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A Randomized, Double-Blind, Placebo-Controlled Trial of Citicoline in Patients with Alcohol Use Disorder

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Abstract

Background: Alcohol use disorder is a major societal and individual burden that exacerbates health outcomes, decreases quality of life, and negatively affects U.S. healthcare spending. Although pharmacological treatments are available for alcohol use disorder, many of them are limited by small effect sizes and used infrequently. Citicoline is a widely available over-the-counter supplement with a favorable side effect profile. It acts through cholinergic pathways and phospholipid metabolism. The current report examines the effect of oral citicoline on alcohol use, craving, depressive symptoms and cognitive outcomes in individuals with alcohol use disorder.

Methods: A 12-week, randomized, double-blind, parallel-group, placebo-controlled, pilot study of citicoline (titrated to 2000 mg/day) in 62 adults (age 18–75) with alcohol use disorder was conducted. Alcohol use, such as number of drinking days, amount used, and number of heavy drinking days, was assessed using the Timeline Followback method and liver enzymes, while alcohol craving was measured using the Penn Alcohol Craving Scale. A neurocognitive battery (e.g., Rey Auditory Verbal Learning Test – RAVLT) and depressive symptoms scales (e.g.,

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Inventory of Depressive Symptomatology Self-Report – IDS-SR) scores were also collected. Data were analyzed using a random regression analysis.

Results: The primary outcome analysis was conducted in the intent-to-treat sample and consisted of n=55 participants (78.2% men and 21.8% women, mean age of 46.47 ± 9.15 years) with a mean of 77% of days accounted for were drinking days. Significant between-group differences were not observed on alcohol use, craving, cognitive or depressive symptom measures. Citicoline was well tolerated.

Conclusions: This proof-of-concept study observed that citicoline was well tolerated, but was not associated with a reduction in alcohol use or other outcomes, as compared to placebo. The favorable effects reported with citicoline for cocaine use, cognitive disorders, and other conditions do not appear to extend to alcohol use disorder.

Keywords

Citicoline; Alcohol Use Disorder; Clinical Trial; Cognition

Introduction

Alcohol abuse and dependence represent major public health concerns, with over 8.5% of the United States adult population meeting criteria for an alcohol use disorder (Grant et al., 2004), and over half of the American families being directly impacted by these illnesses (Dawson and Grant, 1998). Additionally, alcohol use disorder represents a significant financial burden, accounting for over \$200 billion in annual U.S. spending (Rehm et al., 2009).

Although alcohol use is a major health concern and exacerbates other medical and psychiatric conditions, the currently available pharmacotherapy options are limited in their efficacy and scope of use. Several medications, such as acamprosate, naltrexone, disulfiram, and topiramate are commonly prescribed for the treatment of alcohol dependence, while off-label treatment options include ondansetron and gabapentin (Campbell et al., 2018).

Meta-analyses of acamprosate and naltrexone largely suggest their effectiveness in the treatment of alcohol use disorder, including a reduction in alcohol use and craving, although the observed effect sizes are not generally large (Maisel et al., 2013), (Jonas et al., 2014), (Mann et al., 2004). Other medication options, such as disulfiram, are associated with poor adherence and safety concerns (Chick, 1999), but have demonstrated efficacy for highly motivated patients who want to abstain from alcohol completely (Fuller and Gordis, 2004). Recent promising evidence exists for the effectiveness of topiramate in alcohol dependence, with several placebo-controlled clinical trials showing medium to large effect sizes on a variety of alcohol consumption and safety outcomes (Likhitsathian et al., 2012), (Johnson et al., 2003), (Johnson et al., 2007), including cognitive changes, such as mental slowing, and reduction in verbal fluency and working memory (Knapp et al., 2015).

In general, prior research indicates that although several medications do appear effective for decreasing alcohol consumption, these studies have suffered from high attrition due to potential side effects concerns (Palpacuer et al., 2018), and the application of these drugs

may be limited in scope. Thus, novel pharmacological options with a favorable side effect profile, consistent efficacy across different alcohol use patterns, and a widespread availability are needed.

