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Combining Seeking Safety with Sertraline for PTSD and Alcohol Use Disorders: A Randomized Controlled Trial

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Abstract

Objective—The current study marks the first randomized controlled trial to test the benefit of combining Seeking Safety (SS), a present-focused cognitive behavioral therapy for co-occurring posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD), with sertraline, a front-line medication for PTSD shown to also impact drinking outcomes.

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Method—Sixty-nine participants (81% female; 59% African American) with primarily childhood sexual (46%) and physical (39%) trauma exposure, and drug dependence in addition to AUD were randomized to receive a partial-dose (12 sessions) of SS with either sertraline ($n = 32$; $M = 7$ sessions) or placebo ($n = 37$; $M = 6$ sessions). Assessments conducted at baseline, end-of-treatment, 6- and 12-months posttreatment measured PTSD and AUD symptom severity.

Results—Both groups demonstrated significant improvement in PTSD symptoms. The SS plus sertraline group exhibited a significantly greater reduction in PTSD symptoms than the SS plus placebo group at end-of-treatment (M difference = -16.15 , $p = .04$, $d = 0.83$), which was sustained at 6- and 12-month follow-up (M difference = -13.81 , $p = .04$, $d = 0.71$, and M difference = -12.72 , $p = .05$, $d = 0.65$, respectively). Both SS groups improved significantly on AUD severity at all posttreatment time points with no significant differences between SS plus sertraline and SS plus placebo.

Conclusion—Results support the combining of a cognitive behavioral therapy and sertraline for PTSD/AUD. Clinically significant reductions in both PTSD and AUD severity were achieved and sustained through 12-months follow-up. Moreover, greater mean improvement in PTSD symptoms was observed across all follow-up assessments in the SS plus sertraline group.

Keywords

PTSD; alcohol abuse; cognitive-behavioral treatment; sertraline; selective serotonin reuptake inhibitor; randomized clinical trial

Decades of research have documented high rates of trauma exposure among individuals with substance use disorders (SUD; Debell et al., 2014; Torchalla, Nosen, Rostam & Allen, 2012; van Dam, Vedel, Ehling & Emmelkamp, 2012) as well as multiple negative consequences in biological, psychological, and interpersonal domains of functioning (McCauley, Killeen, Gros, Brady & Back, 2012; Norman et al., 2012). Longitudinal studies indicate that for individuals with PTSD, the risk of developing an alcohol use disorder (AUD) or other SUD is approximately six times greater than for those without PTSD (Breslau, Davis, & Schultz, 2003; Creamer, Burgess, & McFarlane, 2001) and among individuals with PTSD, 10 to 61% report alcohol misuse (Debell et al., 2014). This comorbid population seeks treatment more often than alcohol dependent individuals without PTSD, yet the prognosis for treatment is frequently poor (Debell et al., 2014; Ouimette, Ahrens, Moos, & Finney, 1997; Smith & Randall, 2012). Individuals with AUD and comorbid psychopathology are less compliant with treatment, more likely to drop-out, have higher suicide rates, and receive less support for achieving and maintaining sobriety (Smith & Randall, 2012). Additionally, compared to AUD patients without comorbid PTSD, those with comorbid PTSD spend a greater number of hospital overnights for addiction treatment even when there are no differences in substance abuse severity (Brown, Stout, & Mueller, 1999; Sannibale et al., 2013; Smith & Randall, 2012). These findings indicate that the AUD patients with comorbid PTSD have poorer treatment outcomes and may overuse costly inpatient addiction services. PTSD severity is widely reported to worsen early in abstinence (Brady, Killeen, Saladin, Dansky, & Becker, 1994), making treatment of AUD particularly challenging. PTSD symptoms are common triggers of alcohol use relapse that, in turn, can heighten PTSD symptoms

(Ralevski, Olivera-Figueroa, & Petrakis, 2014; Coffey et al., 2002; Waldrop, Back, Verduin, & Brady, 2007), creating a maladaptive feedback cycle.

Despite the widespread impression among clinicians and the converging research findings that PTSD comorbidity hampers the treatment responses of individuals in SUD treatments, the two disorders have only more recently been treated simultaneously (Brown, Recupero, & Stout, 1995; Najavits, Weiss, & Leise, 1996; van Dam et al., 2012). Moreover, although cumulative findings suggest the importance of examining treatment-related alcohol outcomes specifically, most clinical trials on PTSD and comorbid SUD have targeted drug-dependent rather than alcohol-dependent individuals. Integrated behavioral interventions for PTSD+SUD are either *present-focused* or *past-focused* (Najavits & Hien 2013). Past-focused interventions integrate trauma-focused techniques in tandem with relapse prevention strategies (Mills et al., 2012; Sannibale et al., 2013). Trauma-focused strategies include extensive exploration of trauma memories and in-vivo confrontation of avoided (safe) trauma-reminders (e.g., prolonged exposure). In integrated, present-focused treatment approaches, such as Seeking Safety, there is limited exploration of the trauma memories. Instead, the focus in Seeking Safety is on the impact of traumatic stress on current functioning and its relationship to substance and alcohol use, utilizing psychoeducation and cognitive-behavioral techniques to boost current coping strategies (Najavits & Hien, 2013).

Studies suggest present- and past-focused treatments that address PTSD and SUD simultaneously are more likely to succeed, more cost-effective, and more sensitive to patient needs (Hobbs, Kushner, Lee, Reardon, Maurer, 2011; Mills et al., 2012; Sannibale et al., 2013; Torchalla, Nosen, Rostam & Allen, 2012). Seeking Safety is the most widely tested integrated present-focused treatment to date (i.e., in 20 randomized controlled trials and pilot studies) and has been found to significantly reduce substance use as well as PTSD symptoms across a variety of populations (see Najavits & Hien, 2013). However, more than half of PTSD sufferers continue to have a range of symptoms after receiving treatment, a trend that is consistent with other PTSD treatments (Hien et al., 2009).

