Poorer Drinking Outcomes with Citalopram Treatment for Alcohol Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Previous research on the use of selective serotonin reuptake inhibitors (SSRIs) as a treatment for alcohol dependence has yielded mixed results. Depression has been shown to be a predictor of relapse and poor outcome following treatment, and it has been hypothesized that SSRIs would be beneficial in reducing drinking in depressed alcohol-dependent individuals. This randomized, double-blind, placebo-controlled trial was designed to test the effects of citalopram on treatment outcomes among alcohol-dependent individuals with and without depression.

Methods: Two hundred and sixty-five patients meeting criteria for a DSM-IV diagnosis of alcohol abuse or dependence were randomly assigned to receive placebo or citalopram 20 mg per day for the first week, followed by 40 mg per day from weeks 2 through 12. All patients received a standard course of treatment consisting of weekly individual and group psychotherapy. Participants were reassessed at 12 weeks, including dropouts from both treatment groups to determine rates of abstinence, changes in alcohol use, addiction severity, depressive symptoms, and psychiatric status.

Results: Citalopram provided no advantage over placebo in terms of treatment outcomes, and for some measures, citalopram produced poorer outcomes. Patients in the citalopram group had a higher number of heavy drinking days throughout the trial, and smaller changes in frequency and amount of alcohol consumption at 12 weeks. There was no influence of depression severity on outcomes in either medication group. Survival analyses also indicated no differences between depressed and nondepressed patients in the citalopram group for time to first slip or relapse. A diagnosis of personality disorder was associated with poorer treatment responses overall, regardless of treatment condition.

Conclusions: This trial does not support the use of citalopram in the treatment of alcohol dependence. The results suggest that the use of SSRIs among depressed and nondepressed alcohol-dependent individuals early in recovery, prior to the onset of abstinence, may be contraindicated.

Key Words: Alcohol Dependence, Selective Serotonin Reuptake Inhibitors, Citalopram, Treatment Outcome, Depression.

VARIOUS ANIMAL MODELS have demonstrated a significant reduction in alcohol consumption with the administration of selective serotonin reuptake inhibitors (SSRIs) (Gill et al., 1988; Ginsburg et al., 2005; Gorelick, 1989). In contrast to the extensive preclinical literature that links serotonin function to alcohol consumption, randomized controlled trials of SSRI antidepressant in humans have yielded limited and inconsistent results (Kranzler et al., 2006, 2012; Pettinati et al., 2013).

Trials of SSRIs in alcohol-dependent individuals have shown either a moderate decrease in alcohol consumption (Gerra et al., 1992; Naranjo et al., 1987, 2000; Tiihonen et al., 1996) or no advantage compared to placebo (Balldin et al., 1994; Chick et al., 2004; Kabel and Petty, 1996; Kranzler et al., 1995). Furthermore, interindividual variability in response to SSRIs was large, with reductions in alcohol consumption ranging from 10% to more than 70% (Naranjo and Knoke, 2001).

Researchers have attempted to identify patient characteristics that predict treatment response to an SSRI. Factors related to family history, severity of alcoholism, and psychiatric comorbidity (e.g., depression/anxiety) have been examined (Cornelius et al., 2000; Kranzler et al., 1996, 2006; Pettinati et al., 2000). In a 4-week trial, Gerra and colleagues (1992) found that alcohol-dependent individuals with a positive family history of alcoholism experienced a 53% decrease in daily alcohol intake with fluoxetine, compared to only a 23% decrease in nonfamilial alcoholics. The co-occurrence of depression has been associated with poorer addiction treatment outcomes (Charney et al., 2005) and has been shown to be a predictor of relapse following detoxification (Greenfield et al., 1998; Hasin et al., 1996). In a 12-week study, Cornelius and colleagues (1997) found fluoxetine to be effective in reducing both depression symptoms and alcohol

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consumption in patients with concurrent major depression and alcohol dependence. At 1-year follow-up, the fluoxetine group continued to demonstrate less depression and less drinking than the placebo group (Cornelius et al., 2000). In contrast, Gual and colleagues (2003) found that 24 weeks of sertraline treatment conveyed no added benefit versus placebo in terms of either depression or drinking in recently detoxified alcohol-dependent patients with depressive symptoms. Similarly, Kranzler and colleagues (2006) found no significant differences on depressive symptoms or drinking behavior between sertraline and placebo groups with co-occurring major depressive disorder and alcohol dependence. In a 12-week trial, Moak and colleagues (2003) found that patients who received sertraline plus psychotherapy had fewer drinks per drinking day than those that received placebo plus psychotherapy. However, there were no other significant differences in drinking outcomes between the treatment groups, including time to first slip, time to first relapse, and percent days abstinent (Moak et al., 2003).

Overall, alcohol-dependent patients with concurrent depression may constitute a patient group for whom SSRIs are beneficial; however, results to date have been mixed and it is still unclear whether SSRIs are efficacious in reducing drinking in this population. This study was conducted to examine the effects of the SSRI, citalopram, in depressed and nondepressed patients with an alcohol use disorder. Citalopram has been shown to be an efficacious antidepressant for the treatment of major depression with good tolerability and acceptability (Cipriani et al., 2012). The primary hypothesis was that initial treatment with citalopram would improve early treatment outcomes (reduction in early dropout from treatment, increase in duration of abstinence, decrease in number of drinking days, and/or mean number of drinks per drinking day) among alcohol-dependent patients receiving a standardized 12-week course of addiction treatment. It was also hypothesized that depression at intake into addiction treatment, as defined by DSM-IV criteria for a current diagnosis of major depression, would be a significant positive predictor of response to citalopram in terms of drinking-related measures.

