Methodology of a randomized double-blind clinical trial for comorbid posttraumatic stress disorder and alcohol dependence

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STUDY DESIGN

Methodology of a randomized double-blind clinical trial for comorbid posttraumatic stress disorder and alcohol dependence

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Introduction: Alcohol dependence (AD) and posttraumatic stress disorder (PTSD) are each associated with profound disruptions in psychological, social, and physical functioning, and these disruptions are compounded in individuals with both disorders. Comorbidity between the two disorders is high, with the risk for AD increasing substantially among individuals with PTSD and, conversely, PTSD is highly prevalent among people experiencing AD.
Aims: Given the increased impairment associated with this comorbidity, it is imperative to develop effective treatments for individuals who experience both disorders.
Methods: This paper describes the methodology of a study that examines the efficacy of prolonged exposure therapy alone, naltrexone alone, and their combination compared to pill placebo in reducing the severity of PTSD and alcohol use in individuals with comorbid AD and PTSD.
Discussion: Issues related to design, assessment, treatment choice, and challenges posed by the study population are discussed.

Keywords: alcohol dependence; cognitive-behavioral therapy; dual diagnosis; naltrexone; psychotherapy research; posttraumatic stress disorder (PTSD); prolonged exposure

Introduction

Alcohol dependence (AD) and posttraumatic stress disorder (PTSD) are each associated with profound disruptions in psychological, social, and physical functioning, and these are compounded in individuals with both disorders (Riggs, Rukstalis, Volpicelli, Kalmanson, & Foa, 2003; Ullman, Filipas, Townsend, & Starzynski, 2006). Comorbidity is high, with the risk for AD increasing substantially among individuals with PTSD (Kessler, Chiu, Demler, & Walters, 2005a; Mills, Teesson, Ross, & Peters, 2006), and conversely PTSD is highly prevalent among people experiencing AD (Petrakis, Gonzalez, Rosenheck, & Krystal, 2002). Given their increased dysfunction, it is imperative to develop effective treatments for people with these comorbid disorders.

The purpose of this paper is to describe the methodology of a randomized controlled trial (RCT) designed to determine if simultaneous treatment of PTSD and

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AD is more efficacious than treatment that addresses only one of the disorders. The study described compares the efficacy of four treatment conditions in reducing severity of PTSD and alcohol use in individuals with both AD and PTSD: prolonged exposure therapy alone; naltrexone alone; their combination; and pill placebo. All patients received counseling for their drinking problem. This paper is intended as an informative guide for researchers interested in the design issues involved in a study to treat simultaneously PTSD and AD in dually diagnosed individuals. In addition, the rationale for the choice of treatments for this population is presented.

Alcohol dependence

The lifetime prevalence of alcohol abuse and dependence in the US is 15.1% and 6.5%, respectively (Kessler et al., 2005b). Psychiatric disorders (including PTSD) are significantly more common in individuals experiencing alcohol abuse and dependence (Hasin, Srinson, Ogburn, & Grant, 2007; Kessler et al., 2005a), as are severe behavioral and psychosocial disruptions, including employment problems, legal problems, divorce, violence, and victimization (e.g. Dawson, Li, & Grant, 2008; Marshal, 2003). Although treatments for alcohol abuse and dependence are available, relapse is common (Bottlender & Soyka, 2005; De Bruijn, van den Brink, de Graaf, & Vollebergh, 2006).

Posttraumatic stress disorder

PTSD is a common response to trauma, with a lifetime risk of 8.7% in the US population (Kessler et al., 2005b). PTSD often has a chronic course, especially among those exposed to extreme trauma, with up to 40% exhibiting significant symptoms 10 years after onset (Kessler et al., 1995; Owashi & Perkonigg, 2007). Psychiatric comorbidity is approximately three times more likely in individuals with PTSD than those without (Kessler et al., 1995), and people with PTSD experience high rates of suicidal ideation, attempts, and completions (Tarrier & Gregg, 2004). PTSD is associated with significant health problems and higher utilization of medical services (Deykin et al., 2001; Walker et al., 2003), but lower use of psychiatric care (Amaya-Jackson et al., 1999).