Pharmacotherapy plays an increasing role in the treatment of AUD patients specifically. The use of antidepressants in AUD treatment makes sense given the advent of selective serotonin reuptake inhibitors (SSRIs) with excellent safety profiles and the high rates of depression and anxiety disorders that may co-occur with AUDs (e.g., Ralevski, Oliveras-Figueroa, & Petrakis, 2014, Kranzler, Amin, Modesto-Lowe, & Oncken, 1999). In studies of alcohol users without comorbid disorders, findings on the efficacy of SSRIs have been mixed with some studies finding modest but significant reductions (10–26%) in the alcohol consumption of non-clinically depressed heavy drinkers (Naranjo, Kadlec, Sanhueza, Woodley-Remus, & Sellers, 1990; Naranjo et al., 1987; Naranjo et al., 1989) and others finding no effects on alcohol use (Gorelick & Paredes, 1992; Kranzler et al., 1995).

There is compelling evidence supporting the use of SSRIs for PTSD (Friedman, 2013; Ipser & Stein, 2012, Forbes et al., 2010) with findings of significantly greater response to sertraline than placebo leading to FDA approval for both sertraline and paroxetine. However, only one published study has examined the impact of combination SSRI and cognitive behavioral therapy (CBT) among individuals with PTSD and AUD (Brady et al.,

2005) with results indicating that pharmacotherapy with CBT was more efficacious than placebo with CBT. In this study, a subgroup of participants with early onset PTSD and less severe AUD who received sertraline demonstrated significantly greater reductions in drinking compared to individuals with early onset and severe AUD. Because the study's cognitive behavioral component (Project MATCH Research Group, 1997) addressed only AUD symptoms, however, the efficacy of combining sertraline with a CBT that addresses co-occurring PTSD and SUD symptoms remains to be tested.

Research on the classification of AUD into meaningful subtypes has previously identified two clinically distinct groups: a later onset AUD typified by less severity and chronicity of symptoms and an earlier onset presentation with more severe symptomatology (Buydens-Branchey, Branchey, & Noumair, 1989). The claim that SSRI treatment response is moderated by AUD subtypes has been supported by studies reporting significant reduction in alcohol use in later onset AUD treated with sertraline (Pettinati et al., 2000) and poorer drinking outcomes for early onset AUD treated with fluoxetine (Kranzler, Bureson, Brown, & Babor, 1996). However, it remains to be determined whether these subtypes would respond differently to a treatment employing SSRIs and CBT where both AUD and PTSD symptoms are targeted.

Given the existing data suggesting that sertraline 1. decreases alcohol consumption to a modest degree for those with AUD alone; 2. is a first line pharmacotherapy for PTSD; 3. can lead to improvements in drinking and PTSD outcomes among subtypes of individuals with AUD and comorbid depression or PTSD; and 4. has an excellent safety profile, the present study was designed to test the following hypothesis: the combination treatment of Seeking Safety and sertraline would be significantly more efficacious than Seeking Safety and placebo in reducing PTSD and AUD symptoms. An additional exploratory analysis was conducted to examine whether response to treatment was moderated by AUD onset (early vs. late).

Method

All procedures were reviewed and approved by the institutional review boards of The New York State Psychiatric Institute (NYSPI) and The City College of New York. Written informed consent was provided by all participants.

Participants

Inclusion criteria were 1. *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) criteria for full PTSD or subthreshold PTSD (Grubaugh et al., 2005) defined as meeting Criteria A (exposure to a traumatic stressor), B (re-experiencing symptoms), E (symptom duration of at least 1 month), and F (significant distress or impairment of functioning), and either C (symptoms of avoidance and/or numbing) or D (increased arousal symptoms) 2. *DSM-IV-TR* criteria for current alcohol dependence or alcohol abuse with at least 2 heavy drinking days (more than 3 drinks for women and more than 4 drinks for men) in the past 90 days or at least 14 drinks over 30 consecutive days or less than 22 consecutive abstinent days. Individuals who did not meet criteria for alcohol abuse or dependence were eligible if they reported at least one

episode of alcohol misuse during the prior 90 days. Alcohol misuse was defined as either hazardous drinking (for women, more than 7 drinks per week; for men, more than 14 drinks per week) or binge drinking (4 or more drinks over a 2 hour time frame for women and 5 or more drinks over a 2 hour time frame for men; NIAAA, 2013).

Exclusion criteria were: 1. advanced stage medical disease as indicated by global physical deterioration and incapacitation, 2. organic mental syndrome 3. diagnosis of bipolar I or psychotic-spectrum disorders 4. any disorder which might have made antidepressant treatment hazardous, 5. current pregnancy or lactation, 6. history of seizures (not related to alcohol withdrawal), 7. current use or prescription of psychotropic medications by another physician, 8. history of allergic reaction to sertraline, 9. current active suicidal or homicidal ideation, intent, or behavior, 10. age over 65 or under 18, and 11. refusal to be audio and videotaped. Individuals with other SUDs or current major depressive disorder were not excluded.

Procedures

Recruitment and pre-randomization assessments—Participants were recruited through newspaper and radio advertisements, flyers, and referrals from outpatient mental health centers between April 2006 and March 2012. Individuals were screened through a brief telephone interview and then completed a baseline interview where alcohol use, PTSD, and demographic data were collected. After baseline assessment and medical clearance, all eligible participants began a one-week, single-blind placebo lead-in phase, during which they met with a trained clinician for a 30–45 minute motivational enhancement session. Those who completed the lead in phase were accepted into the study and randomly assigned to one of the two treatment conditions.

Randomization—Participants, study psychiatrist, therapists, and assessors were blind to treatment condition assignment. The pharmacy created sertraline and matching placebo kits with single-identifier numbers based on a random code that was provided to an unblinded statistician who instructed the psychiatrist how to distribute kits to subjects. An urn randomization procedure was utilized to balance treatment conditions on baseline severity of alcohol and other substance use and baseline severity of depression. Allocation was concealed from study staff for the length of patient's study participation.