MATERIALS AND METHODS

The study was conducted at the Addictions Unit of the McGill University Health Centre (MUHC). The Addictions Unit provides comprehensive care to adults with all forms of psychoactive substance use disorders; it pursues a treatment philosophy of total abstinence and offers integrated care for concurrent psychiatric disorders. All patients requesting help for alcohol problems were potentially eligible to participate in the study. The study's procedure and consent form were approved by the MUHC Research Ethics Committee. Note that patient consent included permission for investigators to access hospital charts and clinical case files filled out by treating primary therapists and psychiatrists.

The clinical research coordinator (CRC), who was not involved in clinical care, conducted the baseline assessments. Assessments included the collection of information regarding socio demographics, treatment history, and severity of alcohol-related problems in a variety of areas using the Addiction Severity Index (ASI) (McLellan et al., 1990). The ASI is a structured clinical interview that collects a wide range of information, including socio demographics, and evaluates problem severity in 7 areas: alcohol use, drug use, family/social functioning, medical status, employment/support, legal status, and psychological status. Within each of these problem areas, severity is measured in terms of number, duration, frequency, and intensity of symptoms experienced during the past 30 days, and a composite score is obtained with a range from 0 to 1. The psychometric properties of the ASI have been found to be excellent, with high inter-rater reliabilities for all composite scores (Alterman et al., 1994). Internal consistency reliability of ASI composite scores in this study was good, ranging from 0.56 (employment composite) to 0.90 (medical composite score) as assessed using Cronbach's standardized alpha statistic (Cronbach, 1951).

The assessment also established current and lifetime Axis I psychiatric diagnoses using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1996), depression severity using the Beck Depression Inventory (BDI) (Beck and Steer, 1987), anxiety severity using the Beck Anxiety Inventory (BAI) (Beck and Steer, 1993), levels of impulsivity using the Barratt's Impulsiveness Scale (Barratt and Patton, 1983), and general psychological distress using the Symptom Checklist (Derogatis, 1992). Study participants also provided urine samples for toxicology analysis (cloned enzyme donor immunoassay.

All assessments were reviewed by an Addictions Unit psychiatrist (DAC), who conducted a brief interview with each patient to screen for suicidal ideation, psychosis, or other psychiatric conditions that necessitated immediate intervention, as well as to apply study inclusion/exclusion criteria. Patients were included if they were between 18 and 65 years of age and met criteria for a DSM-IV diagnosis of alcohol abuse or dependence. Patients were excluded if they suffered from a second substance use disorder (other than nicotine dependence) and a psychotic or organic brain disorder; if they were taking any psychiatric medications including SSRIs; if they required inpatient detoxification or psychiatric admission; if a female patient was pregnant or breastfeeding; or if they had a history of serious adverse reactions or intolerance to SSRIs.

Trial participants were randomly assigned to receive citalopram or placebo; citalopram was started at 20 mg per day for the first week to minimize adverse effects and optimize adherence. Citalopram was administered at a dose of 40 mg per day from weeks 2 through 12. The medications were supplied in identical opaque capsules, with the same number of capsules in both groups. The CRC, clinicians, and patients were blind to the medication group assignment.

Prescriptions for ongoing medical conditions were continued during the clinical trial. However, the use of psychiatric medications or anticraving agents was an exclusion criterion, and new prescriptions were not permitted during the trial. However, if clinically indicated at the baseline assessment, an Addictions Unit psychiatrist prescribed a tapering regimen of diazepam for alcohol detoxification (max. duration of 14 days) prior to randomization.

During the 12-week clinical trial, participants met biweekly with the CRC to obtain medications and report on adverse events and daily alcohol/drug use diaries. The CRC also completed ratings on the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression Scale (CGI) at each visit to monitor addiction and psychiatric status for any significant clinical deterioration.

Patients who consented to participate in the study were reassessed at 12 weeks, including dropouts from both treatment groups. They were re-interviewed by the CRC using the SCID-I, ASI, HAM-D, and BDI to determine changes in alcohol use, addiction severity, depressive symptoms, and psychiatric status. Personality disorders (PDs) were assessed using the SCID-II (First et al., 1997) at the 12-week time point when subjects were in a more stable state. This procedure was adopted to increase diagnostic reliability, as active substance, mood, and anxiety disorders have been shown to impact PD diagnoses (Verheul et al., 2000).

Treatment During the Double-Blind Trial

All study participants began a 12-week course of standard addiction treatment. Standard treatment consisted of weekly 50-minute individual and 90-minute group psychotherapy sessions. All addiction therapists had >5 years of experience as addiction counselors and held degrees in nursing, occupational therapy, or psychology. Study participants provided a random weekly urine sample for alcohol/drug screening. They were encouraged, but not required, to attend Alcoholics Anonymous.

The individual psychotherapy sessions were based on the principles of motivational interviewing (Miller and Rollnick, 1991). The individual sessions emphasized and promoted self-efficacy and personal responsibility for change, evaluated and enhanced the motivational level of the patient and readiness for change through an empathetic counseling style, and educated the patient about strategies to produce change and prevent relapses. The group therapy sessions combined psycho-educational, supportive, and relapse prevention interventions.

