A Randomized Controlled Trial of Antidepressant Continuation for Major Depression Following Traumatic Brain Injury

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Objective: This study examines whether continuation therapy with citalopram can prevent a relapse following remission of major depression due to traumatic brain injury.

Method: After 65 subjects with *DSM-IV*–diagnosed major depression following traumatic brain injury were treated with open-label citalopram (20 mg to 50 mg/d), 25 subjects (38.5%) met criteria for remission. Of those, 21 (84.0%) were randomly assigned to either same-dose citalopram or placebo and followed monthly over 40 weeks. Remission was defined as a Hamilton Depression Rating Scale (HDRS) score of ≤ 7 or a Clinical Global Impressions-Improvement rating of "much improved" or better. The main outcome variable was the presence of relapse, as defined by meeting criteria for major depressive episode according to the *DSM-IV* and an HDRS score ≥ 16. Data were collected from February 16, 2005, to May 5, 2008.

Results: Ten subjects were randomly assigned to citalopram and 11 to placebo. There were 3 dropouts, including 1 for adverse drug effects (diarrhea). Relapse occurred in 11 subjects (52.4%), with a mean ± SD time to relapse of 23.52 ± 16.6 weeks. The groups did not differ in relapse rates (drug: 50.0% [5/10] vs placebo: 54.5% [6/11], Fisher exact test, $P = .835$) or time to relapse (log rank test $\chi^2 = 0.148$, $P = .700$).

Conclusions: The present study suggests important limitations of continuation pharmacotherapy in the prevention of relapse of major depression following traumatic brain injury.

Trial Registration: clinicaltrials.gov Identifier: NCT00162916

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Major depression is the most commonly cited disorder following traumatic brain injury (TBI), present in approximately one-third of individuals within the first year postinjury.[1,2] Major depression after TBI has been associated with a less favorable recovery, including greater cognitive impairment,[3] prolonged postconcussal symptoms,[4] reduced benefit from rehabilitation,[5] and poorer psychosocial adjustment.[5–9]

Despite the heightened morbidity among TBI patients who develop depression, there is a paucity of research concerning its treatment. Clinical experience suggests that selective serotonin reuptake inhibitors (SSRIs) are useful in this population.[10,11] Nonetheless, published studies to date of SSRIs among TBI patients with depression are limited to 5 open-label studies[12–16] and 2 small controlled studies.[17,18]

There have been many studies to date in the non-TBI population that strongly demonstrate the prophylactic efficacy of antidepressants in preventing a relapse of depression following an initial response.[19–24] As a result, continuation or maintenance treatment is now typically recommended for those with primary depressive disorders, particularly if the illness is recurrent.[25] Whether this is appropriate for depression in the setting of TBI is unknown.

While continuation or maintenance antidepressants prevent relapse of major depression in the highly recurrent primary depressive disorders, the course of depression following TBI is more variable and likely of shorter duration.[7,26] It is, thus, clearly worth examining the need for ongoing antidepressant treatment in TBI after remission. At present, there are no studies examining the role of continuation or maintenance antidepressants in preventing relapse of depression following TBI, once remission has been achieved.

We previously conducted an open-label study examining the effectiveness of SSRI treatment for patients with depression following mild to moderate TBI.[15] In that study of acute treatment, 65 subjects with major depression were given citalopram, a prototypical SSRI, which was chosen based on its tolerability, ease of dosing, and safety profile. After 10 weeks, we observed a response rate of 46.2% and a remission rate of 26.9%. Notably, these results were quite similar to those from the recent Sequenced Treatment Alternatives to Relieve Depression trial, which evaluated the effectiveness of citalopram among 2,876 subjects with primary depression.[27] Our open-label study of acute treatment served as the preliminary phase for the current study. The aim of the present continuation study was to examine the efficacy of citalopram in preventing a relapse of major depression following TBI once remission had been achieved.