Treatments

1. Integrated, Present-Focused Cognitive Behavioral Therapy: Seeking Safety (Najavits, 2002) is a manualized intervention, based on five central ideas: 1.) safety as the priority; 2.) integrated treatment of PTSD and SUD; 3.) a focus on ideals; 4.) four content areas: cognitive, behavioral, interpersonal, and case management; and 5.) attention to therapist processes. Session content was structured to engage in themes relevant to both PTSD and SUD, and to learning a specific CBT skill. In consultation with its developer, Lisa Najavits, Ph.D., the Seeking Safety treatment was abbreviated from 25 to 12 core sessions to better fit within a feasible time-frame for community-based outpatient treatment programs. Treatment sessions were delivered in a 60-minute weekly individual format by eight experienced (PhD or LCSW level) research therapists who underwent rigorous training in the Seeking Safety

protocol which included a 3-day introduction to the treatment manual followed by delivery of a test case in which all sessions were reviewed by the expert supervisor for adherence and competence, and ongoing weekly supervision and case review during the study period.

2. Medication: Matching capsules contained sertraline or placebo as well as riboflavin to assess medication adherence. Compliance was also monitored by pill count. Participants receiving sertraline started on 50 mg daily and titrated up to 200 mg daily over a 2-week period. Participants continued on their full sertraline dose until the end of the trial and were tapered after unblinding. Responders were offered the option to remain on medication.

Supervision and fidelity—All Seeking Safety sessions were audiotaped and a proportion (>50%) of session recordings reviewed and rated using the *Seeking Safety Session Format Checklist* (Najavits, 2003) by an expert supervisor (Lisa Litt, Ph.D.) for curriculum adherence. Throughout the course of the study research therapists met weekly for supervision. If curriculum adherence fell below the competency criterion, more supervision was provided. A randomly selected 25% of sessions reviewed by the supervisor were also rated by one of the lead investigators as a means of confirming supervisor fidelity and interrater reliability. Supervisor fidelity was defined as agreement at a 70% level with specific adherence measures for the Seeking Safety curriculum.

Measures

During the intervention phase of the study, participants met weekly with a research assistant for the collection of a urine sample, alcohol breathalyzer test, and self-report assessments of PTSD symptoms, alcohol and drug use, and any adverse events. After the study treatment phase, assessment interviews were conducted by blind independent assessors at end-of-treatment, 6- and 12-months posttreatment.

Sociodemographics—Age, race/ethnicity, education, marital status, employment pattern, and prior AUD treatment episodes were collected at the baseline assessment. See Table 1.

Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995)—The CAPS is a structured, clinical interview for assessing the frequency and intensity of *DSM-IV-TR* PTSD symptoms, impairments in social and occupational functioning, diagnosis, and overall symptom severity. The scale consists of the Re-Experiencing, Avoidance/Numbing, and Hyperarousal symptom cluster subscales. The frequency and intensity scores for each symptom cluster subscale are summed to obtain an overall total scale score. CAPS were administered by trained Master's or PhD level clinicians, and scoring data demonstrated good to excellent internal consistency reliability across baseline and all follow-up assessments ($\alpha = .86 - .92$).

Structured Clinical Interview for DSM-IV for Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002) modules for Mood Disorders, Alcohol and Psychoactive Substance Use Disorders, and Psychotic Disorder screen. The SCID-I, a semi-structured interview, was administered at baseline and follow-up points to assess current AUD/SUD diagnoses, age of AUD/SUD onset, and the presence of any other current or past mood disorder [e.g., major depressive disorder or dysthymic disorder]. Axis II (personality)

disorders were not assessed. AUD/SUD diagnoses were considered current if diagnostic criteria were met in the prior 6 months. High inter-rater reliability has been demonstrated for the SCID-I (First et al., 2002).

Timeline Follow-Back (TLFB; Sobell & Sobell, 1992)—TLFB was used to assess alcohol use patterns before the start of treatment, weekly during the trial, and at each follow-up timepoint. Participants retrospectively estimated their daily alcohol consumption in the previous 90 days with a detailed calendar to help orient them to patterns in their drinking and specific episodes of erratic or binge drinking. TLFB has demonstrated good reliability as an instrument for the estimation of daily alcohol consumption (Sobell, Sobell, Leo, & Cancilla, 1988).

An alcohol breathalyzer test was administered at all study visits in order to measure participants' blood alcohol concentration. Urine toxicology tested for the presence of cocaine, opiates, methadone, cannabis, phencyclidine and amphetamines at all assessment timepoints. In addition, two pregnancy tests were conducted at baseline and week six of treatment. Urine samples were also tested for riboflavin to assess medication compliance.

Participants were compensated \$30 for the completion of baseline, end-of-treatment, and follow-up assessments. They received \$15 at each treatment session with the return of their pill-bottles and completion of weekly assessments.

Statistical Methods

Bivariate analyses were utilized to compare demographics and baseline symptom severity between the combined Seeking Safety with sertraline group (SS+Sertraline) and the Seeking Safety with placebo group (SS+Placebo), and to explore the data for potential covariates for the main omnibus analyses. The main outcome variable for PTSD was CAPS total score, which is comprised of the sum of frequency and intensity ratings across 17 symptoms, and was administered at baseline and all follow-up assessments. The main outcome variables for AUD were average number of drinks per drinking day in the past 7 days (DDD), number of heavy drinking days in the past 7 days (HDD; five or more drinks per day for men and four or more drinks per day for women are considered heavy drinking days), and self-reported abstinence from alcohol in the prior 7 days and negative breathalyzer tests at follow-up assessments.