Safety Measures and Withdrawal from the Trial

At any time during the study, patients were withdrawn from the trial and treated outside the protocol if they were "much worse" or "very much worse" based on the CGI completed by the CRC, as manifested by severe alcohol withdrawal symptoms, other medical complications, psychosis, suicidal ideation, or any serious adverse event. If a patient still required benzodiazepines after 2 weeks, they were withdrawn from the study and treated outside the protocol.

Primary Drinking-Related Outcomes

The CRC reviewed patients' alcohol/drug use daily diaries and clinic charts for information on drug/alcohol consumption during the 12-week trial, as well as slips and relapses. Additional sources of information included self-reports of alcohol use collected during the treatment, the results of weekly urine drug screenings, as well as information on progress in treatment filled out by the patient's primary therapist (monthly primary care records included reports on drug/alcohol use and treatment attendance). The citalopram and placebo groups were compared in terms of primary drinking-related variables collected during the trial (e.g., number of heavy drinking days, time to first slip or relapse, maximum duration of abstinence during the trial) as well as 12-week outcome variables collected at the end of the trial including the ASI alcohol and drug composite severity scores, total number of drinking days, drinks per drinking day, and abstinence status at the end of the trial. In accordance with other clinical trials for alcohol dependence, relapse was defined as: (i) drinking 5 or more days within 1 week or (ii) drinking 5 or more drinks on 1 day (Volpicelli et al., 1992).

Intent-to-Treat Analysis: Definition of a Treatment Responder

To examine clinically relevant outcomes of interest within the context of the Addictions Unit's "abstinence-oriented" treatment program, the continuous primary drinking outcome measures described above were classified into complete, partial, and nonresponse categories. The proportion of responders in the citalopram and placebo groups was calculated based on a composite of percentage change in number of drinking days and percentage change in the mean number of drinks per drinking day (comparing past 30 days at baseline vs. 12 weeks). Response was defined as follows: complete response = 100% reduction in both number of drinking days and mean number of drinks per drinking day; partial response = at least a 50% reduction in both parameters; and no response = all other values, or worsening on any parameter.

Data Analysis

Data for each patient, across all variables collected at initial assessment, during the trial from the clinic and hospital charts as well as at the 12-week follow-up interviews were coded and entered into a database using Microsoft Excel (Redmond, WA). Baseline comparisons between the citalopram and placebo groups were conducted using Student's *t*-tests for continuous variables and chi-square test for categorical variables using SPSS 22 (IBM Corp., Armonk, NY). Groups were compared in terms of other continuous primary drinking-related variables (e.g., maximum duration of abstinence, ASI alcohol composite scores) using 2-way analysis of variance (ANOVA) with between-group factors treatment (citalopram vs. placebo) and depression (depressed vs. nondepressed). All analyses were corrected for multiple comparisons.

The rates of dropout from the trial and time to first relapse were examined using the SPSS life tables survival program. Treatment groups were compared and statistical analyses of the survival functions were performed using the Wilcoxon (Gehan) statistics in SPSS.

Missing data from in-trial and 12-week follow-up were imputed using the multiple imputation procedures in SPSS v22. An expectation-maximization analysis was performed prior to multiple imputation, and Little's MCAR test was found to be not significant ($p > 0.8$), supporting the hypothesis that systematic biases were not present in the data (Little, 1998). Multiple imputation analysis has been found to be one of the least biased methods for treating missing data in clinical trials (Hallgren and Witkiewitz, 2013). The imputation model included all variables considered during the analysis, as omission of any variable would bias possible estimates (StataCorp, 2013). All baseline measures with complete observed data were constrained as predictors, and variables with missing data were used as both predictors and dependents in the model. The number of imputations was set to 20 (StataCorp, 2013), and values were imputed within their plausible ranges (e.g., 0 to 1 for ASI composite scores). Multiplicative terms, such as the percent frequency of change in days and amount of alcohol intake, were created prior to imputation so as not to bias the regression parameters of the interaction terms (Von Hippel, 2009).

Linear regression models were used to analyze imputed data, with the medication group (citalopram or placebo) as the independent variable and the in-trial or 12-week outcomes as the dependent variables. Regression parameter estimates were computed for each of the imputation data sets as well as for the pooled data (Hallgren and Witkiewitz, 2013). For categorical dependent variables (e.g. abstinence status at 12 weeks), logistic regression was performed and statistics for pooled data were reported.

RESULTS

Figure 1 provides a summary of the participant flow in the clinical trial. A total of 504 patients requesting help for alcohol problems were assessed for study eligibility. Approximately 35% ($N = 176$) of these patients were ineligible to participate in the clinical trial. The most common reason for exclusion from the trial was the use of serotonergic medications by patients (largely SSRIs); the second most common reason was the presence of polysubstance dependence (largely cocaine dependence). Among the eligible patients, 60 declined to participate and a total of 265 patients were randomized: 141 subjects (53%) completed all 12 weeks of the clinical trial, 110 subjects (42%) discontinued the trial prior to the 12-week mark, and 14 (5%) were withdrawn for medical reasons (including severe psychiatric symptoms or