METHOD

Subjects

Twenty-five of 65 subjects (38.5%) from an open-label study of citalopram for the treatment of major depression following TBI[15] met criteria for remission and were asked to participate in the present study of continuation treatment. Twenty-one subjects (84%) were randomly assigned

to either citalopram or placebo for 40 weeks. Four subjects declined to take part in the current study, as they preferred to continue taking citalopram rather than risk possible randomization to placebo.

Before entry into the initial open-label study, all subjects met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[28] criteria for "major depression secondary to TBI, with a major depressive–like episode" within 1 year of their TBI. All subjects were assessed by a psychiatrist using the depression module of the Structured Clinical Interview for *DSM-IV* Axis I disorders[29] and had a baseline 17-item Hamilton Depression Rating Scale (HDRS) score of 16 or greater[30,31] (ie, prior to open-label citalopram treatment). Traumatic brain injury severity was defined according to commonly used criteria, with mild TBI defined by an initial Glasgow Coma Score (GCS) of 13–15, posttraumatic amnesia duration < 24 hours, and an initial loss of consciousness of ≤ 20 minutes.[32] Moderate-to-severe TBI was defined as a GCS < 13 and a posttraumatic amnesia duration ≥ 24 hours.[33] Subjects with otherwise "mild" parameters who had focal TBI-related findings on CT scan were classified as moderate.[33] We excluded any subjects with a prior history of nontrivial TBI prior to the presenting TBI; other focal brain diseases (eg, stroke or tumor); or a diagnosis of schizophrenia, dementia, or bipolar disorder, as well as any subjects who had prior treatment with citalopram. The study was approved by the local research ethics board, and all subjects provided written, informed consent.

Study Design

The study was a randomized, double-blind placebo-controlled continuation trial. Twenty-one subjects in remission following flexible-dose, open-label treatment with citalopram were randomly assigned either to continue citalopram or to switch to placebo. Although the initial open-label study[15] was of 10 weeks' duration, to assist with recruitment of subjects who had achieved remission, the duration of open-label treatment was extended to a mean of 16 weeks (SD = 7; range, 9–36), with only one-third of cases (33.8%) randomly assigned at 10 weeks. Subjects were randomly assigned according to a computer-generated code in blocks of 4. All study personnel and patients were blinded to treatment assignment for the duration of the study. Blinding was achieved by overencapsulation, in which citalopram was added to a gelatin capsule and back-filled with inert filler to prevent rattling. The placebo capsules were filled with the identical inert filler. Opaque gelatin capsules with interlocking shells were used to make it difficult to open without causing damage. The active and placebo capsules were visually identical and thus maintained the blind. Ten subjects were randomly assigned to citalopram (at the dose corresponding to their end-dose in the open-label trial), and 11 subjects were randomly assigned to placebo (citalopram gradually discontinued in the blinded capsules over a period of 2 weeks). Subjects were assessed at monthly visits for a total of 40 weeks postrandomization or until the point of relapse. The primary outcome was the presence or absence of relapse. Pill counts were used as the primary compliance measure. Data were collected from February 16, 2005, to May 5, 2008.

Measures

The 17-item HDRS was used to assess the severity of depression in the subjects.[31] Remission following treatment with citalopram in the open-label study was defined by an HDRS score of 7 or less and no longer meeting criteria for "major depression secondary to TBI." The Clinical Global Impressions-Improvement scale, a clinician-administered rating of overall improvement posttreatment, was used as a secondary measure of remission.[34] After randomization, subjects were monitored for relapse, which was defined as an increase in HDRS score to 16 or greater and once again fulfilling criteria for "major depression secondary to TBI." Background information collected from hospital charts and subject interviews included age, gender, marital status, educational history, litigation status relating to injury, the presence or absence of a prior diagnosis of psychiatric disorder (major depressive disorder, bipolar disorder, schizophrenia, anxiety disorder, or dementia), history of substance abuse, and presence/absence of a formal diagnosis of major depressive or bipolar disorder in first or second degree biologic relatives. Medical history was coded using the Cumulative Illness Rating Scale (CIRS)[35,36] (presence of illnesses unrelated to injury). Injury data, namely the mechanism of accident, duration of loss of consciousness, GCS in the emergency room, duration of posttraumatic amnesia, other significant extracranial injuries, and results of the brain CT scans (coded as yes/no regarding focal abnormalities) were recorded.

