 years of age). Subjects were eligible for entry into the study if they had a diagnosis of major depression determined from both clinical interview and the Schedule for Affective Disorders and Schizophrenia for Children Present and Lifetime (K-SAD-PL) and scored > 16 on the first 17 items of the 29-item Hamilton Rating Scale for Depression (HAM-D) (Chambers et al., 1985; Hamilton, 1960; Kaufman et al., 1997). Subjects were excluded if they had experienced a past or current hypomanic or manic episode, current psychotic symptoms, substance dependence in the last three months, a significant medical condition that would contraindicate the use of antidepressants or that if untreated may require medical attention, current pregnancy, or past treatment with citalopram for major depression.

There were two phases to the study:

- 1) a 12-week acute phase; and
- 2) a 24-week continuation phase. Initial citalopram dose during the acute phase was 10 mg daily with increases of 10 mg every two weeks at the treating clinicians' discretion, up to a maximum of 40 mg daily.

Subjects were assessed every two weeks throughout this phase. Those who responded to acute phase treatment, defined as two consecutive HAM-D scores < 9 and greater than a 50% reduction in HAM-D score within 12 weeks, were offered entry into the continuation phase.

Responders were entered into the continuation phase and were randomized to continue citalopram or to take placebo. Randomization was conducted by the study pharmacist using a computer generated randomization schedule. Subjects, clinicians and research staff remained blinded to treatment during the randomized continuation phase. During the continuation phase, no treatment changes were permitted. Subjects were assessed every two weeks except during the first four weeks when they were seen or contacted weekly. In this final phase, every second visit was also conducted in person while the other assessments could be conducted either by telephone or in person.

Relapse during the continuation phase was determined according to the clinical judgment of the treating physician or an intervention beyond what was permitted by the study protocol was required.

Inter-rater reliability for the HAM-D was tested annually with site project coordinators and research assistants.

Further training and evaluation were implemented until the inter-rater reliability was 0.8 or greater. As described above, relapse during the continuation phase was determined according to the clinical judgment of the treating physician or an intervention beyond what was permitted by the study protocol was required. The HAM-D score was not used to determine relapse or recurrence but HAM-D scores were available to the treating physician when determining clinical status. This clinical judgment was based on the presence of depressive symptoms and level of impairment. Unfortunately, it is virtually impossible to standardize the concept of clinical judgment. We chose it as a pragmatic outcome that reflects what occurs in everyday clinical practice, and to ensure that clinicians felt free to make alterations in treatment in this susceptible population.

Survival analyses were conducted based on the primary outcome (time to clinical recurrence) in the continuation phase. Subjects who were randomized and who received at least one dose of citalopram/placebo were included in the analyses. A log rank test was run assessing for the effects of treatment assignment. A secondary survival analysis was run controlling for the possible influence of gender and residual symptoms after acute treatment (baseline HAM-D scores at entry to the continuation phase) on the likelihood of relapse during the continuation phase. All analyses were run using SAS version 9.1 (SAS Institute, Cary, NC, USA). All statistical analyses were conducted by an independent statistician blinded to patient allocation.

Adverse events were collected using the Common Adverse and Side Effects Scale (CASES). The scale was administered every two weeks during the acute phase and every four weeks during the continuation phase. The CASES did not include any suicidality items and no suicidality assessment instruments were included in the study. Therefore, worsening or new onset suicidality was captured only by spontaneous reporting by subjects. A structured suicide assessment tool was not used in this study as it was planned prior to the 2004 Health Canada and FDA Black Box warnings regarding SSRIs and suicidality.

## Results

In total, 59 subjects were recruited for this study. Forty-five subjects were female and 14 were male. The age range was 13 to 18 (mean 15.4 years). The mean (SD) HAM-D score at entry was 20.2 (4.7). A detailed description of patient flow and disposition is shown in Figure 1. Table 1 also shows the participants' baseline characteristics.