Citicoline is an over-the-counter (OTC) supplement that has shown promise in studies on addiction (Wignall and Brown, 2014), particularly bipolar disorder and cocaine use disorder where two positive clinical trials have been reported (Brown et al., 2007, Brown et al., 2015). Citicoline is a pharmacological agent that consists of cytosine, choline, ribose, and pyrophosphate, and is rapidly metabolized to cytidine and choline after oral administration (D'Orlando and Sandage, 1995). Animal studies show that citicoline increases incorporation of phospholipids into membranes, improves structural phospholipid synthesis, and increases cerebral metabolism (Secades and Lorenzo, 2006). In animal models, chronic heavy alcohol consumption decreases the phospholipid phosphatidylcholine (PC) due to alterations of enzymes involved in the citicoline pathway (Carrasco et al., 2002). The relatively uninvestigated possible role of cholinergic systems in alcohol use has been recognized for many years (Ho and Kissin, 1975). Citicoline may also reduce brain glutamate activity by increasing expression of excitatory amino acid transporter-2 (Hurtado et al., 2005). Modulation of glutamate transmission has been proposed as a potential treatment target for alcohol use disorder (Goodwani et al., 2017). Citicoline may also have neuroprotective properties (Alkan et al., 2001), which can have important implications for cognitive decline frequently seen in patients with alcohol dependence (Oscar-Berman and Marinkovic, 2007), (Kopelman et al., 2009). Citicoline appears to attenuate brain injury following ischemic stroke (Secades et al., 2016). A suggested mechanism is an increase in glutathione levels and reduction of arachidonic acid and attenuation of the loss of phosphatidylcholine, cardiolipin, and sphingomyelin following an ischemic event (Adibhatla and Hatcher, 2002). In rats, citicoline reduces spatial memory deficits and increases extracellular acetylcholine level following traumatic brain injury, suggestive of a neuroprotective effect related to cholinergic pathways (Dixon et al., 1997). In a randomized trial of citicoline vs. placebo in 20 patients with alcohol dependence, the citicoline group showed greater improvement in attention, concentration and temporo-spatial orientation, at 60 day follow-up, as well as a 143 point decrease in gamma-glutamyl transferase (GGT) levels compared to 38 points for placebo (Chinchilla A, 1995). Other studies have shown a reduction in cocaine use, and good safety and tolerability of citicoline in patients with both bipolar disorder and cocaine use (Brown et al., 2007), (Brown et al., 2015). These reports, while preliminary, may suggest the benefit of citicoline in alcohol use, including a reduction in consumption, as well as cognitive benefits.

The objectives of this clinical trial was to examine whether citicoline was associated with less alcohol use and craving, as well as better cognitive functioning, such as executive functioning and declarative memory, compared to placebo.

Materials and Methods

A 12-week, randomized (1:1), double-blind, parallel-group, placebo-controlled trial of citicoline in 62 outpatient adults with alcohol use disorder was conducted at the University of Texas Southwestern Medical Center, Dallas, TX between 6/2014 – 10/2016. Potential participants were identified through flyers, as well as through free and paid forms of

advertising in the community. The study protocol was reviewed and approved by the UT Southwestern Institutional Review Board (IRB), and all participants signed an informed consent form prior to undergoing any study procedures. The trial was registered at clinicaltrials.gov under NCT02074735.

The primary aim of the study was to determine whether citicoline treatment was associated with less alcohol use than placebo in participants with alcohol use disorder, using Timeline Followback (TLFB) method (Sobell and Sobell, 1992), including the number of heavy drinking days per week (primary outcome measure), days of alcohol use per week, and number of standard drinks per week. The secondary aim of the study was to determine whether citicoline treatment was associated with greater improvement in cognition, including executive functioning and declarative memory, than placebo, using a neurocognitive battery described below.

The included participants were men and women between 18 and 75 years old, who met criteria for the alcohol use disorder using the modified Structured Clinical Interview for DSM IV (SCID-IV) clinician version (First et al., 1995). The alcohol and substance abuse/dependence sections of the SCID-IV were modified to fit DSM 5 diagnostic criteria for alcohol and substance use disorders. Additionally, the SCID-IV was used to rule out any exclusionary psychiatric illness during the baseline assessment. As part of the inclusion criteria, candidate participants had to report at least 28 drinks per week and at least 7 heavy drinking days (4 drinks/day for women, 5 drinks/day for men) in the past 28 days, measured using TLFB. Penn Alcohol Craving Scale (PACS) was used as a self-report measure of alcohol craving (Flannery et al., 1999). Participants had to abstain from alcohol for 72 hours prior to their randomization visit (no more than 7 days between the baseline and the randomization visits), and had to have a Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (CIWA-Ar) (Sullivan et al., 1989) score ≥ 10 at randomization. Abstinence at randomization was verified based on self-report and a negative breathalyzer test.

The excluded participants were vulnerable populations (i.e., pregnant or nursing women, cognitively impaired, prisoners); patients with history of delirium tremens, cirrhosis, arrhythmia, myocardial infarction, coronary artery bypass graft surgery in the past 6 months, with active angina, blood pressure $> 170/105$, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels > 3 times normal limit, or other unstable medical conditions; patients at high risk of suicide (suicide attempt in the past 6 months or current suicidal ideation with plan and intent) or violence (assault in the past 6 months or violent thoughts with evidence of a plan and intent); patients undergoing intensive outpatient treatment for substance abuse other than a 12-step program or weekly therapy or treatment that started at least 28 days prior to randomization; patients with history of bipolar disorder, schizophrenia, substance use disorder other than alcohol or nicotine, or in a current major depressive episode.