All analyses were conducted on the intent-to-treat sample. Generalized estimating equations (GEE) were utilized to model PTSD and drinking outcomes (Ballinger, 2004). This method is an extension of the generalized linear model that handles correlated data arising from repeated measurements, requires no parametric distribution assumption, and provides robust inference with respect to misspecification of the within-subject correlation (Zeger & Liang, 1986; Zeger, Liang, & Albert, 1988). A temporal within-subjects autoregressive [AR(1)] correlation matrix was used to model participants across timepoints. Models were specified according to the distributions of the outcome measures. For example, identity link functions for normal distributions were used to model CAPS severity scores, negative binomial models with log link were applied to the alcohol consumption measures of HDD and DDD, and past 7 days abstinence rate was modeled using logit link for binary distribution.

Accordingly, results are reported using parameter estimates for CAPS, incidence rate ratios for HDD and DDD, and odds ratios for abstinence rate.

All models included variables of time, treatment, time-by-treatment interaction, and any demographic or baseline diagnostic covariates for which there was a significant difference between groups. Consistent with prior studies applying similar analytic methods to comparable sample sizes (Schneier et al., 2012), and to reduce the probability of Type-II errors (Selvin, 1996), interactions that were at least trend-level (i.e., $\alpha < .10$) were probed for simple effects at end-of-treatment and follow-up timepoints. When an interaction did not meet this criterion, outcomes were modeled as main effects with covariates of time and baseline values of the outcome measures included in the model. All simple and main effects were considered significant at the $\alpha = .05$ level (two-tailed). Since three drinking variables were analyzed, Bonferroni corrections were applied to all models of AUD outcomes in order to control for Type I error. Sensitivity analyses with multiple imputation were conducted to further assess the influence of missing data in models that were significant.

Additional exploratory analyses were conducted to examine differences in treatment effects associated with age of AUD onset. Based on evidence that subtyping of AUD by age of onset may moderate medication effects, 25 was utilized as the study's cut-off for early vs. late onset AUD classification (Roache, Wang, Ait-Daoud, & Johnson, 2008; Kranzler, Feinn, Armeli, & Tennen, 2012). AUD age of onset was ascertained from the SCID. Three way interactions of time-by-treatment-by-AUD subtype were probed for simple effects if they approached significance at the $\alpha = .10$ level, and simple effects were considered significant at the $\alpha = .05$ level.

Results

Demographic and Baseline Characteristics

Figure 1 illustrates the participant flow from initial eligibility screening through 6-month follow-up. A total of 69 individuals were randomized into the study. Table 1 presents baseline demographic and descriptive characteristics. No differences were found between treatment conditions with regard to alcohol use frequency/severity, PTSD severity, other SUD comorbidities, or demographic characteristics. Three participants were removed due to serious medical illness. These incidents were reported to the study's institutional review boards and none were determined to be study-related.

Treatment Adherence

Adherence to medication as measured by riboflavin levels in weekly urine collection did not differ between treatment conditions, $\chi^2(1) = 0.77, p = .44$. Rates of riboflavin detection during treatment period for SS+Sertraline and SS-Placebo were 46% and 40% respectively. Overall, 91% attended at least one medication visit and 90% attended at least one Seeking Safety session. Sixty-one participants (88%) attended at least one follow-up assessment. The eight participants who missed all three follow-up assessments could not be included in the outcome models. Attendance rates of Seeking Safety sessions were equivalent across treatment groups [SS+Sertraline: $M = 6.7, SD = 4.0$; SS+Placebo: $M = 6.0, SD = 4.3; t(67) =$

0.71; $p = .48$]. Study retention rates did not differ across treatment groups [$\chi^2(1) = 0.05$; $p = .83$]; 59.4% of SS+Sertraline and 56.8% of SS+Placebo attended at least half of treatment (six or more therapy sessions and six or more medication visits).

PTSD Outcome

Table 2 depicts PTSD severity scores at baseline, end-of-treatment, 6- and 12-month follow-up. The final model for PTSD outcome included time, treatment type, and a time-by-treatment interaction term. Not all participants attended all three follow-up assessments (end-of-treatment, 6- and 12-month follow-ups), and preliminary data analyses indicated that across each of the dependent variables there was not sufficient evidence to conclude that data was not missing completely at random (all $ps > .20$; Little's MCAR test; Little, 1988). Under this assumption, GEEs are equipped to handle missing data without compromising parameter estimates (Ballinger, 2004). Significant decreases in CAPS scores were observed in both groups from baseline to end-of-treatment (SS+Sertraline: M difference = -32.79 , CI_{95} : -43.38 to -22.20 , $p < .001$; SS+Placebo: M difference = -16.70 , CI_{95} : -27.38 to -6.02 , $p = .002$) which were sustained at 6-month follow-up (SS+Sertraline: M difference = -35.20 , CI_{95} : -44.80 to -25.60 , $p < .001$; SS+Placebo: M difference = -20.92 , CI_{95} : -29.71 to -12.12 , $p < .001$) and 12-month follow-up (SS+Sertraline: M difference = -42.22 , CI_{95} : -50.48 to -33.96 , $p < .001$; SS+Placebo: M difference = -29.30 , -38.97 to -19.63 , $p < .001$).

To examine differences between groups, a trend-level time-by-treatment interaction ($p = .096$) was probed for simple effects, which revealed a significantly greater reduction in CAPS scores at end-of-treatment in the SS+Sertraline group relative to the SS+Placebo group (M difference = -16.15 , CI_{95} : -31.18 to -1.13 , $p = .035$, $d = 0.83$), as well as 6-month follow-up (M difference = -13.81 , CI_{95} : -26.88 to -0.74 , $p = .038$, $d = 0.71$) and 12-month follow-up (M difference = -12.72 , CI_{95} : -25.40 to -0.03 , $p = .049$, $d = 0.65$). Effect sizes were calculated following guidelines for models employing GEEs (Feingold, 2009), and can be characterized as large for end-of-treatment, and medium for 6- and 12-month follow-ups (Cohen, 1977). Although the impact of missing data cannot be fully ascertained, a comparison of results from the GEE model (which uses maximum likelihood estimation) with another recommended approach (Hallgren & Witkiewitz, 2013) utilizing multiple imputation demonstrated comparable parameter estimates in the pooled results of five imputed datasets (end-of-treatment: M difference = -16.86 , CI_{95} : -30.21 to -3.52 , $p = .013$; 6-month follow-up: M difference = -14.61 , CI_{95} : -27.83 to -1.38 , $p = .031$; 12-month follow-up: M difference = -13.15 , CI_{95} : -24.27 to -2.04 , $p = .020$).