Comorbid AD and PTSD

Many studies (e.g. Chilcoat & Menard, 2003; McFarlane, 1998; Najavits, Weiss, & Shaw, 1997) have found a relationship between AD and PTSD, with 28% of women and 52% of men showing alcohol abuse or dependence among individuals with PTSD (Kessler et al., 1995). These rates are substantially higher than population base rates for either disorder individually (Breslau, Davis, & Schultz, 2003).

Among people who misuse alcohol, trauma history is associated with more severe substance dependence (e.g. Schumacher, Coffey, & Stasiewicz, 2006), with greater levels of general psychopathology (Harvey, Rawson, & Obert, 1994), and higher rates of antisocial personality, depression, generalized anxiety, and suicidality (Tarrier & Gregg, 2004; Windle, Windle, Schedit, & Miller, 1995). These findings suggest that alcohol abuse or dependence is directly associated with posttrauma reaction severity and constitutes part of a constellation of psychopathological responses to trauma.

Most studies of clinical samples with comorbid PTSD and AD have indicated onset of trauma prior to onset of AD (e.g. Bremner, Southwick, Darnell, & Charney, 1996). Moreover, PTSD increases the subsequent risk for developing a substance use disorder (Chilcoat & Breslau, 1998). However, AD symptoms may appear earlier than symptoms of PTSD (Cottler, Compton, Mager, Spitznagel, & Janca, 1992), suggesting that alcohol misuse may constitute a risk for trauma exposure (Stewart, 1996). The relationship between AD and PTSD forms a vicious cycle in which PTSD symptoms elicit drinking, drinking perpetuates and intensifies PTSD symptoms, and, in turn, PTSD symptoms further escalate drinking and AD (e.g. Coffey, Stasiewicz, Hughes, & Brimo, 2006). Thus, it is not surprising that treatment of one disorder is likely to be compromised by failure to attend to its effect on the other, underscoring the importance of developing treatment strategies that simultaneously address PTSD and AD.

Combined treatment

There is limited information about the treatment of comorbid PTSD and AD. Traditionally, people with AD were excluded from exposure-based studies because it was believed that the anxiety associated with exposure to trauma-related feared situations would result in increased drinking. Likewise, it was thought that treatment for AD among people with PTSD would also be problematic, as drinking is thought to reduce the distress caused by PTSD; therefore, comorbid patients treated for AD would be likely to relapse as a means of coping with PTSD-related anxiety (Riggs et al., 2003).

Treatment with the opiate antagonist naltrexone (NAL) combined with counseling has been effective in treating AD (e.g. Guardia et al., 2002), but at least one study has shown some limited efficacy among comorbid AD–PTSD patients in reducing drinking (Petrakis et al., 2006). Prolonged exposure, a cognitive-behavioral treatment for PTSD, has proven effective (Foa, Hembree, & Rothbaum, 2007; Institute of Medicine, 2008), but its efficacy in PTSD patients with comorbid AD has not been examined in well-controlled studies.

Goals of current study

The impetus for this study was the high comorbidity of AD and PTSD and the absence of empirically established, effective treatments for individuals experiencing these two disorders. This is the first randomized controlled trial of comorbid PTSD and AD, using a combination of medications and psychotherapy, making it a critically important study that will inform clinicians how to best treat those who suffer from both disorders. This study has several important goals, including evaluating:

(1) the efficacy of naltrexone (NAL) in reducing drinking in patients with comorbid PTSD;
(2) the efficacy of prolonged exposure (PE) therapy in reducing PTSD symptoms in patients with comorbid AD;
(3) the efficacy of treatment targeted at one disorder (i.e. NAL for alcoholism or PE for PTSD) on the comorbid condition (symptoms of PTSD or drinking); and

(4) whether concurrent treatment with NAL and PE produces greater and more persistent improvement in comorbid patients than treatment with NAL or PE alone.