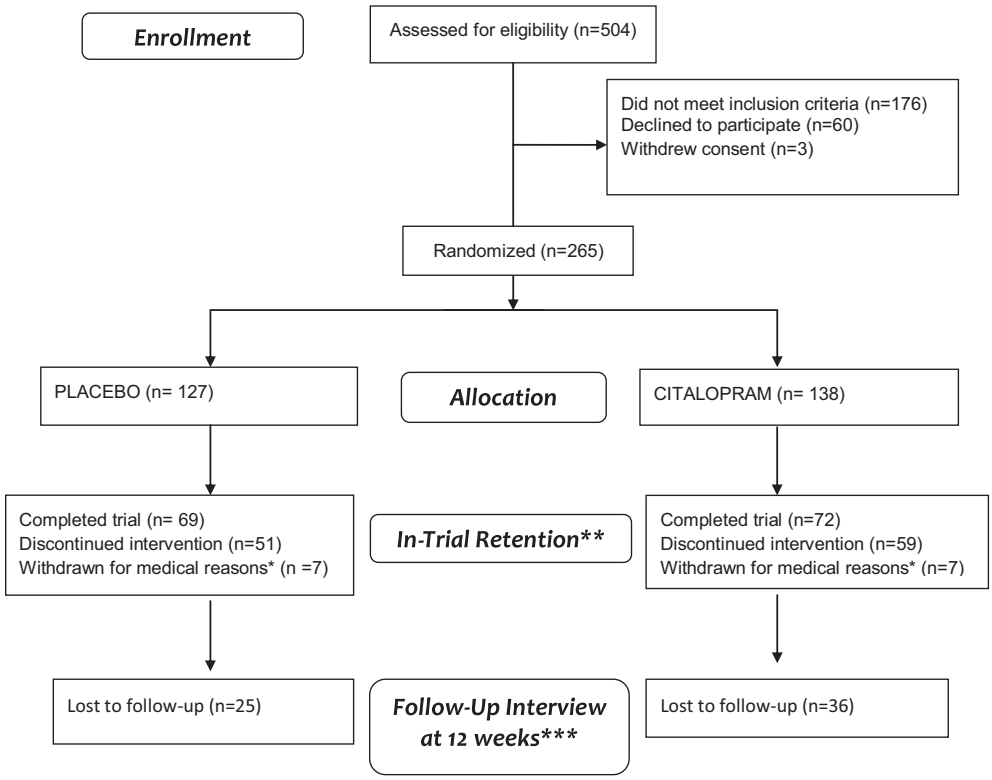

Fig. 1. Participant flow in the clinical trial. *Withdrawal from the trial due to worsening psychiatric symptoms, or adverse events.**In-trial retention – status in the trial, as well as data on substance use during the trial was available from the drug/alcohol use diaries, urine screens, and clinical charts. ***Follow-up interviews were complete for 204 cases (77%) at 12 weeks. Data was missing for 61 cases (23%) that could not be contacted, or refused participation at follow-up. There were no significant differences between retained and those lost to follow-up in terms of medication group allocation, baseline severity of substance dependence or demographic variables. Multiple imputation procedures using SPSS v22 were conducted on 12-week outcome variables where indicated on the data tables.

adverse events requiring additional medication or hospitalization). Other known reasons for withdrawal included unremitting alcohol use or relapse requiring additional medication or hospitalization (n = 28). Patients who were withdrawn from the study prior to 12 weeks due to unremitting alcohol use or medical reasons (n = 42) were classified as treatment nonresponders in the intent-to-treat analysis described below.

Characteristics of the Sample at Baseline

See Tables 1 and 2 for a summary of the baseline demographic, psychiatric, alcohol use, and addiction severity characteristics stratified by intervention group. The sample was 92% Caucasian with no difference in ethnicity between groups. The average duration of problem alcohol use was 18.4 $\pm$ 0.81 years (mean $\pm$ SEM) with a mean age of onset of 26.4 $\pm$ 0.59 years. The majority (84%) of participants had a family history of substance problems. Initial semistructured psychiatric interviews (SCID-I) revealed that 22% of the sample met DSM-IV criteria for a current diagnosis of a depressive disorder (either primary or substance induced), and 27% for a current anxiety disorder. Subsequent interview using the SCID-II at 12-week follow-up showed that 47% of the sample was diagnosed with a PD (24% Cluster B PD). There were no differences in the rates of diagnosis for PDs using imputed versus original data. The ASI interview revealed that 31% of the sample reported having suicidal thoughts in the past (lifetime) and 18% had made at least 1 suicide attempt. The mean BDI score was 18.6 $\pm$ 0.69 indicating a moderate level of depression, as well as anxiety (mean BAI 18.9 $\pm$ 0.77) at the time of assessment.

Demographic comparisons of the medication groups found that differences were limited to marital status and the need for medical detoxification. Specifically, the citalopram group was less likely to be married and more likely to be separated/divorced than the placebo group, $\chi^2 = 6.50$, df = 2, $p = 0.039$, not significant when corrected for multiple comparisons. The citalopram group was significantly more likely to require benzodiazepine-based detoxification prior to the trial, compared to the placebo group, $\chi^2 = 8.89$, df = 1, $p = 0.003$. There were no group differences on any other measure of baseline alcohol or drug use including the ASI composite severity scores (see Table 2).