These results were further underscored by differences between the groups in the amount of participants who achieved clinically significant change, as defined by a 15-point drop on CAPS total score (Weathers, Keane & Davidson, 2001). At end-of-treatment, 79% of SS+Sertraline patients met this criterion, compared to 48% in the SS+Placebo group, highlighting the significant advantage of combined treatment, $\chi^2(1) = 5.12$, $p = .02$. At 6-month follow the SS+Sertraline group maintained a higher rate of improvement relative to the SS+Placebo group (82% vs. 64%) but this difference was no longer significant, $\chi^2(1) = 1.89$, $p = .17$. Seeking Safety + Sertraline's relative advantage over SS+Placebo was most

pronounced at 12-month follow-up where the SS+Sertraline group exhibited a significantly higher rate of clinically significant change than the SS+Placebo group, 95% vs. 64%, $\chi^2(1) = 6.48, p = .01$.

Alcohol Use Outcomes

Table 2 displays alcohol use outcomes (based on weekly assessment measures) at baseline, end-of-treatment, 6- and 12- month follow-ups. At end-of-treatment and both follow-up periods, both treatment groups exhibited significant reductions in all drinking outcomes (adjusted for multiple comparisons). Decreases were observed in DDD at end-of-treatment (SS+Sertraline: $IRR = 0.32, CI_{95}: 0.18 \text{ to } 0.57, p < .001$; SS+Placebo: $IRR = 0.22, CI_{95}: 0.11 \text{ to } 0.46, p < .001$) at 6-month follow-up (SS+Sertraline: $IRR = 0.35, CI_{95}: 0.19 \text{ to } 0.64, p = .003$; SS+Placebo: $IRR = 0.48, CI_{95}: 0.27 \text{ to } 0.84, p = .03$), and 12-month follow-up (SS+Sertraline: $IRR = 0.34, CI_{95}: 0.20 \text{ to } 0.59, p < .001$; SS+Placebo: $IRR = 0.38, CI_{95}: 0.19 \text{ to } 0.76, p = .02$), number of HDD at end-of-treatment (SS+Sertraline: $IRR = 0.33, CI_{95}: 0.16 \text{ to } 0.67, p = .006$; SS+Placebo: $IRR = 0.19, CI_{95}: 0.05 \text{ to } 0.68, p = .03$), at 6-month follow-up (SS+Sertraline: $IRR = 0.27, CI_{95}: 0.13 \text{ to } 0.54, p < .001$; SS+Placebo: $IRR = 0.27, CI_{95}: 0.12 \text{ to } 0.60, p = .003$), and 12-month follow-up (SS+Sertraline: $IRR = 0.09, CI_{95}: 0.04 \text{ to } 0.20, p < .001$; SS+Placebo: $IRR = 0.09, CI_{95}: 0.04 \text{ to } 0.21, p < .001$), and seven day abstinence rate at end-of-treatment (SS+Sertraline: $OR = 0.09, CI_{95}: 0.02 \text{ to } 0.49, p = .02$; SS+Placebo: $OR = 0.11, CI_{95}: 0.04 \text{ to } 0.33, p < .001$), at 6-month follow-up (SS+Sertraline: $OR = 0.06, CI_{95}: 0.01 \text{ to } 0.34, p = .003$; SS+Placebo: $OR = 0.16, CI_{95}: 0.05 \text{ to } 0.50, p = .006$), and at 12-month follow-up (SS+Sertraline: $OR = 0.12, CI_{95}: 0.02 \text{ to } 0.60, p = .03$; SS+Placebo: $OR = 0.09, CI_{95}: 0.03 \text{ to } 0.29, p < .001$). However, between-groups analyses revealed no significant time-by-treatment interaction or overall main effect of the addition of sertraline to SS treatment on any of the alcohol outcome variables.

Exploratory AUD subtype analysis

Participants were categorized as early ($n = 29$) or late ($n = 36$) onset AUD based on their age of onset of alcohol abuse or dependence (25 or less for early, over 25 for late). Four participants could not be categorized due to missing age data. Mean age of AUD onset was 19.1 ($SD = 3.0$) in the early subgroup and 37.0 ($SD = 8.6$) in the late subgroup. Mean age of PTSD onset was 20.6 ($SD = 13.0$) in the early onset AUD subgroup and 29.3 ($SD = 14.2$) in the late onset AUD subgroup. Both of these age means were significantly different between groups [AUD onset: $t(63) = -10.6, p < .001$; PTSD onset: $t(63) = -2.6, p = .01$]. However, none of the baseline symptom characteristics of either disorder were significantly different between groups [CAPS: early onset AUD $M = 62.7, SD = 19.6$ vs. late onset AUD $M = 62.9, SD = 20.4, t(63) = -0.03, p = .98$; DDD: early onset AUD $M = 6.6, SD = 4.5$ vs. late onset AUD $M = 7.5, SD = 5.2$, Kolmogorov-Smirnov (KS; nonparametric comparison) $z = 0.73, p = .66$; HDD: early onset AUD $M = 3.0, SD = 2.1$ vs. late onset AUD $M = 2.9, SD = 2.2, KS z = .28, p = .99$; abstinence: early onset AUD 11.1% abstinence rate vs. late onset AUD 10.3% abstinence rate, $\chi^2(1) = 0.01, p = .92$].