Both short-term and long-term efficacy of the treatments will be examined by assessing patients' severity of PTSD and amount of alcohol consumption during treatment, immediately after treatment, and 24 weeks post-treatment. The secondary aim of the study is to examine the effects of the treatments on symptoms such as alcohol cravings, problems related to drinking, depression, anxiety, and general dysfunction. This paper aims to present the methodology of the study and to discuss design issues inherent in a study designed to simultaneously treat substance dependence and PTSD in dually diagnosed individuals.

Choice of prolonged exposure for PTSD

Almost every form of psychotherapy has been advocated for trauma-related problems, including PTSD. We limited our consideration of psychotherapy for this study to programs with demonstrated efficacy in RCTs where treatment was compared with waitlist or minimal control treatment. The psychotherapy with demonstrated efficacy consists of several cognitive-behavioral therapy (CBT) programs. These include variants of exposure therapy, stress inoculation training, variants of cognitive therapy, eye movement desensitization and reprocessing, and combinations of these treatments.

Studies directly comparing one form of CBT with another have generally found differences to be small, but favoring exposure therapy (e.g. Institute of Medicine, 2008). Therefore, in this study we opted to use prolonged exposure (PE), a treatment program with the most empirical evidence for its efficacy (Foa et al., 2007; Williams, Cahill, & Foa, 2010). Because fear activation is critical to successful outcome of PE (Foa, Riggs, Massie, & Yarczower, 1995), alcohol consumption is expected to interfere with recovery due to its anxiolytic effects. Drinking among PTSD patients has been conceptualized as promoting emotional numbing or cognitive avoidance of engagement with trauma-related distress (Zaslav, 1994; Zweben, Clark, & Smith, 1994). Therefore, the abuse of alcohol during treatment for PTSD is thought to impede treatment efficacy.

Choice of naltrexone for alcohol dependence

Opiate antagonists reduce alcohol preference in animals (e.g. Ulm, Volpicelli, & Volpicelli, 1995), particularly after stressors that otherwise elicit alcohol consumption (Volpicelli, Davis, & Olgin, 1986). NAL may reduce the pleasurable effects of alcohol in normal (Swift, Whelihan, Kuznetsov, Buongiorno, & Huang, 1994) and high-risk social drinkers (King, Volpicelli, Frazer, & O'Brien, 1997) as well as in people with AD (Volpicelli, Watson, King, Sherman, & O'Brien, 1995). For AD, NAL in conjunction with psychosocial support or CBT produces superior outcome than placebo with support or CBT (e.g. Streeton & Whelan, 2001). Of particular relevance to this study, one case review suggests that NAL can be useful in treating AD in patients diagnosed with a mental illness (Maxwell & Shinderman, 2000).

Notwithstanding the short-term efficacy of NAL for alcoholism, relapse after discontinuation of the medication is not uncommon (Guardia et al., 2002). The importance of treatment adherence and the difficulties associated with discontinuation from NAL highlight the need for treatments that will improve long-term prospects for patients with AD. This is particularly important among patients with comorbid PTSD who are likely to be less treatment adherent and may lack motivation, because abstinence from drinking may exacerbate PTSD symptoms.

Generally, the rates of relapse during 12 weeks of treatment with NAL are about half that reported for patients on placebo (e.g. Anton, Brady, & Moak, 1999; O'Brien, Volpicelli, & Volpicelli, 1996). Several studies also report that NAL leads to lower alcohol consumption (Chick et al., 2000; Morris, Hopwood, Whelan, Gardiner, & Drummond, 2001) and decreased cravings (Balldin et al., 2003; Rubio et al., 2002). Traditionally, patients treated with medication for AD have been provided with some concurrent psychological intervention such as addiction counseling (e.g. Volpicelli, Alterman, Hayashida, & O'Brien, 1992) or cognitive-behavioral coping skills (e.g. O'Malley, Jaffe, Chang, & Schottenfeld, 1992). The use of BRENDA with NAL for AD has been used successfully at the Treatment Research Center (TRC) at the University of Pennsylvania (Pettinati, Volpicelli, Pierce, & O'Brien, 2000), with positive effects on both treatment retention and medication compliance. The BRENDA intervention is a bio-psychosocial strategy for use in primary care settings (Volpicelli, Pettinati, McLellan, & O'Brien, 2001), combining standard medication management with compliance enhancement techniques based on motivational interviewing (Miller & Rollnick, 2001).