At the end of the acute phase, 25 subjects were eligible to enter the continuation phase and were randomized. There were no significant differences between the citalopram and placebo groups in terms of percentage female (Fisher's

Exact,  $P = 0.99$ ), mean age ( $t = 0.58$ ,  $P = 0.57$ ) or mean baseline HAM-D scores at entry to the acute phase ( $t = -0.43$ ,  $P = 0.63$ ) and at entry to continuation phase ( $t = 0.59$ ,  $P = 0.56$ ).

Nine of 12 subjects (75%) in the citalopram group remained well during the 24-week randomization phase. In contrast, eight of the 13 subjects (62%) on placebo remained well.

Time to relapse was compared between drug assignments using the log rank test and was not found to be significantly different ( $\chi^2(1) = 0.35$ ,  $P = 0.55$ ). A Cox proportional hazards model including drug assignment (hazard ratio (HR) = 0.51, 95% CI 0.11 to 2.36,  $P = 0.39$ ), gender (HR = 0.58, 95% CI 0.14 to 2.37,  $P = 0.44$ ), or HAM-D score at entry to continuation phase (HR = 1.33, 95% CI 0.90 to 1.95,  $P = 0.95$ ) did not produce any significant findings (Figure 2).

## Adverse Events

Five subjects (8.5%) discontinued the study during the acute phase due to adverse effects: nausea ( $n = 2$ ); rages ( $n = 1$ ); suicidal thoughts ( $n = 1$ ); and, mania ( $n = 1$ ). In addition, another subject discontinued due to worsening depression and suicidality. There were no spontaneous reports of new onset or worsening suicidality in any other subjects during the study. There were no serious adverse events reported during the course of the study. Adverse effects were reported by more than 40% of subjects at some point during the acute phase and these are shown in Table 2.

During the continuation phase, only one adverse effect, increased salivation, was numerically more likely to affect subjects on citalopram compared to those on placebo (> 5% difference). Similarly, there were several adverse effects that were numerically more likely to affect subjects on placebo compared to those on citalopram (> 5% difference) including inner tension, anxiety/worry, nausea/vomiting, palpitations, feeling disinterested/detached, and cough. Subjects in the two groups were compared for differences in the proportion experiencing these side effects using Fisher's exact tests. Subjects on placebo were significantly more likely to experience palpitations ( $P = 0.047$ ) and report feeling detached/disinterested compared to subjects on citalopram ( $P = 0.019$ ).