In the SS+Sertraline group, 41% of participants were categorized as early onset AUD, and in the SS+Placebo group, 48% of participants were categorized as early onset AUD.

Preliminary analyses indicated that there were no significant differences in the proportion of

AUD subtypes in each treatment condition, $\chi^2(1) = 0.41, p = .52$. To explore potential differences between early and late AUD onset to sertraline treatment, the main outcome models were rerun with three-way time-by-treatment-by-subgroup interaction terms. However, this interaction was not significant in any of the models (all $ps > .10$) suggesting that there were no differences between the treatments in how individuals with early vs. late AUD onset changed over time.

Discussion

The current study marks the first randomized controlled trial to test the benefit of combining Seeking Safety, an integrated, present-focused CBT for the treatment of co-occurring PTSD and AUD and sertraline, a front-line medication for PTSD which has been shown to also impact drinking outcomes. Overall, clinically significant pre- to post- mean improvements in PTSD symptoms and on all drinking outcomes were observed in both treatment arms that received Seeking Safety. Further, results demonstrated that adding sertraline to Seeking Safety *significantly improved* PTSD symptom reductions among individuals with co-occurring AUD or alcohol misuse in comparison to Seeking Safety with placebo. The addition of sertraline did not confer any further benefits to the psychotherapy for any of the alcohol use outcomes. Study strengths included: the overall advantages of a rigorous randomized controlled trial with high internal and external validity; inclusion of a wide range of AUD and PTSD symptom severity including subthreshold PTSD that suggests treatment gains were not simply a regression to the mean; no requirement for abstinence during the lead-in phase; excellent treatment (i.e., Seeking Safety) fidelity; and a heterogeneous sample of racial/ethnic minorities who are typically underrepresented in alcohol clinical trials.

The impact of co-occurring PTSD and AUD on treatment entry, retention, and outcome has been broadly recognized and represent significant challenges to the effective recovery of both disorders. Research from the past decade has underscored the utility of addressing these disorders concurrently and from an integrative approach (Hien et al., 2009; Mills et al., 2012; Smith & Randall, 2012; van Dam et al., 2012). Nevertheless, investigations that combine effective pharmacological and cognitive behavioral therapies for comorbid PTSD and AUD, in contrast to those which have examined PTSD and SUD, have been sparse (Foa et al., 2013; Ralevski, Olivera-Figueroa & Petrakis, 2014; Sannibale et al., 2013), with few published trials and only one (Sannibale et al., 2013) to date that employs an integrative cognitive behavioral approach to traumatic stress and alcohol misuse.

Although on average, study participants in both conditions improved in their PTSD outcomes, those who received sertraline *in combination with* Seeking Safety demonstrated a 16 point advantage in their CAPS score reduction at the end-of-treatment and achieved clinically significant improvements in PTSD symptoms beyond those achieved by those receiving Seeking Safety and placebo, which were sustained through the 12-month follow-up (95% versus 64%). Notably, more than half of those who received Seeking Safety and placebo also achieved high levels of symptom reduction in both the PTSD and AUD domains. Given that these kinds of symptoms can be so intractable (e.g., people with PTSD describe living with their unrelenting, haunting memories and other symptoms for years past

the original trauma), chronically interfering with daily functioning, the importance of reductions at this level over the course of time should be emphasized. Indeed, Foa and colleagues' (2013) recent study of naltrexone in combination with prolonged exposure did not demonstrate a significant impact of exposure therapy (another type of CBT that focuses on processing past traumatic experiences) on PTSD among those with PTSD/AUD. We speculate that the addition of sertraline may have facilitated patients' ability to derive greater benefits from their psychotherapy, corroborating commonly held clinical wisdom suggesting that psychotropic medications promote a patient's ability to use psychotherapy more effectively. This is noteworthy, given that sertraline has only been tested for comorbid PTSD and AUD in one other study (Brady et al., 2005), where only a trend-level effect on PTSD symptoms was observed.

Seeking Safety, with and without sertraline, was associated with reductions in alcohol use frequency and severity at end of treatment, which was sustained at 6- and 12- month follow-ups, underscoring the benefits of cognitive behavioral strategies for addressing safe coping in this comorbid population. This is particularly striking given that there was no requirement for abstinence during the lead in phase. Moreover, there was no additional effect of sertraline on drinking outcomes. The literature has been mixed regarding the use of SSRIs in the treatment of heavy or regular drinking, particularly among those with comorbid conditions such as PTSD or depression (e.g., Ralevski, Olivera-Figueroa & Petrakis, 2014; Ipser & Stein, 2012). Reviews of controlled medication trials for comorbid AUD and depression revealed that antidepressants decreased drinking in only 38% of studies compared to the reduction of depressive symptoms in 75% of studies (Pettinati, 2004). Among the few studies treating comorbid PTSD and AUD with antidepressants, sertraline improved drinking outcomes in the less severe, late AUD onset subtype (Brady et al., 2005). In a more recent study, Petrakis and colleagues (2012) reported no effects of the SSRI paroxetine on alcohol outcomes.

Notably, the present findings showed no evidence of any *negative* alcohol response from combining sertraline with Seeking Safety. Indeed, the main effect analyses revealed that *both* treatment conditions were associated with significant reductions in PTSD symptoms *and* alcohol consumption rates from baseline to end-of-treatment; these were sustained over the follow-up periods. These findings are in line with a growing body of psychotherapy research in the area of trauma and addiction comorbidity conducted over the past twenty years, which clearly demonstrates that integrative cognitive behavioral interventions for PTSD and substance use—like Seeking Safety—can have an impact on both disorders (Najavits & Hien, 2013, Dass-Brailsford & Myrick, 2010; Torchalla, Nosen, Rostam, & Allen, 2012; van Dam et al., 2012). In the present study, clinically significant reductions in *both* alcohol use and PTSD symptom frequency and severity at the end of twelve weeks of treatment, sustained through the 12-month follow-ups, highlight the benefit of the Seeking Safety intervention.