Retention in Treatment and Loss to Follow-Up

Among the 265 trial participants, 185 patients (70%) completed 6 weeks or more of the trial, and 141 patients (53%) completed all 12 weeks. All patients, including those

Table 1. Baseline Demographic and Psychiatric Variables by Intervention Group

Demographic/psychological variables at baseline	Placebo $N = 127$	Citalopram $N = 138$
Age (mean ± SEM)	44.7 ± 1.01	46.0 ± 0.88
Sex, % (*n*)		
Male	69.3 (88)	70.3 (97)
Female	30.7 (39)	29.7 (41)
Marital status, % (*n*)		
Single	26.8 (34)	28.3 (39)
Married/remarried	53.5 (68)	39.9 (55)
Separated/divorced	19.7 (25)	31.9 (44)
Employment status, % (*n*)		
Full-time	63.0 (80)	63.2 (86)
Part-time	15.0 (19)	16.2 (22)
Unemployment	11.0 (14)	9.6 (13)
Other	11.0 (14)	11.0 (15)
Number of days worked (past 30 days) (mean ± SEM)	10.93 ± 0.86	11.05 ± 0.80
Education in years (mean ± SEM)	13.9 ± 0.24	13.8 ± 0.23
Current SCID diagnosis, % (*n*)		
Depression only	23.6 (30)	21.0 (29)
Anxiety only	23.6 (30)	29.7 (41)
Mixed anxiety and depression	37 (45)	40.6 (56)
Personality disorder	48.3 (58)	45.8 (54)
HAM-D (mean ± SEM)	8.0 ± 0.52	8.7 ± 0.49
Beck Depression Inventory (mean ± SEM)	18.0 ± 1.01	19.1 ± 0.95
Beck Anxiety Inventory (mean ± SEM)	19.0 ± 1.05	18.9 ± 1.11

HAM-D, Hamilton Rating Scale for Depression; SCID, Structured Clinical Interview for DSM-IV.

Note that all values are based on the original baseline data without imputation.

There were no significant differences between groups when corrected for multiple comparisons using Bonferroni.

Table 2. Baseline Alcohol Use and Addiction Severity Scores by Intervention Group

Alcohol/addiction variables at baseline	Placebo $N = 127$	Citalopram $N = 138$
# Days alcohol intake (past 30 days) (mean ± SEM)	20.00 ± 0.79	20.96 ± 0.75
Mean # drinks per drinking day (past 30 days) (mean ± SEM)	9.87 ± 0.46	10.65 ± 0.54
# Years problem drinking (mean ± SEM)	18.05 ± 0.81	18.64 ± 0.81
Early age of onset of alcohol problems (≤ 25 years of age), % (*n*)	54.3 (69)	57.2 (70)
Family history of substance problems, % (*n*)	82.8 (101)	85.9 (116)
# Prior alcohol treatments (mean ± SEM)	1.12 ± 0.15	1.33 ± 0.15
Detoxification required, % (*n*)**	26.0 (33)	43.5 (60)
Baseline Composite Severity Scores—Addiction Severity Index (ASI)		
ASI alcohol (mean ± SEM)	0.75 ± 0.01	0.76 ± 0.01
ASI drug (mean ± SEM)	0.05 ± 0.01	0.04 ± 0.01
ASI psychological (mean ± SEM)	0.23 ± 0.02	0.24 ± 0.02
ASI social (mean ± SEM)	0.27 ± 0.02	0.26 ± 0.02
ASI medical (mean ± SEM)	0.38 ± 0.03	0.34 ± 0.03
ASI employment (mean ± SEM)	0.45 ± 0.03	0.44 ± 0.02
ASI legal (mean ± SEM)	0.03 ± 0.01	0.03 ± 0.01

**Significant difference $p < 0.05$, corrected for multiple comparisons using Bonferroni.

Note that all values are based on the original baseline data without imputation.

who had dropped out of treatment, were recontacted and invited to attend the follow-up interviews. At 12 weeks, 200 patients completed in-person follow-up interviews and questionnaires, 4 (2%) provided information about their substance use during telephone interviews and returned completed questionnaires by mail, and the remaining 61 (23%) could not be contacted or refused to participate in the follow-up interview. (In this context it is important to note that for the majority of cases, information on in-trial variables [slips, relapses, heaving drinking days] was available from the drug/alcohol use diaries, the clinical charts, random urine screens, and the therapist notes). Analyses were conducted to compare baseline characteristics of retained versus lost patients. There were no significant differences in loss to follow-up by medication group, gender, employment, marital status, depression status, ASI composite alcohol severity scores, age at onset, or years of problem alcohol use (all p-values > 0.05). Those lost to follow-up were significantly younger (40.5 ± 1.46 years) than the retained group (46.8 ± 0.72 years), $t(263) = 4.1$, $p = 0.0001$. There were also significant differences between groups in terms of in-trial measures. For example, the majority (65.6%) of those lost to follow-up had discontinued treatment prior to 6 weeks, $\chi^2 = 84.96$, df = 1, $p = 0.0001$, and a large majority (85.1%) had relapsed during the trial, $\chi^2 = 10.94$, df = 1, $p = 0.001$.

Comparisons of Citalopram and Placebo Groups on Drinking-Related Outcomes

Due to loss to follow-up, multiple imputation procedures were conducted as described in the Data Analysis section. As shown in Table 3, there was no significant difference between intervention groups for the number of days in trial. During the trial, patients in the citalopram group had a greater number of heavy drinking days compared to the placebo group, $t(263) = 2.689$, $p = 0.007$. Table 4 shows that in the 30 days prior to the 12-week interview, the citalopram group had a higher number of drinking days, $t(263) = 2.683$, $p = 0.007$, more drinks per drinking day, $t(263) = 2.179$, $p = 0.03$, and they spent more money on alcohol $t(263) = 2.059$, $p = 0.041$. The citalopram group also showed a smaller percentage decrease in the frequency of alcohol consumption than that of patients in the placebo group, $t(263) = 2.414$, $p = 0.016$, as well as a smaller percentage decrease in the quantity of alcohol consumed per drinking day, $t(263) = 2.254$, $p = 0.025$. Table 4 indicates those variables that remained significant following correction for multiple comparisons.