Other tests administered included the Mini Mental State Examination (MMSE), administered as an index of general cognitive function,[37] and the Rivermead Post Concussion Symptoms Questionnaire (RPQ).[38] The RPQ is a self-reported measure of physical and emotional symptoms that are commonly seen following TBI. The MMSE and RPQ were administered at baseline prior to the acute treatment phase, at randomization, and at final visit (40 weeks or at the point of relapse, whichever came first). Treatment-emergent adverse effects were recorded at the first visit postrandomization and at the final visit.

Statistics

Descriptive statistics were calculated for all variables of interest. Continuous measures such as age were summarized using means and standard deviations, whereas categorical measures were summarized using counts and percentages.

Background variables were compared between drug and placebo groups using analysis of variance (ANOVA), χ^2 test, or Fisher exact test. We compared the relapse rates between drug groups and across gender using a χ^2 test or Fisher exact test, respectively. The effect of drug group on time to relapse was analyzed using Kaplan-Meier survival analysis, along

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with the log rank Mantel-Cox statistic. Treatment-emergent side effects were examined descriptively and compared between the drug and placebo groups using Fisher exact test.

Exploratory post hoc analyses were conducted without correcting for multiple comparisons. The associations between risk of relapse and age, baseline postconcussive symptoms (RPQ), MMSE, and mean HDRS were assessed independently using ANOVAs. The relationship between relapse and the presence or absence of moderate-to-severe symptoms on individual HDRS items and current employment was assessed using Fisher exact test. All analyses were carried out using SPSS 16.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Subjects

Eighteen of the 21 (85.7%) subjects who were randomly assigned completed the study. Reasons for dropouts included adverse effects of the medication (diarrhea, n = 1; 4.8%) and subject's preference to stop using the medication (n = 2; 9.5%). The mean age of the subjects was 47.67 years (SD = 19.9; range, 21–85 years). Eleven of the subjects (52.4%) were male. Traumatic brain injury severity was mild in 16 subjects (76.2%) and moderate in 4 subjects (19.0%). A single subject had an early GCS rating of < 9, but this was artificially low due to hemorrhage from a mesenteric tear and sedation, and he was recovering well cognitively when seen at his first follow-up. He was recruited as he met criteria for major depression at the 4-month mark. Analyses were unchanged when this 1 subject was excluded. One subject (4.8%) had a remote prior history of mood disorder. The majority of subjects were married (n = 14; 66.7%) and had an education level of "high-school or less" (n = 12; 57.1%). The majority of subjects had not determined their litigation status relating to the injury (n = 15; 71.4%). Twelve of the subjects (57.1%) were taking concomitant psychoactive medication, including 3 subjects (14.3%) taking concomitant low-dose tricyclic antidepressants for sleep and pain (2 subjects taking amitriptyline 20 mg/d and 1 subject taking nortriptyline 25 mg/d).

Medication Assignment

For the most part, subjects continued their medication at the acute treatment doses that had been achieved at the end of the open-label phase. Eleven of the subjects (52.4%) began the randomization phase at a dose of 40 mg/d, 8 subjects (38.1%) at 20 mg/d, and 1 subject (4.8%) at 30 mg/d. Although 1 subject (4.8%) completed open-label treatment at 50 mg/d, he began the study at 40 mg/d after randomization to the placebo arm in order to complete the taper protocol by 2 weeks.

Pill counts were taken at the first postrandomization visit and then at the final visit to assess compliance. At the first visit, pill counts were available in 16 subjects (76.2%) and revealed a mean compliance of 91.9%, with 14 out of 16 subjects (87.5%) having a compliance of 85% or greater. At the final visit, pill counts were available for 18 subjects (85.7%) and revealed a mean compliance of 94.8%, with all 18 subjects having a compliance of 85% or greater.