Seeking Safety with placebo or sertraline also worked equally well with both early and late onset AUD. Although there is literature suggesting differential responses to SSRIs between early and late onset AUD (e.g., Brady et al., 2005; Jonas et al., 2014), our exploratory analysis found no evidence of this in the sample's PTSD or AUD outcomes. Nevertheless,

the role of AUD typologies in SSRI treatment response requires further examination. Kranzler et al. (2011) recently investigated the contribution of genotypic polymorphism at a prime serotonin transporter site and found that the moderating effect of AUD age of onset on SSRI treatment outcome was only present in late onset AUD possessing a specific allele variation (L' homozygotes at 5-HTTLPR). If sertraline response is predicated on a subgroup within those with late onset AUD, it is possible that the study's sample size may have limited the ability to detect differential sertraline effects on drinking outcomes among its identified AUD subtypes.

That placebo did not outperform sertraline on alcohol outcomes must be interpreted in the context of several limitations including the single-site context and modest sample size, particularly with regards to men, who represented less than 20% of the sample. Indeed, with regards to comorbid PTSD and AUD in men, this study should be considered hypothesis-generating rather than hypotheses-confirming. A ceiling effect on alcohol treatment gains, particularly with respect to heavy drinking days, may have obscured any additional advantage sertraline conferred over and above Seeking Safety. Moreover, since all participants also received one session of motivational enhancement therapy (MET), disentangling the benefits of Seeking Safety from MET without a no-treatment control group is not possible. The interpretability of these findings would have been enhanced by a medication-only and/or comparative behavioral treatment arm, but the added benefits of such a design must be weighed against its considerable financial and recruitment burden. Findings must also take participant attrition into account, as well as modest medication adherence, although analyses did not reveal differential attrition or adherence by treatment condition.

In sum, results suggest that adding sertraline to an integrated, present-focused cognitive behavioral treatment of co-occurring PTSD and AUD can lead to synergistic benefits for PTSD. The significant reductions of PTSD symptom severity and drinking experienced across both treatment conditions at end-of-treatment and sustained over 6- and 12-month follow-up provide further support to extant research on the benefit of Seeking Safety (e.g., see for example van Dam et al. for a review of this literature) in amelioration of SUD outcomes. Since PTSD improvements have been shown to lead to later substance use improvements (Hien et al., 2010; Mills et al., 2012; Morgan-Lopez et. al, 2014), these findings provide a positive indication for the use of sertraline in the treatment of PTSD among those with AUD.

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Public health significance

For individuals with PTSD and AUD, this study demonstrated that the combination of Seeking Safety, a present-focused trauma therapy, and sertraline, enhanced PTSD symptom reduction when compared to Seeking Safety and placebo. Drinking outcomes were significantly improved with and without sertraline. These findings suggest the benefit of an integrated cognitive behavioral treatment and SSRI approach to co-occurring PTSD and AUD.

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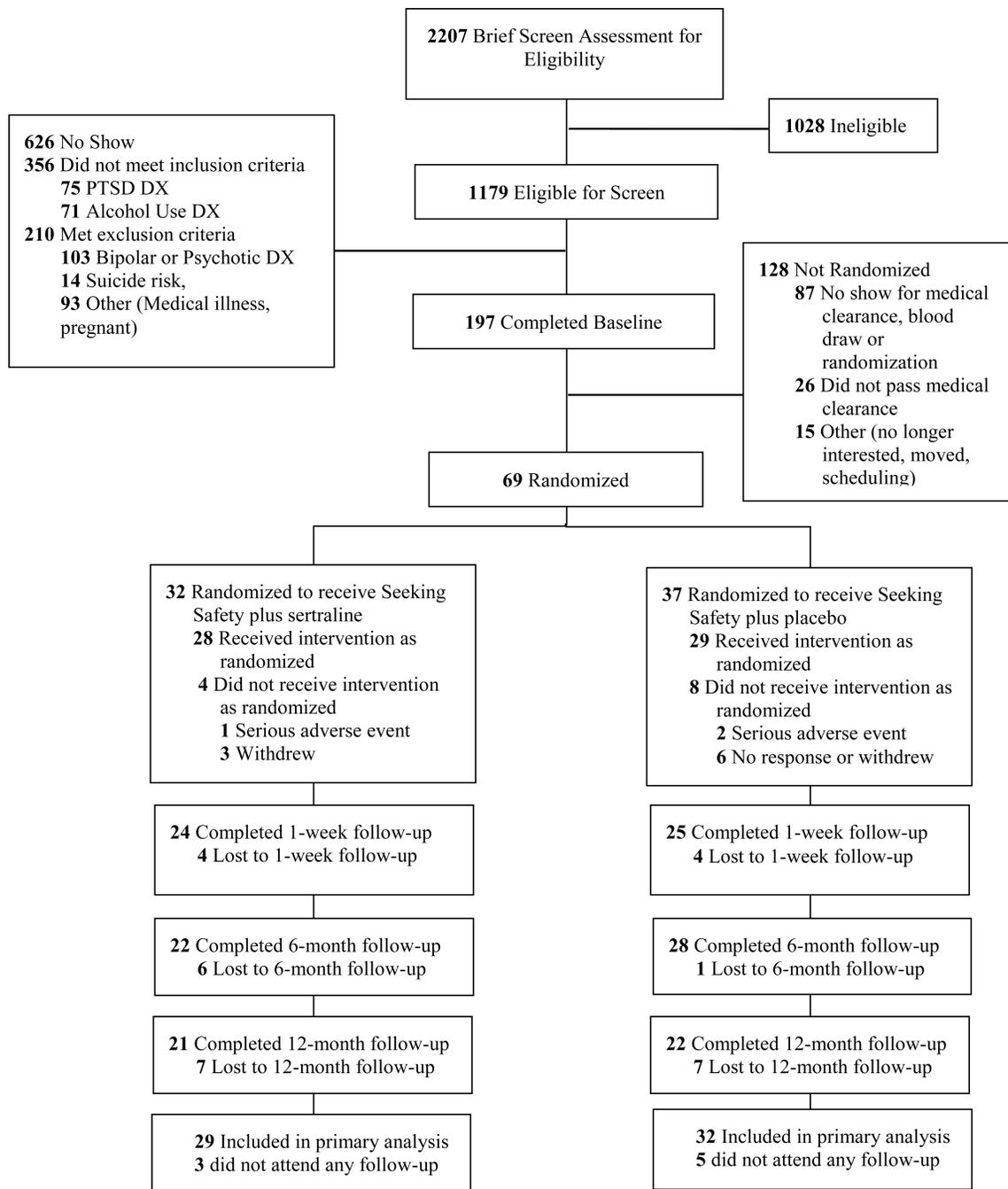