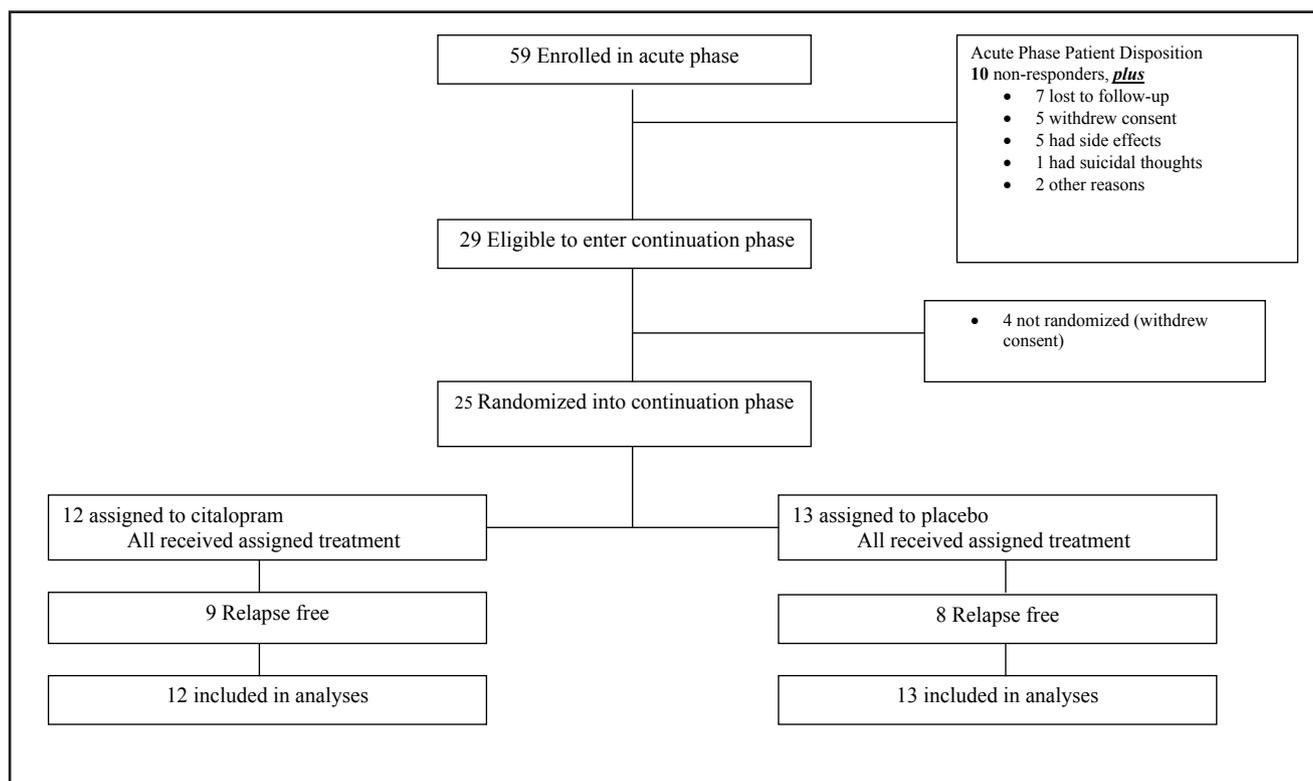
## Discussion

This study did not find statistically significant differences between citalopram and placebo in preventing relapse into depression in adolescents who responded to acute treatment with citalopram. Numerically, the group treated with citalopram after acute treatment was more likely to remain well

| Table 1. Baseline characteristics of participants in treatment groups |                    |                 |      |
|---|--------------------|-----------------|------|
|   | Citalopram<br>N=12 | Placebo<br>N=13 | P    |
| Age   | 15.17              | 15.46           | 0.57 |
| (SD)  | (1.27)             | (1.27)          |      |
| Female  | 7                  | 8               | 0.99 |
| (%)   | (58%)              | (62%)           |      |
| Acute Phase Entry HAM-D   | 20.67              | 19.85           | 0.63 |
| (SD)  | (4.38)             | (5.18)          |      |
| Continuation Phase Entry HAM-D  | 1.42               | 1.85            | 0.56 |
| (SD)  | (1.44)             | (2.12)          |      |