Table 1. Demographic and Background Characteristics of 21 Subjects

Variable	Citalopram (n = 10)	Placebo (n = 11)	Significance Test	Significance *P*
Sex, n			Fisher exact test	.395
Male	4	7		
Female	6	4		
TBI severity, n			Fisher exact test	1.000
Mild	8	8		
Moderate/severe	2	3		
Education, n			Fisher exact test	.030[a]
≤ High school	3	9		
≥ College	7	2		
Marital status,			Fisher exact test	1.000
Married	7	7		
Not married	3	4		
CT focal, n			Fisher exact test	.361
Positive	2	5		
Negative	8	6		
CGI-I score at randomization, n			…	…
Improved	10	11		
Worse	0	0		
MMSE score at baseline, mean (SD)	28.8 (1.0)	25.9 (3.9)	$F_{1,19} = 5.17$	.036[a]
HDRS score at baseline, mean (SD)	21.3 (6.1)	26.2 (5.9)	$F_{1,19} = 3.50$	.077
HDRS score at randomization, mean (SD)	5.7 (4.6)	6.7 (4.2)	$F_{1,19} = 0.29$	.599
Rivermead postconcussive symptoms, mean (SD)	42.5 (12.1)	43.9 (9.6)	$F_{1,19} = 0.69$	.796
Time post-injury, mean (SD), d	105 (49)	107 (111)	$F_{1,19} = 0.003$	.955
Length of open-label treatment, mean (SD), wk	15.3 (6.9)	15.7 (8.1)	$F_{1,19} = 0.017$	.898

[a]No significant differences in the majority of background variables between citalopram and placebo groups, with the exception of education and mean baseline MMSE score.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement, CT = computed tomography, HDRS = Hamilton Depression Rating Scale, MMSE = Mini Mental State Examination, TBI = traumatic brain injury.

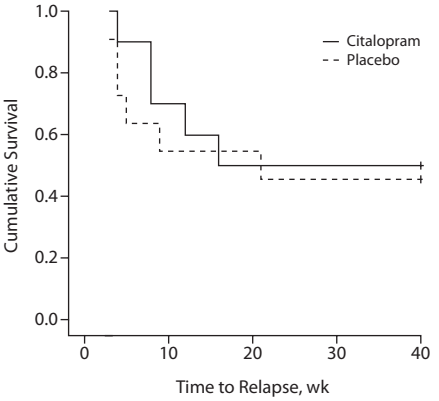
Comparison of Background Variables

There were no significant differences in background variables, injury variables, or psychiatric history between groups—except for a lower education level in the placebo group and differences in MMSE scores, with the citalopram group having a higher mean score (28.8; SD = 1.0) than the placebo group (25.9; SD = 3.9; $F_{1,19} = 5.17$; $P = .036$) (Table 1). There was no significant difference in CIRS scores between the citalopram group (0.69) and the placebo group (0.90), ($F_{1,19} = 0.289$; $P = .597$). There were no significant differences between treatment groups with respect to concomitant medication.

Relapse Rates

Relapse was seen in 11 of 21 subjects (52.4%). We examined relapse rates between the citalopram group and placebo

Figure 1. Time to Relapse in Citalopram and Placebo Groups[a]



[a]The citalopram group took a mean of 24.80 weeks (SD = 16.3) to relapse, while the placebo group relapsed at 22.36 weeks (SD = 17.6). No significant differences were observed in the time to relapse between both groups (log rank Mantel-Cox test $\chi^2 = 0.148$, $P = .700$).

group and found that 5 of 10 subjects (50.0%) in the citalopram group relapsed before 40 weeks, while 6 of 11 subjects (54.5%)in the placebo group relapsed. Thus, the groups did not differ significantly in relapse rates ($\chi^2_1 = 0.043$, $P = .835$).