Synergy between naltrexone and prolonged exposure

It has been suggested that NAL may be a particularly suitable intervention for treating AD with comorbid PTSD (Petrakis et al., 2002), and several theoretical and empirical considerations suggest a possible synergistic effect in combining NAL and PE on both AD and PTSD outcomes.

Exposure to stressful stimuli is associated with a rise in endogenous opioids (Thyer & Mathews, 1986). Following prolonged elevations of endorphin levels there may be a deficiency in opioid receptor activity (Volpicelli, Davis, & Olgin, 1987). Experimental studies show that alcohol consumption increases with stress (e.g. Wilson, 1988); however, this increase typically occurs following, not during or in anticipation of, exposure to the stimulus. These findings led Volpicelli et al. (1987) to propose an 'endorphin compensation hypothesis' to account for drinking in stressful situations, arguing that alcohol consumption is driven not by stress per se, but by the drop in endorphin receptor activity following stress.

This hypothesis has direct implications for the treatment of PTSD comorbid with AD. If trauma-related stimuli are stressful, then patients treated with PE but without NAL would be expected to experience a flood of endorphins during exposure exercises followed by a subsequent deficit in endorphin receptor activity, resulting in increased craving for alcohol. A study by Schumacher, Coffey, and Stasiewicz (2006) found such a relationship, as PTSD patients with AD reported increased alcohol craving and emotional distress when presented with personally relevant trauma-related cues. The addition of NAL to PE would block the endorphin reaction and the alcohol craving, which would otherwise undermine the efficacy of PE by

interfering with emotional engagement and habituation of anxiety during exposure exercises. Thus, the addition of NAL to PE is expected to increase the efficacy of PE in reducing PTSD symptoms in this comorbid population. Additionally, most patients with AD and PTSD express a preference for treatment that addresses the two disorders simultaneously (Brown, Stout, & Mueller, 1996), suggesting that such treatment may enhance compliance by better meeting patients' own perceived needs.

Methodology

Study design

The study adopted a 2 (NAL vs. placebo) × 2 (PE vs. no-PE) design to assess the efficacy of NAL, PE, and their combination (NAL + PE), vs. pill placebo on AD and PTSD symptoms and changes in general functioning. Thus, patients received one of four treatments combinations:

- NAL alone;
- placebo alone;
- NAL + PE;
- placebo + PE.

All patients received a medication adherence enhancement intervention in the context of medical management using the BRENDA intervention.

Both study personnel and participants were blind as to whether patients received NAL or placebo but not to receipt of PE. Independent evaluators were blind to all treatment conditions. Patients who exhibited significant PTSD symptoms at follow-up and did not receive PE were offered 10 sessions of PE at no cost. Symptomatic patients who received PE and patients with continued alcohol-related problems were offered treatment referrals.

Participants

Participants met DSM-IV (American Psychiatric Association (APA), 2000) criteria for AD and PTSD following a variety of traumas. The goal was to enroll 185 patients, with 110 patients completing the 6-month treatment and 88 at follow-up, a sufficiently large sample to test our primary hypotheses.

All participants were 18–65 years old, reporting heavy alcohol drinking in the past 30 days. Heavy drinking was defined as above 12 drinks per week, where each drink was 0.6 ounces of ethanol. All participants were required to agree to medical detoxification.

Exclusion criteria were: current DSM-IV diagnosis of any substance dependence (other than alcohol, nicotine, or cannabis) in the past 30 days, serious medical illness, current severe psychiatric symptoms (e.g. psychosis), pregnancy or nursing, or no use of reliable contraception. Additional exclusion criteria were significant risk of serious violent behavior during the past year, and/or the index trauma consisted of an assault by an intimate partner with whom there was a continuing intimate relationship. Antidepressant medications, such as SSRIs, were permitted; however, participants who reported recent changes to psychiatric medication were not seen until a sufficient amount of time had passed so that their regimen was stable (typically 8–12 weeks).