There were no significant differences between the citalopram and placebo groups in terms of ASI composite scores, psychiatric symptoms, or levels of psychological distress at follow-up (all p-values > 0.05).

Logistic Regression Analyses to Predict Treatment Response

A logistic regression model was constructed to assess baseline patient characteristics that predicted treatment response. For this analysis, the response variable was dichotomized into 2 categories, nonresponse versus partial/complete response. Step 1 included treatment variables (benzodiazepine detoxification, number of individual and group psychotherapy sessions); Step 2 included demographic and social variables; Step 3 included alcohol and drug use severity such as ASI composite scores, age of onset, and duration of problem use; and Step 4 included predictors related to DSM-IV Axis I and II psychopathology and psychological distress. As shown in Table 5, the hierarchical regression model accounted for 55.5% of the variance in treatment response, $\chi^2 = 119.99$, df = 23, $p = 0.0001$, with an excellent Hosmer–Lemeshow goodness of fit ($p = 0.886$). Predictors that accounted for the largest proportion of the variance were treatment utilization (number of psychiatric sessions ($p = 0.001$), or group therapy sessions attended ($p = 0.0001$)), as well as comorbid PD ($p = 0.007$). Note that there was no influence of current mood or anxiety disorders on the treatment response variable within the model tested in Table 5.

Table 3. In-Trial and Alcohol Use Variables by Intervention Group

In-trial and alcohol use variables	Placebo $N = 127$	Citalopram $N = 138$	p-Value
Trial response, % (n)			
Complete response	32.3 (41)	31.9 (44)	0.899
Partial response	10.2 (13)	8.7 (12)	
No response	57.5 (73)	59.4 (82)	
Number of days in trial (mean ± SEM)	60.62 ± 2.54	57.36 ± 2.71	0.382
Early trial discontinuation (<6 weeks in trial), % (n)	29.9 (38)	30.4 (42)	0.928
Completed trial, % (n)	54.3 (69)	52.2 (72)	0.725
Continuous abstinence during trial, % (n)	23.6 (30)	21.0 (29)	0.593
# Days from randomization to 1st slip (mean ± SEM) (imputed data)	34.14 ± 3.11	30.37 ± 2.86	0.374
# Days from randomization to 1st relapse (mean ± SEM) (imputed data)	42.12 ± 3.21	38.64 ± 3.01	0.424
# Heavy drinking days during the trial** (mean ± SEM) (imputed data)	7.78 ± 1.15	13.02 ± 1.66	0.007

**Significant difference $p < 0.05$, corrected for multiple comparisons using Bonferroni.

Data collected during the trial from drug/alcohol use diaries, urine screens, clinic charts, and primary care records. Note that variables with imputed data are indicated.

Comparisons of Medication Groups—Stratified by Concurrent Psychiatric Diagnoses

There were considerable improvements in psychological functioning over the course of the trial. Notably, there were significant decreases from baseline to 12-week follow-up in terms of self-reported depressive symptoms as measured by the BDI (18.60 ± 0.69 vs. 11.65 ± 1.12) and anxiety as measured by the BAI (18.99 ± 0.77 vs. 11.00 ± 1.41). In addition, HAM-D scores significantly decreased from baseline to follow-up (8.35 ± 0.36 vs. 5.25 ± 0.64), all p-Values < 0.0001.

Analyses were conducted to compare medication groups (citalopram, placebo) with and without a concurrent diagnosis of a mood or anxiety disorder on a number of outcomes of interest, using 2-way ANOVA. There were main effects of diagnosis and no significant interactions between medication group and any mood or anxiety diagnosis across a number of outcome variables including the number of days in the trial, maximum days of continuous abstinence, and fre-

Table 4. Twelve-Week Alcohol Use and Psychological Variables by Intervention Group—Imputed Data

Alcohol-related variables (at 12 weeks)	Placebo $N = 127$	Citalopram $N = 138$	p-Value
# Days alcohol intake (past 30 days) (mean ± SEM)**	4.78 ± 0.68	7.60 ± 0.85	0.007
Mean # drinks per drinking day (past 30 days) (mean ± SEM)	3.60 ± 0.55	5.37 ± 0.72	0.030
% Change in # days alcohol intake (12 weeks vs. baseline) (mean ± SEM)	−74.72 ± 3.75	−57.92 ± 6.14	0.016
% Change in mean # drinks per drinking day (12 weeks vs. baseline) (mean ± SEM)	−62.64 ± 5.23	−42.02 ± 8.70	0.025
$ Spent on alcohol (past 30 days) (mean ± SEM)	$147.68 ± $39.94	$247.58 ± $49.08	0.041
Max # days abstinent at 12 weeks (mean ± SEM)	49.20 ± 2.67	44.37 ± 2.78	0.170
% Abstinent at 12-week follow-up, % (n)	56.6 (72)	50.7 (70)	0.416
Psychological variables(at 12 weeks)			
HAM-D (mean ± SEM)	5.20 ± 0.66	5.30 ± 0.83	0.892
Beck Depression Inventory (mean ± SEM)	11.47 ± 1.19	11.81 ± 1.57	0.841
Beck Anxiety Inventory (mean ± SEM)	10.79 ± 1.54	11.20 ± 1.71	0.800

HAM-D, Hamilton Rating Scale for Depression.