Time to Relapse

The mean time to relapse in 21 subjects was 23.5 weeks (SD = 16.6). We examined time to relapse between placebo and citalopram groups and found that the citalopram group took a mean of 24.8 weeks (SD = 16.3) to relapse, while the placebo group relapsed at a mean of 22.3 weeks (SD = 17.6) (Figure 1). There was no significant difference seen in the time to relapse between citalopram and placebo groups (log rank Mantel-Cox test $\chi^2 = 0.148$, $P = .700$).

Adverse Effects

A list of treatment-emergent adverse effects was collected during the visit after randomization (n = 17, as 4 subjects had missing data) and at the final visit (n = 21). All subjects, regardless of treatment type (drug or placebo), described 1 or more adverse effect. In the first postrandomization visit, common adverse effects reported by both treatment groups included fatigue (52.4%), headache (52.4%), dizziness (52.4%), muscle pain (47.6%), light-headedness (42.9%), and dry mouth (42.9%), with no statistical differences between groups. The only dropout from the study related to adverse effects was due to diarrhea.

At the final visit, common adverse effects reported by both treatment groups included headache (61.9%), muscle or joint paint (60%), dizziness (52.4%), insomnia (47.6%), feelings of detachment or disinterest (47.6%), anxiety (42.9%), dry mouth (42.9%), and a change in sexual interest or function (42.9%), with no statistical differences between treatment groups.

Post Hoc Exploratory Analyses

Subsidiary analyses were undertaken to explore whether certain variables might be associated with relapse. We found no significant differences between relapse rates associated with sex (relapse in 5 of 11 men [45.5%], relapse in 6 of 10 women [60.0%], Fisher exact test $P = .670$), age (relapse mean age of 50.5 years [SD = 21.6], nonrelapse mean age of 44.6 years [SD = 18.5], $F_{1,19} = 0.44$; $P = .515$), employment (8 of 11 relapsing individuals were employed [72.7%] while 9 of 10 nonrelapsing individuals were employed [90.0%], Fisher exact test $P = .331$), baseline MMSE score (relapse mean MMSE score of 26.9 [SD = 3.0], nonrelapse mean MMSE score of 27.9 [SD = 3.4], $F_{1,19} = 0.47$; $P = .504$), or PCS score (relapse mean PCS score of 44.8 [SD = 11.8], nonrelapse mean PCS score of 41.0 [SD = 9.7], $F_{1,19} = 0.54$; $P = .473$). There was a nonsignificant trend observed for subjects who relapsed to have a slightly higher baseline HDRS score (relapse mean baseline HDRS score of 25.6 [SD = 5.5], nonrelapse mean baseline HDRS score of 21.9 [SD = 6.9], $F_{1,19} = 1.91$; $P = .184$).

We then examined the relationship between individual HDRS items rated at baseline (prior to antidepressant treatment) and rate of relapse/time to relapse. Hamilton Depression Rating Scale scores for each item were dichotomized into categories of "none to mild" (scores 0 to 1) versus "more than mild" (scores ≥ 2). We found that only 2 HDRS variables, "psychic anxiety" and "agitation," were predictive of time to relapse. Specifically, subjects who reported "more than mild psychic anxiety" relapsed at a mean of 19.7 weeks (SD = 3.9), in contrast to subjects who were noted to have "none to mild psychic anxiety," all of whom completed the study without relapsing (40.0 weeks, SD = 0, log rank Mantel-Cox test $\chi^2 = 3.997$, $P = .046$). This finding remained when relapse rates themselves were examined; all those who ultimately relapsed had "more than mild" anxiety ratings at baseline (11/11 cases), in contrast to only 6 of 10 of those who did not relapse (Fisher exact test, $P = .035$).