Assessment

The goal in selecting assessment tools was to measure treatment outcome comprehensively but efficiently to minimize participant burden and project expense. The domains assessed included psychopathology and disability, with an emphasis on AD and PTSD symptoms, treatment readiness and expectancy. Some measures of general health were determined by laboratory measurements. Measures were administered for screening weekly, monthly, post-treatment, and 6- and 12-month follow-up, as shown in Table 1 (which does not include medical assessment schedule).

Psychopathology instruments

For assessing alcohol use, four measures were administered:

(1) the Timeline Follow-Back Interview (TLFB; Sobell & Sobell, 1995), a semi-structured interview regarding patients' daily alcohol use;
(2) the Collateral Interview (Miller & Marlatt, 1987), a 15-minute telephone interview with a significant other;
(3) the Penn Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999), a 5-item self-report evaluation of the urge to drink;
(4) the Drinker Inventory of Consequences (DrInC; Miller, Tonigan, & Longabaugh, 1995), a 10-minute self-report of drinking consequences.

Four PTSD measures were included: the Standardized Trauma Interview (STI; Foa et al., 2007), a semi-structured interview about the trauma; the PTSD Symptom Scale Interview, a 20-minute clinical interview that evaluated DSM-IV PTSD symptoms on a frequency/severity scale (PSS-I: Foa, Riggs, Dancu, & Rothbaum, 1993); the PTSD Diagnostic Scale (PDS), a self-report measure of PTSD that yielded both a DSM-IV PTSD diagnosis and a measure of PTSD severity (Foa, Cashman, Jaycox, & Perry, 1997); and the Posttraumatic Cognitions Inventory (PTCI; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999) a measure of trauma-related thoughts and beliefs.

Three assessments of other psychopathology were used: the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1994) which provided current and lifetime DSM-IV Axis I diagnoses of major psychiatric disorders; the Beck Depression Inventory II (BDI-II; Beck,Steer, Ball, & Ranieri, 1996), a popular self-report measure of depressive symptoms; and the State-Trait Anxiety Inventory (STAI; Spielberger, 1988), a 10-minute inventory that evaluated anxiety at the time the questionnaire was completed, as well as the enduring tendency to experience anxiety.

Treatment assessment instruments

To assess current difficulties and resources, two measures were administered: the Treatment Services Review (TSR; McLellan, Alterman, Cacciola, & Metzger, 1992), a 5-minute interview that assessed services received in seven areas; and the Sheehan Disability Scale (SDS; Sheehan, 1983), a widely used, three-item scale that assessed disruption caused by symptoms in work, social/leisure activities, and family/home life.

Table 1. Schedule of treatment and psychological assessments.

| Procedure | Pre-treatment | | Treatment phase | | | Post-treatment |
	Intake	Initial	Weekly 1–12, biweekly 14–22	Monthly: weeks 4, 8, 12, 16, 20	Quarterly: weeks 12, 24	Biannually: weeks 38, 52
Treatment						
Detoxification program		X				
Medication management			X	X	X	X
Prolonged exposure			X	X	X	X
Interviews						
Phone screening	X					
Evaluation and treatment history	X					
Informed consent		X				
PSS-I		X		X	X	X
SCID*, collateral interview		X			X	X
STI		X				
TLFB & TSR		X	X	X	X	X
Self-report measures						
PACS, PDS, BDI-II		X	X	X	X	X
DrInC, URICA, STAI, SDS		X			X	X
ETO		X				

* SCID not given at weeks 12 or 38.

Two measures were included to assess treatment readiness and expectancy: the University of Rhode Island Change Assessment (URICA; McConnaughy, Prochaska, & Velicer, 1983), a 10-minute, 32-item self-report of motivation and readiness for change; and the Expectancy of Therapeutic Outcome (ETO; Foa, Rothbaum, Riggs, & Murdock, 1991), a 3-item scale to evaluate the credibility of treatment.