Figure 1. CONSORT Diagram of participant flow through the protocol. PTSD = posttraumatic stress disorder; DX = diagnosis.

Table 1

Baseline Demographic and Diagnostic Characteristics by Treatment Group (N = 69).

Characteristic	Seeking Safety + Sertraline (n = 32)		Seeking Safety + Placebo (n = 37)	
	n	%	n	%
Women	26	81.3	30	81.1
Race/ethnicity				
African American	16	50.0	25	67.6
Caucasian	10	31.3	6	16.2
Latina/o	3	9.4	4	10.8
Other	3	9.4	2	5.4
Marital Status				
Married	9	28.1	5	13.5
Single	17	53.1	25	67.6
Divorced/separated/widowed	6	18.8	7	18.9
Employment				
Employed	23	71.9	30	81.1
Unemployed	8	25.0	4	10.8
Student/retired/disabled	1	3.1	3	8.1
Past 7-day abstinence rate	3	9.7	4	10.8
Alcohol Dependence	28	87.5	33	89.2
Alcohol Abuse	3	9.4	0	0
Early onset AUD	13	40.6	16	48.5
Drug Dependence				
Cannabis	5	15.6	3	8.1
Cocaine	8	25.0	13	35.1
Comorbid AUD and SUD	16	50.0	22	59.5
Lifetime traumatic experiences *				
Child physical	14	43.3	18	48.5
Adult physical	16	50.0	16	42.4
Child sexual	12	36.7	15	41.2
Adult sexual	12	36.7	13	35.3
Transportation accident	19	60.0	27	73.5
Life-threatening illness	7	23.3	8	20.6
Exposed to violent death	14	43.3	10	26.5
Current Major Depression	20	62.5	22	59.5
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (years)	42.2	9.8	42.5	8.5
Education (years)	13.7	3.1	13.0	2.0
Age at PTSD onset	28.1	14.4	22.8	13.5
CAPS severity, total	65.8	19.4	59.0	19.2

Characteristic	Seeking Safety + Sertraline (n = 32)		Seeking Safety + Placebo (n = 37)	
DDD**	6.8	5.1	6.9	4.7
HDD**	3.3	2.2	2.9	2.4
Prior alcohol treatment episodes	1.1	1.9	1.6	4.3

Note. PTSD = posttraumatic stress disorder; DDD = drinks per drinking day; HDD = heavy drinking day (5+ drinks for men, 4+ for women); CAPS = Clinician Administered PTSD Scale; AUD = alcohol use disorder (abuse or dependence); SUD = substance use disorder (abuse or dependence).

* No participants endorsed natural disaster event.

** in past 7 days.

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Observed means of PTSD and alcohol use outcomes at baseline, end-of-treatment and 6 and 12 month follow-up with model-based treatment effects.

Table 2

Outcome	Seeking Safety + Sertraline (n = 32)			Seeking Safety + Placebo (n = 37)			Treatment Group Effect (SS+Sertraline vs. SS+Placebo)		
	n	M	SD	n	M	SD	Estimate	95% CI	p
CAPS total									
Baseline	32	65.50	20.03	37	59.50	18.97	-	-	-
End-of-treatment	24	36.25	28.23	25	41.88	29.30	-16.15	-31.18, -1.13	.04
6-month	21	30.09	20.70	28	37.46	25.88	-13.81	-26.88, -0.74	.04
12-month	21	24.90	19.95	22	31.82	24.44	-12.72	-25.40, -0.03	.05
Drinking									
	n	M	SD	n	M	SD	IRR	95% CI	p
HDD									
Baseline	32	3.13	2.17	37	2.89	2.35	1.60	0.61, 4.23	.34
End-of-treatment	22	1.05	1.79	25	0.48	1.69			
6-month	22	0.86	1.46	28	0.75	1.53			
12-month	20	0.30	0.47	21	0.24	0.44			
DDD									
Baseline	32	7.03	5.00	37	6.89	4.69	1.38	0.63, 3.04	.42
End-of-treatment	22	2.45	3.00	25	1.40	2.52			
6-month	22	2.41	3.06	28	3.14	4.84			
12-month	20	2.55	3.01	21	2.62	4.63			
Abstinence									
	n	%		n	%		OR	95% CI	p
Baseline	32	9.40		37	10.80		1.54	0.62, 3.83	.35
End-of-treatment	22	45.50		25	60.00				
6-month	22	54.50		28	46.40				
12-month	20	40.00		21	57.10				

Note. PTSD = Post-traumatic stress disorder; CAPS = Clinician Administered PTSD Scale; HDD = drinks drinking days; DDD = heavy drinking days; IRR = incidence rate ratio; OR = odds ratio; CI = confidence interval. Drinking outcomes are for previous 7 days. PTSD outcomes were probed at each timepoint after trend-level time-by-treatment interaction. Drinking outcomes were modeled for main treatment effects after no interactions were observed.