In addition to the alcohol use measures, eligible participants were assessed on the secondary cognitive outcome measures consisting of Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996), the Golden Stroop Color Word Test (Stroop) (Golden, 1978), Trail Making

Test (TMT) (Spreen and Strauss, 1998), the Running Memory Continuous Performance Test (RMCPT) (Baddeley, 1986), and the Sternberg Memory Task (SMT) (Sternberg and Koster, 1969). The side effects were assessed using The Psychobiology of Recovery in Depression III – Somatic Symptoms Scale (PRD-III) (Thase et al., 1996), and the medication adherence was tracked every visit using the Medication Event Monitoring System (MEMS®) and pill counts.

Blood was drawn for routine laboratory analyses to ensure participant health and safety, including the Complete Blood Count (CBC), the Comprehensive Metabolic Panel (CMP) with liver enzymes, such as ALT and AST, and the γ -glutamyltransferase (GGT). A physical examination was performed, along with a urine drug screen and a urine pregnancy test for all women of childbearing potential. At each follow up visit, the participants were given TLFB, CIWA-Ar, PRD-III and PACS, and also met with a study physician for a safety assessment. The neurocognitive assessments were repeated at weeks 4, 8, and 12.

Computer-based randomization was performed by an unblinded statistician to allocate participants to either a citicoline group or an identical placebo group for 12 weeks. The study drug was initiated at 500 mg/day at baseline, increased to 1000 mg/day at week 2, 1500 mg/day at week 4, and 2000 mg/day at week 6. The 2000 mg/day dose was selected because this is the upper limit of doses used in prior substance use disorder research (Wignall and Brown, 2014). Slower titration or dose adjustments were allowed, if needed, based on clinician judgment and presenting side effects. All research personnel involved in participant assessment and evaluation were blinded to the treatment conditions.

Statistical Analysis

Demographic and other baseline characteristics were compared between treatment groups using t-tests for continuous variables and chi-square test for categorical measures. Intent-to-treat (ITT) sample was used in the analysis, such that all participants who completed the baseline visit and at least one post-baseline assessment were included in the analysis. Data on drop-outs and non-completers were analyzed up to the point of study discontinuation.

To analyze drinking days, alcohol craving, and cognitive outcomes, a random regression analysis was performed using SAS Proc Mixed. The terms included in the model were the treatment group as a between-subject factor, time as a within-subject factor, and a group by time interaction term. Baseline values of the outcome measures were included in the model as covariates.

The sample size was selected as follows. Complete data from 50 participants would provide 80% power when comparing groups with an alpha of .05 and a large effect size (Cohen's d 0.8). To account for possible attrition, we randomized 62 participants. Based on our pilot data and $n = 50$ we estimated approximately 90% power on heavy drinking days, 80% power on alcohol craving, 60% power on days/weeks of alcohol use, and over 90% power on declarative memory changes.

Results

Of the 62 participants randomized, 55 participants completed at least one post-baseline visit and were included in the randomized regression analyses. At baseline, the citicoline (n=29) group was older than the placebo (n=26) group, but the groups were similar on all other demographic characteristics (Table 1).

On the primary outcome of heavy drinking days, there was a main effect of time ($p = .0006$), with weeks 8 and 12 being significantly different ($p = .05$). There were no differences between treatment groups ($p = .31$) or an interaction between group and time ($p = .48$) (Figure 1). Similarly, for drinking days, there was a main effect of time ($p = .0008$) on the number of drinking days controlling for baseline 1, with a significant difference in the number of drinking days between week 4 and week 12 ($p = .02$), where participants reported more drinking days on week 12 compared to week 4. A similar effect held when controlling for baseline 2 with a significant difference between week 4 and 12 in the number of drinking days ($p = .03$). There was no difference between those who received citicoline compared to those who received placebo ($p = .24$), nor was there a significant time by treatment interaction ($p = .79$).

The alcohol craving, as measures by PACS, the overall sample showed a main effect of time ($p = .002$) and a significant difference between week 4 and week 12 ($p = .03$). There were no group ($p = .13$) or group by time interaction ($p = .99$) effects (Figure 2).

On the secondary cognitive outcomes for RAVLT, there were no significant treatment group effects for the total T score ($p = .83$), the delay T score ($p = .70$) or group by time interactions (total $p = .86$; delay $p = .58$). When looking at RAVLT change scores from Baseline to Week 12, there was no statistically significant difference in total T score ($p = .82$) or the delay T score ($p = .61$) between citicoline ($M = -1.43$) and placebo ($M = -2.00$) groups.