Laboratory measurements

Several laboratory measures were administered to participants to assess physical health, including liver function tests. A blood specimen was taken at screening, monthly during the trial and at the two follow-ups.

Two tests were used to monitor adherence. For NAL-treated patients, Beta-Naltrexol was used to confirm that medication was taken. Urine Riboflavin tests (100 mg) were used for NAL and placebo groups to monitor medication compliance (Baros, Latham, Moak, Voronin, & Anton, 2006). Urine toxicology drug screen tests for benzodiazepines, methadone, amphetamines, barbiturates, cocaine, opiates, and marijuana were obtained at pre-treatment, monthly during the trial, and at each follow-up. A breathalyzer test was also required at each visit for the presence of alcohol.

Recruitment and intake

Patient recruitment was primarily accomplished through public advertising and professional referrals. Based on previous experience, advertisements in local newspapers were thought to yield the largest number of inquiries that could be converted into entrants. Outreach and advertising efforts instructed prospective patients to contact the Intake Coordinator, who screened individuals to assess eligibility. Intake included medical history, physical examination, an electrocardiogram (ECG), routine laboratory tests, psychiatric diagnostic interview (SCID), treatment history, and self-report measures.

The intake laboratory tests included a complete blood count (CBC), serum electrolytes, urine toxicology, serologic test for pregnancy, and liver function tests. Hepatitis C antibodies were measured, and testing and counseling for HIV-1 was offered to all patients. Patients with lab results indicating severe abnormalities or elevated bilirubin were ineligible for the study; however, a positive hepatitis C or HIV test alone did not exclude patients.

Study entry procedures

Eligible participants provided informed consent to participate in the study, and comprehension of the consent form was evaluated with a quiz. Participants then completed outpatient medical detoxification of at least 3 consecutive days of abstinence from alcohol via self-reports and breathalyzer levels, which included visits to the nurse for 3–7 days of medical monitoring.

At the pre-treatment assessment, an independent evaluator (IE) administered the PSS-I, to confirm that patients met PTSD severity criteria, and the STI. These assessments were completed after detoxification to ensure that PTSD symptoms evaluated at intake were not confounded with withdrawal symptoms. The research technician administered the TLFB to confirm AD and no recent opiate use.

The research technician also assessed other treatment via the TSR measure and administered the remainder of the pre-treatment self-report battery.

Treatment

Patients were randomly assigned to placebo or NAL, and were randomly assigned either to receive PE or no PE. These interventions are described in detail below.

Prolonged exposure therapy

The PE condition consisted of 12 weekly sessions of 1.5–2 h, each followed by 6 bi-weekly sessions. Each PE session began with a review of the homework assignment and presentation of the agenda for that session, and ended with assignment of homework.

The first two sessions of PE were devoted to: gathering information about the trauma, education about common reactions to trauma, relaxation training with breathing retraining, presentation of the rationale for PE, and development of an in-vivo exposure hierarchy for homework assignments. The remaining sessions consisted of imaginal revisiting of the trauma memory and discussion of in-vivo exposure activities. Following each imaginal exposure, the therapist processed with the patient his or her thoughts and feelings about the experience, and, if necessary, instituted relaxation to help the patient manage anxiety.

The final session of PE was devoted to terminating the treatment program. It involved reviewing progress and discussing the applications of treatment principles to daily life, including how to manage continuing urges to drink and potential lapses in abstinence as well as temporary increases in PTSD symptoms. A detailed description of PE is provided elsewhere (Foa et al., 2007).

Medication treatment procedures

NAL is a US Food and Drug Administration (FDA) approved opiate antagonist for AD and is available by prescription. On the first three days of treatment, patients were given one 50 mg tablet of NAL or an identical placebo, paired with one 100 mg riboflavin tablet. On the fourth day, the dose increased to two 50 mg tablets of NAL or placebo, along with the riboflavin tablet. Thus, for the remainder of the study, patients were asked to take three tablets once daily in the morning (2 NAL/placebo + 1 riboflavin). The single-dose schedule was to enhance adherence (Cramer, Mattson, Prevey, Scheyer, & Ouellete, 1989).