**Significant difference $p < 0.05$, corrected for multiple comparisons using Bonferroni.

Data collected during 12-week follow-up interviews.

Note that all values are based on data subjected to multiple imputation procedures in SPSS.

Table 5. Logistic Regression—Treatment Response (Partial/Complete Response = 1)

Predictors	Wald (df)	*p*-Value	R^2 (Nalkerke)
Step 1: Treatment utilization (at 12 weeks)			
Medication group (citalopram)	0.65 (1)	0.79	0.427
Benzodiazepine detox prior to trial	2.52 (1)	0.11	
# Group therapy sessions	45.03 (1)	0.0001	
# Individual therapy sessions	0.52 (1)	0.47	
# Psychiatric visits	11.13 (1)	0.001	
	Step: $\chi^2 = 86.04$, df = 5, $p = 0.0001$		
Step 2: Demographic/ social variables (baseline)			
Sex	4.30 (1)	0.038	0.485
Age	0.06 (1)	0.81	
Marital status	3.41 (2)	0.18	
Addiction Severity Index (ASI) composite severity scores—social	1.76 (1)	0.18	
	Step: $\chi^2 = 14.77$, df = 5, $p = 0.011$		
Step 3: Alcohol use (at baseline)			
ASI composite severity scores—alcohol	0.26 (1)	0.61	0.492
ASI composite severity scores—drugs	0.49 (1)	0.48	
Quantity of EtOH used	0.003 (1)	0.96	
Duration of EtOH problems	0.019 (1)	0.89	
Age of onset EtOH problems	0.040 (1)	0.84	
	Step: $\chi^2 = 1.72$, df = 5, $p = 0.887$		
Step 4: Psychopathology (baseline)			
HAM-D scores	0.02 (1)	0.88	0.555
Beck Depression Inventory scores	0.23 (1)	0.63	
Beck Anxiety Inventory scores	4.36 (1)	0.037	
ASI composite severity scores—psychological	1.32 (1)	0.25	
Symptom Checklist total scores	1.97 (1)	0.16	
Any current SCID anxiety diagnosis	0.036 (1)	0.85	
Any current SCID depression diagnosis	1.23 (1)	0.27	
Any current SCID-II personality disorder	7.26 (1)	0.007	
	Step: $\chi^2 = 17.46$, df = 8, $p = 0.026$		

EtOH, ethanol; HAM-D, Hamilton Rating Scale for Depression; SCID, Structured Clinical Interview for DSM-IV.

Overall, the model accounted for 55.5% of the variance in treatment response, $\chi^2 = 119.99$, df = 23, $p = 0.0001$, with an excellent Hosmer–Lemeshow goodness of fit ($p = 0.886$). There was no difference between the model fit, significant steps, and/or significant variables when comparing original ($n = 224$) to imputed data ($n = 265$). Parameters of the logistic regression model for the original data are provided in the table.

quency or quantity of alcohol intake (all main effects for diagnosis, and/or interaction terms for medication group × diagnosis were not significant, $p > 0.05$). In an analysis of pooled imputed data for the number of heavy drinking days during the trial, there was a main effect for medication group, $t(262) = 2.74$, $p = 0.006$, but not current depression diagnosis, $t(262) = 1.4$, $p = 0.16$. Results were similar for 12-week outcome data collected at follow-up. Analysis of pooled imputed data for the percentage change in drinks per drinking day demonstrated that the citalopram-treated groups had poorer outcomes overall, $t(262) = 2.76$, $p = 0.023$, with no effect of SCID depression diagnosis, $t(262) = 0.8$, $p = 0.424$. All citalopram-treated groups had less improvement in drinking outcomes, compared to the placebo-treated groups.

Survival analyses were conducted to compare medication groups (citalopram, placebo) to those with and without depression on time-dependent outcomes such as time to first relapse. Although there were notable differences in median survival time to first relapse (citalopram–depressed = 14 days, citalopram–nondepressed = 24.5 days, placebo–depressed = 19.25 days, placebo–nondepressed = 35 days), the survival analysis failed to show any significant effects for medication group, Wilcoxon (Gehan) = 0.17, df = 1, $p = 0.68$, or depression, Wilcoxon (Gehan) = 1.45, df = 1, $p = 0.23$.

Due to the significant effect of SCID-II PD diagnosis on treatment response (Table 5), this variable was further examined for impact on treatment retention and relapse. Individuals with any PD diagnosis had significantly higher rate of dropout from the trial, Wilcoxon (Gehan) = 25.33, df = 1, $p = 0.0001$, and a shorter time to first relapse, Wilcoxon (Gehan) = 8.57, df = 1, $p = 0.003$. The effect of PD diagnosis on relapse is illustrated in Fig. 2, and it is notable that the overall impact of a PD was considerably higher than any other diagnostic variable collected during the study including mood and anxiety disorders.

DISCUSSION

This randomized, double-blind, placebo-controlled trial did not support the primary hypothesis that citalopram treatment for alcohol dependence would improve drinking-related outcomes. Analyses indicated that the randomized groups were well matched and there were no significant differences in baseline characteristics between groups across a wide variety of alcohol-related severity measures, other than the requirement for detoxification prior to the trial.