Perhaps consistent with this, subjects who were rated as having "more than mild" agitation at baseline relapsed sooner (mean = 8.0 weeks, SD = 2.8) than subjects without this level of agitation (mean 27.18 weeks, SD = 3.9; log rank Mantel-Cox test $\chi^2 = 6.164$, $P = .013$). However, there was no significant difference among the rates of subjects who eventually relapsed by the end of the study. Of note, the HDRS "somatic anxiety" rating was not associated with either time to or rate of eventual relapse.

DISCUSSION

To our knowledge, this is the first study to specifically examine the issue of continuation antidepressant therapy among TBI patients following remission from major depression. Our principal finding was a relatively high rate of relapse in both the placebo and active treatment conditions, despite adequate compliance. Nonetheless, SSRIs are recommended by a number of sources as a first-line treatment option for depression following TBI.[11,16,39] Our attempt to taper and discontinue treatment following remission was reasonable, given the absence of any literature data concerning continuation or maintenance antidepressant treatment

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in those with TBI, as well as the suggestion that episodes may be shorter and the course more variable.[6]

The relapse rate observed in this study was higher than those seen in similar continuation studies in the non-TBI population, whereas relapse rates in the drug-treated group ranged from 16% to 33%[20–24] and were significantly different from relapse rates observed in placebo or discontinuation groups. An exception to this is a recent, 5-year, naturalistic study of continuation therapy in a non-TBI cohort, which found a relatively high relapse rate in the continuation group (45%) and in the group that discontinued antidepressant (77%), with a combined relapse rate in both groups of 55%.[40] Our data suggest that the TBI population is particularly vulnerable to relapse, regardless of antidepressant prophylaxis. In support of this, a community study[1] found that subjects who had experienced a prior, significant TBI remained at heightened risk for persisting or recurring depression for a period of up to 50 years.

In spite of this, the relatively high rate of relapse in our study was somewhat surprising. With respect to the placebo group, it is possible that the 2-week cross-titration from citalopram to placebo was too rapid, perhaps hastening relapse. However, this cannot account for the high observed relapse rate in the active treatment group. Another possible explanation for this observation is that citalopram may not be the most effective antidepressant agent for the TBI population. An 8-week open-label study of depression after TBI among 15 subjects[17] yielded a remission rate of 67% using sertraline, an antidepressant that offers dopaminergic input in addition to SRI effects.[41] Citalopram, by contrast, is a very selective SSRI with little activity on other neurotransmitter systems. Nonetheless, the small sample size and the use of newspaper advertisements for recruitment in that study preclude comparison of response rates with the current study.

An important, although tentative, finding was the association between prominent "psychic anxiety" at baseline and subsequent relapse, suggesting that individuals with anxious depression after TBI should be monitored with particular care. Our exploratory findings are consistent with research in the non-TBI population demonstrating that depression with coexistent anxiety has a significantly longer duration than nonanxious depression,[42] may be harder to treat,[43] and poses an increased risk of relapse.[44] The small sample size of the current study precluded analysis of other nonpharmacologic risk factors that may be associated with more prominent depressive features and relapse.

This study highlights the relatively high risk of relapse within depression after TBI and raises questions about the effectiveness and potential limitations of citalopram continuation treatment in preventing relapse of major depression. Future studies should compare various antidepressant agents, assess risk factors for persistent depressive symptoms, and attempt to determine the optimum duration of continuation treatment. Additional research should also take into account the reality and limitations of SSRI therapy for treatment of depression in the TBI population. Sample sizes in this group may be bolstered by including subjects who have exhibited a response, rather than full remission, after an open-label phase of treatment, as seen previously.[45] In addition, future studies should continue to emphasize combining pharmacologic agents with individual and family psychotherapy targeted at developing compensatory strategies and coping skills for the functional difficulties that are most distressing to persons with TBI. Depression post-TBI remains a prominent concern given its associated morbidity. The fact that this occurs in a relatively young population without increased mortality suggests that this can be a persisting, costly problem that is in need of further clarification.

Drug names: citalopram (Celexa and others), nortriptyline (Pamelor, Aventyl, and others), sertraline (Zoloft and others).

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