HAM-D = Hamilton Depression Rating Scale

Figure 1. Patient flow



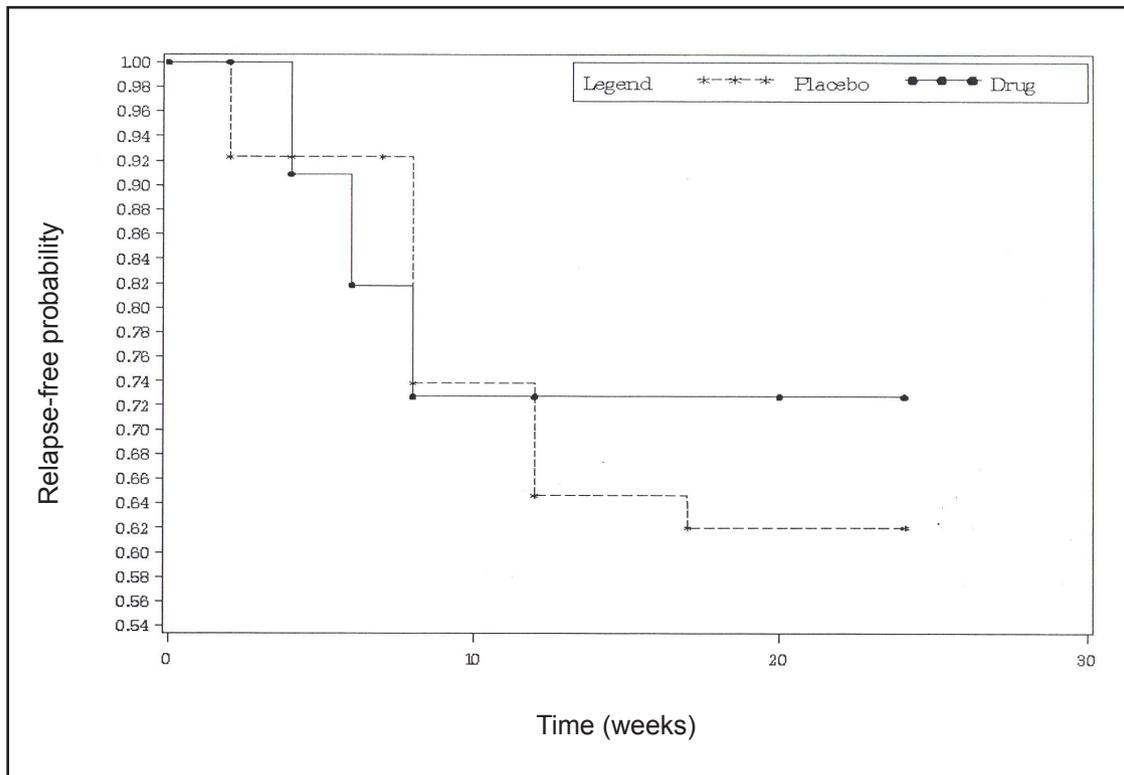
and this is consistent with the only previous continuation study (Emslie et al., 2008).

Unlike the previous study, we did not find that gender significantly influenced the risk of relapse during the continuation phase. This finding is consistent with other treatment trials of antidepressants in adolescents and with the only maintenance treatment trial for adolescent depression (March et al., 2004; Brent et al., 2008; Brent et al., 2009; Cheung et al., 2008). Furthermore, Emslie's finding that males are more responsive to continued fluoxetine treatment may

have resulted from an imbalance in gender between treatment groups as well as differences in age between males and female participants, as has been suggested by the study authors themselves (Emslie et al., 2008).

In general, citalopram was found to be well tolerated with few serious adverse effects. One interesting finding is the higher rate of physical side effects experienced by adolescents taking placebo compared to those taking citalopram during the continuation phase. These physical symptoms

**Figure 2. Survival curve for continuation phase**



**Table 2. Adverse effects during acute phase**

Acute phase (Reported by >40% of subjects)

- Fatigue (62.7%)
- Drowsiness (57.5%)
- Irritability (54%)
- Headaches (47.5%)
- Feeling disinterested/detached (44.1%)
- Excitement or agitation (42%)
- Insomnia (40.7%)

could be a result of withdrawal from citalopram or simply a re-emergence of the symptoms of depression.

A significant limitation of this trial is the small sample size, which may have affected our ability to detect real differences between the two groups. However, the findings are numerically consistent with previous treatment trials. The low power to detect differences means that these results can neither confirm nor refute the assertion that SSRIs, in this case citalopram, are effective in preventing relapse after acute antidepressant response in adolescents.

Although we did not find statistically significant differences between citalopram and placebo, the findings suggest a possible benefit of continued treatment with citalopram over placebo. A larger clinical trial with adequate power is required to confirm or disconfirm these findings. Future trials should use strategies to enhance recruitment and retention. The first author and colleagues have outlined these strategies for the Canadian setting in a previous publication (Furimsky, Cheung, Dewa, & Zipursky, 2008).

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