In terms of in-trial variables, there were no significant differences between the medication groups in relation to the number of days in the trial, the rates of discontinuation, or the number of days to first slip or relapse. However, patients in the citalopram group exhibited significantly more heavy drinking days over the 12-week trial. The logistic regression model indicated that medication had no significant benefit

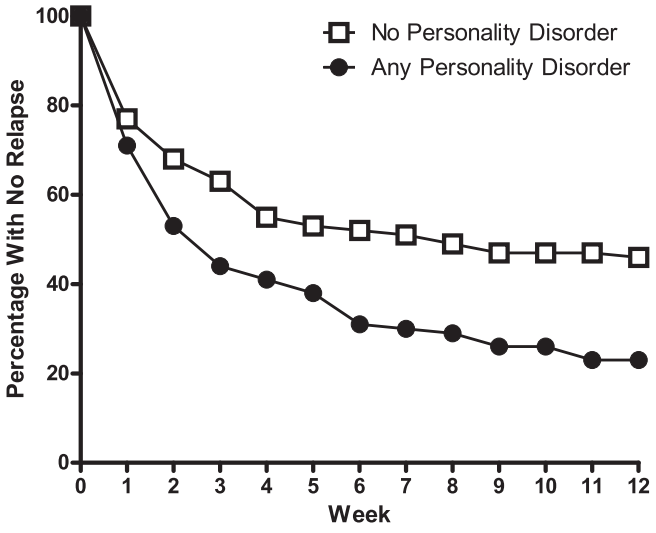

Fig. 2. Survival analysis for the number of days to first relapse by the presence of a Structured Clinical Interview for DSM-IV II diagnosis of any personality disorder.

in terms of treatment response; treatment utilization variables such as the number of group therapy sessions and psychiatric visits were significant predictors of partial/complete treatment response, in addition to the presence of any current PD.

Comparison of groups at 12 weeks also demonstrated a pattern of poorer outcomes for the citalopram-treated patients including a higher frequency of alcohol use in the 30 days prior to the interview and a less robust percentage change in mean drinks per drinking day. There were no significant differences between the 2 groups in terms of ASI composite scores or depression or anxiety ratings. While these negative results contradict the original hypothesis, they are consistent with several other studies in the addiction literature. For example, Kranzler and colleagues (1996) found that fluoxetine resulted in poorer drinking-related outcomes among high risk/severity patients compared to placebo. Pettinati and colleagues (2001) found that sertraline was no better in terms of drinking outcomes compared to placebo in patients with a lifetime diagnosis of depression. However, Dundon and colleagues (2004) found that high risk/severity alcoholics treated with sertraline seemed to fare worse (more heavy drinking) than those treated with placebo at 6-month follow-up.

The use of SSRIs for treatment of cocaine dependence has also been investigated with mixed results. While 1 study showed sertraline to be significantly associated with a longer time to relapse among recently abstinent cocaine-dependent patients with depressive symptoms (Oliveto et al., 2012), 2 recent randomized controlled trials did not find SSRIs to be efficacious in reducing cocaine use (Winstanley et al., 2011) nor the subjective effects of cocaine (Verrico et al., 2014).

Additionally, a recent study reported 93 cases in which SSRI treatment was associated with increased cravings and alcohol consumption (Brookwell et al., 2014). Pretreatment alcohol consumption ranged from minimal drinking to alcohol dependence. Regardless of pattern of alcohol consumption prior to treatment, over 70% of cases showed an increase in consumption and cravings during SSRI treatment that reverted to the original drinking pattern upon cessation of SSRI administration (Brookwell et al., 2014). It is important to note that these were subjective reports, and a causal link between SSRI treatment and increased alcohol consumption cannot be confirmed. Nonetheless, a study by Fahlke and colleagues (2012) provides a possible explanation for the poor efficacy of SSRIs among individuals that are consuming alcohol at the start of treatment. Fahlke and colleagues (2012) examined central serotonergic neurotransmission as assessed by the prolactin (PRL) response to citalopram among alcohol-dependent individuals and controls. PRL responses were significantly reduced by 45% in comparison with controls, suggesting that the serotonin system functioning was impaired in alcohol-dependent drinkers. SSRIs may be ineffective—particularly among severe alcohol-dependent individuals that continue to consume alcohol.

Many studies have identified comorbid psychopathologies such as depression and anxiety as predictors for poorer treatment outcomes among alcohol-dependent individuals (Charney et al., 2005; Driessen et al., 2001; Greenfield et al., 1998). The second study hypothesis that a current diagnosis of major depression would be a significant positive predictor of response to citalopram was not confirmed in terms of drinking-related measures. Among the citalopram-treated group, patients with depressive symptoms fared as poorly as those with self-reported moderate-to-severe depressive symptoms.

In summary, this randomized, double-blind, placebo-controlled trial yielded results that not only showed a lack of efficacy of citalopram on improving treatment outcomes for alcohol dependence, but also indicated poorer outcomes compared to placebo. These results are novel in that the poorer treatment response was consistent across patients with and without concurrent mood or anxiety disorders. The results are counterintuitive and may have significant clinical implications. In particular, these results suggest that the use of SSRIs among alcohol-dependent patients early in recovery, prior to the onset of abstinence, may be contraindicated.

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