When NAL was used at 50 mg/day for 12 weeks, there was a significant improvement in liver function in an alcohol dependent population (Volpicelli et al., 1992). The 100 mg/day used in this study is higher than the 50 mg/day recommended for AD, but is not in the 300 mg/day range that has been associated with elevations in liver enzymes (Berg, Pettinati, & Volpicelli, 1996). Liver enzymes were monitored at pre-treatment and every 4 weeks during the trial. NAL can produce temporary side effects such as abdominal pain and headache (Guardia et al., 2002). We anticipated few patients would have difficulty tolerating the 100 mg daily dose of NAL. For patients unable to tolerate side effects, dosage was reduced to 50 mg/day, and the patient was returned to 100 mg at the research physician's discretion. Patients who could not tolerate a 50 mg dose were removed from the trial. Although

all patients were instructed to take the medication once a day in the morning, modest changes in the regimen were permitted if it encouraged adherence.

Patients in all treatment conditions received 18 visits of 30 minutes with the study nurse. The nurse dispensed medication, monitored adherence, provided education about alcohol dependency, gave supportive counseling, and provided direct advice concerning drinking. Visits took place weekly during the first 3 months of the trial and bi-weekly during the remaining 3 months. Blister cards were dispensed at each medication visit and returned empty each week. Patients were encouraged to call the nurse or physician between visits with questions or concerns. The physician regularly reviewed all patient data. If the patient reported an adverse event to any of the project staff, including exacerbation of PTSD symptoms, the research physician followed-up with the patient and appropriate clinical services were provided as indicated.

Adherence with the dosing regimen was monitored by pill counts and urine riboflavin. In addition, the blood specimen taken at one month was analyzed for NAL and beta-naltrexol. These results were evaluated after the blind was broken to determine compliance and assess the relationship of NAL levels to pill counts and urine riboflavin measures.

Discontinuation

Patients' participation in the trial was subject to discontinuation in the event of serious medication side effects, relapse, or if continued participation was deemed unsafe by study personnel. Patients who were discontinued from the trial had a final evaluation within one week and were given appropriate treatment referrals. If patients were discontinued due to a serious adverse event, they continued to be followed by medical staff until the adverse event was resolved. If the clinician concluded that the patient was relapsing, a final IE rating was carried out one week later. If relapse was confirmed, the patient was referred to open community treatment.

Fidelity monitoring

All therapy sessions were videotaped, and all BRENDA contacts were audiotaped. Fifteen percent of sessions were rated for adherence to the PE or BRENDA manual by independent raters. Satisfactory integrity was defined as 90% or more of overall percentage adherence to criterion areas. Feedback of treatment adherence was given to the study supervisors, who communicated any deviation from the manuals to the therapist or nurse.

Statistical analysis

Dependent variables for analyses included dropout rates and scores on the following measures: alcohol consumption as per the TLFB, PSS-I, and the PACS. The intent to treat (ITT) analyses included data collected at pre-treatment and at the last available monthly assessment (up to week 24) for the participants who attended at least one treatment session. We examined effect sizes as well as significance values.

The data were analyzed using a form of random-effects regression modeling called hierarchical linear modeling (HLM; Bryk & Raudenbush, 1992).

Random-effects regression is capable of accepting unbalanced, randomly missing, hierarchically structured data; accommodating real-time rather than scheduled assessments for each participant; and permitting the assumptions of constant slopes and intercepts be relaxed.

To examine the adequacy of our randomization procedures, a 2 (NAL vs. placebo) × 2 (PE vs. No PE) HLM analyses was performed on pre-treatment data of the intent to treat sample. Analyses of the ITT sample were conducted using data from the participants who received at least one dose of NAL or placebo. For each of the outcome variables, a 3 (pre-treatment vs. mid-treatment vs. post-treatment) × 2 (NAL vs. placebo) × 2 (PE vs. No Therapy) HLM analysis was performed with the assessment point serving as a within-subjects factor and the two treatments as between-subjects factors. This was then repeated for the analyses of treatment completers.