The number of side effects that were reported did not differ between groups ($p = .62$) or weeks ($p = .11$), and there was not a significant group by time interaction ($p = .97$). Furthermore, type of side effects reported did not differ between groups at week 4 ($p = .54$), 8 ($p = .28$), and 12 ($p = .27$). Overall, there were no differences between treatment groups on tolerability.

Discussion

This study did not find significant between-group differences in any of the alcohol-related or other outcome measures (e.g. cognition). Thus, the findings are in contrast to our two studies suggesting that citicoline reduced cocaine use in people with bipolar disorder and cocaine dependence. The differences in the results could be due either to the different substance of abuse (cocaine vs. alcohol) or the presence vs. absence of bipolar disorder. The findings also do not replicate those of Chinchilla et al. in which 20 patients (17 males, 3 females) with alcohol dependence were randomized to citicoline or placebo. After 60 days, the group receiving citicoline showed greater improvement than placebo on measures of attention, concentration and temporo-spatial orientation, and had a 143 point decrease in gamma-

glutamyl transferase (GGT) levels as compared to 38 points for placebo (Chinchilla A, 1995). Similarly to the current study, participants in Chinchilla et al were predominantly middle age males (average age 41.3 for citicoline group and 45.3 for placebo); however, conflicting findings between the two studies could be due to differences in the outcome measures used or, given the modest sample sizes in both reports, the possibility of type I or type II error. While citicoline appears to be a promising potential treatment for a variety of conditions, the present findings do not suggest that it holds promise for the population studied in this report. In the current report, craving showed a sustained reduction by week 4, and then continued through week 12, while alcohol use showed an initial reduction followed by a slight increase from week 8 to week 12. These somewhat contradictory findings between the two alcohol measures are not inconsistent with prior research. Haass-Koffler et al. describe alcohol craving as a subjective experience that is influenced by mood and emotions as well as length of abstinence, and that it is not necessarily related to the ability of a medication to reduce alcohol consumption (Haass-Koffler et al., 2014).

Citicoline appeared to be quite safe and well tolerated in patients with AUD and active alcohol use. Neither overall side effect burden nor study survival differed significantly between the two groups. This finding is consistent with prior reports by our group (Brown and Gabrielson, 2012, Brown et al., 2015, Brown et al., 2007), and in systematic reviews (Fioravanti and Yanagi, 2004, Meshkini et al., 2017).

The study has several limitations. Because this was a proof-of-concept study the sample size was modest. The observation period of 12 weeks, while typical for a clinical trial for AUD, might not be long enough to see the effects of citicoline on alcohol use. While retention was good, some participants discontinued early or had missing data. In summary, statistically significant improvement in alcohol use and craving was not observed with citicoline as compared to placebo in outpatients with AUD. Previous reports suggest that citicoline may decrease alcohol use. However, based on the current findings, it does not appear to decrease alcohol use.

In summary, this 12-week trial found did not suggest the effectiveness of citicoline over placebo for patients with AUD and ongoing alcohol use. This finding did not lend support to previous findings that suggested potential efficacy of citicoline for both cocaine and alcohol dependence. However, both the current and the past study on alcohol use was limited by a fairly small sample size, which could explain the variability in the findings.

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Figure 1. Heavy drinking days by group.

Note: Fraction of heavy drinking days in the citicoline and placebo groups over 12 weeks.

Figure 2. Alcohol craving by group.

Note: Alcohol craving (PACS scores) in the citicoline and placebo groups over 12 weeks.

PACS – Penn Alcohol Craving Scale.

Table 1.

Demographic characteristics by treatment group.

	Placebo (N = 26)	Citicoline (N = 29)	Test Statistic
Gender	N(%)	N(%)	
Female	5 (19.2%)	7 (24.1%)	$\chi^2(1) = .19, p = .66$
Male	21 (80.8%)	22 (75.9%)	
Race			$\chi^2(2) = 1.39, p = .50$
African American	16 (61.5%)	15 (51.7%)	
Caucasian	7 (26.9%)	12 (41.4%)	
Hispanic	3 (11.5%)	2 (6.9%)	
	M(SD)	M(SD)	
Age	43.61(9.30)	49.03(8.36)	$t(53) = -2.27, p = .03$
Education	13.69(2.81)	13.72(2.03)	$t(53) = -0.05, p = .96$
Fraction of days using alcohol	0.87(0.19)	0.87(0.17)	$t(53) = 0.02, p = .99$
Fraction of heavy drinking days	0.82(0.24)	0.72(0.29)	$t(53) = 1.44, p = .16$

Note: Heavy drinking days = number of heavy drinking days divided by the number of days in the assessment period.