Discussion

Challenging populations: special issues

To date, we have screened 1233 participants who were potentially eligible to enter the study and were scheduled for clinical evaluations. Of these, 508 (41%) attended appointments and began the evaluation. Approximately half did not qualify for the study; the main reasons were not meeting criteria for PTSD, illicit drug dependence (excluding marijuana), psychotic symptoms, and not meeting criteria for alcohol dependence. Altogether, 173 (34%) of the individuals who attended the clinical evaluations were eligible and consented to participate in the study. Of those, four dropped from the study before they were randomized into a condition. Of the 169 individuals who completed the full baseline evaluation and who were randomized into a treatment condition, 157 began treatment and attended the first treatment session.

Patients with comorbid AD and PTSD constitute a particularly challenging population due to the increased impairments that accompany both disorders. Thus, much effort is required to prevent attrition (Riggs et al., 2003). In anticipation of these difficulties, extensive contact information from participants was obtained, including addresses and phone numbers of family members, to locate them should their current contact information become out of date. Another strategy of reducing attrition is to help participants manage life problems that emerge during the study. The study nurse assists patients with practical concerns regarding abstinence from drinking, such as strategies for managing social situations and family gatherings without alcohol, and provides psychoeducation about the physical effects of AD. The study nurse also counsels patients on relationships issues, including changes to family dynamics when the balance of power shifts as the study participant becomes increasingly functional. This problem-solving assistance facilitates the ability of patients to stay in the program despite their chaotic lives.

Many of the study patients also struggled with primary needs, including housing, employment, nutrition, and basic health care. The flexibility built into the BRENDA protocol allows the study nurse to assist patients with these needs, in effect doubling as a social worker when necessary. The patients' degree of disability contributed to an unstable lifestyle and multiple personal crises, which necessitated intervention on a case-by-case basis. Thus study personnel expended greater time and effort managing patients' crises during treatment. Unexpected issues included the involvement of some female patients in sex trade to support themselves, requiring special health care

management. A study social worker should be included in future studies with this population.

The steps taken to prevent attrition have been relatively successful to date. Of the 157 participants who attended at least one treatment session, 94 completed the 6-month program, and 7 are still in active treatment. Drop-outs represent 36% of the 157 participants to date. The drop-out rate in our ongoing study is comparable to or better than rates reported in previous treatment studies of NAL (Balldin et al., 2003) and comorbid PTSD-AD (Coffey et al., 2006; Heinala et al. 2001). Among those consented, 91% attended the first session, 80% completed one month of treatment, and 72% completed two months.

Closing comments

Designing and implementing this study has raised a number of issues concerning psychotherapy research. In addition to the methodological challenges of any large study, the dual diagnosis patients in our program present complex issues not typically encountered in our treatment-outcome studies of anxiety-disordered patients without AD. The careful design, the implementation of the treatments selected, and the use of the BRENDA protocol have been essential in the management and retention of participants.

When completed, the study results will provide important information in the provision of guidelines of how to conduct effective treatment programs for people suffering from PTSD and AD. Currently, many clinicians believe that treatments addressing the traumatic event may be harmful for the dually diagnosed PTSD patient. As a result, these patients are often requested to abstain from alcohol for at least three months before receiving exposure therapy, the only treatment found to have sufficient evidence for its efficacy with PTSD (Institute of Medicine, 2008). If this study finds that PE (with or without NAL) is effective rather than harmful for individuals who suffer from PTSD with AD, clinicians will cease to be reluctant to administer this beneficial treatment. In this respect, it will be very important to ascertain whether PE reduces drinking and urges to drink, in addition to reducing PTSD symptoms, and if the combination of PE and NAL will be more beneficial for treating PTSD and AD than either treatment alone.

We expect to begin data analysis of the outcome measures at the end of 2010 and complete the manuscripts describing the results in early 2011. The results of the study will contribute to the much-needed guidelines of how to conduct effective treatment for individuals with comorbid PTSD and AD.

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