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Exclusion of participants based on substance use status: Findings from randomized controlled trials of treatments for PTSD

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ABSTRACT

Individuals with posttraumatic stress disorder (PTSD) are more than four times as likely as those without PTSD to have substance use disorder (SUD), making it critical to understand the interaction of substance use status and PTSD outcomes. Using the broader treatment literature, we examined PTSD treatment effects, with and without co-morbid SUD, by extending a published meta-analysis to include recent studies. From reports of 156 Randomized Controlled Trials (RCTs), we extracted exclusion criteria based on substance use and findings involving substance use as a predictor or outcome. Almost three-quarters of RCT designs excluded participants based on substance use status. Only 29.5% reported descriptive statistics characterizing substance use within the study sample and only 7.7% reported substance use-related outcomes. There was no clear relationship between exclusion criteria based on substance use and PTSD outcome or participant retention, suggesting either that SUD does not impede treatment effects, or that available studies lack sufficient data for these analyses. Importantly, no studies reported significant increases in substance use in the course of PTSD treatment. We conclude that patients with PTSD and co-morbid SUD have been largely neglected in PTSD RCTs; thus findings may not be fully applicable to those meeting criteria for both conditions.

1. Background

Multimorbidity—the coexistence of two or more chronic diseases— is now the most common condition among older adults (Tinetti, Fried, & Boyd, 2012). Comorbidity is a related construct, defined as the presence of a concurrent medical or psychiatric disorder (e.g., substance use disorder) in addition to a primary condition (e.g., posttraumatic stress disorder [PTSD]; Strakowski et al., 1993). Co-occurring disorders can have additive or interactive effects on health status, physical function and quality of life (Tinetti & Basu, 2014). Despite this, most research focuses on individual diseases. Accordingly, primary outcomes of randomized controlled trials (RCTs) are almost uniformly single disease-specific due to complexity and prohibitive costs (Tinetti & Basu, 2014). Continued inattention to comorbidity and multimorbidity is believed to lead to even greater costs and harm (Tinetti & Studenski, 2011). Perhaps the biggest concern is that efficacious treatments for one condition may be ineffective or harmful in patients with comorbid conditions (Tinetti et al., 2012).

Alcohol and other substance use disorders (SUDs), are highly relevant to this issue, due to frequent comorbidity with mood, anxiety, and traumatic disorders. Notably, there is substantial

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overlap between PTSD and substance use, with 46% of those meeting lifetime criteria for PTSD meeting criteria for a lifetime SUD (alcohol: 42%, drug: 22%) in a national sample in the United States (U.S.; Pietrzak, Russo, Ling, & Southwick, 2011). Individuals with PTSD were 4.3 times more likely than those without to have alcohol or other SUDs in a longitudinal epidemiologic study in the U.S. (Breslau, Davis, & Schultz, 2003). Among veterans, 23% of patients in Veterans Administration (VA) specialty mental health programs meeting PTSD criteria also met current SUD criteria, with even higher SUD rates among younger veterans with PTSD (31%) (Kerfoot, Petrakis, & Rosenheck, 2011). Similarly, in Germany and the Netherlands, approximately one-third of individuals in alcohol and drug treatment met PTSD criteria (Driessen et al., 2008; Gielen, Havermans, Tekelenburg, &Jansen, 2012).

Moreover, individuals with comorbid PTSD and SUD tend toward more severe SUD presentation, experience poorer SUD-related outcomes and inferior physical health, compared to those with SUDs without trauma history (Driessen et al., 2008; Mills, Teesson, Ross, & Peters, 2006). This pattern may relate, in part, to observations that efficacious treatments for one disorder may not work the same way in the presence of comorbid conditions (Back, Brady, Sonne, & Verduin, 2006; Tinetti et al., 2012). In contrast, there is evidence that improving PTSD symptoms can indirectly reduce substance use (Hien et al., 2010) and conversely, that improving SUD outcomes is associated with better PTSD outcomes (Manhapra, Stefanovics, & Rosenheck, 2015). Relatedly, there is compelling evidence that patients with comorbid PTSD/SUD may fare better in treatment than those with PTSD only (Fontana, Rosenheck, & Desai, 2012). Nonetheless, studies examining treatments for individuals with primary diagnoses of PTSD appear to be conducted primarily among those without SUDs. For example, Stein, Ipser, and Seedat (2006), planned several subgroup analyses in their meta-analysis of pharmacotherapy for PTSD, but none involved substance use status. Among the 35 included trials, only five *did not* exclude based on substance use status, suggesting this is a common practice.

Findings from RCTs conducted expressly to test integrated interventions for PTSD/trauma and SUD have been summarized in multiple meta-analyses and literature reviews (Kelly, Daley, & Douaihy, 2012; Roberts, Roberts, Jones, & Bisson, 2016; Sofuoglu, Rosenheck, & Petrakis, 2014; Torchalla, Nosen, Rostam, & Allen, 2012). But overall, there is not strong evidence to recommend any particular intervention, nor to conclude whether treating both conditions simultaneously or serially is advantageous. Further, efficacy of integrated treatment may depend upon patient (e.g., sex, veteran status) or study design (e.g., active vs. inert control) characteristics, (Watts et al., 2013).

Given that findings from RCTs testing integrated interventions have been summarized effectively, our goal was to formulate conclusions regarding relationships between PTSD treatments and both SUD and PTSD outcomes based on the broader PTSD treatment literature. We were interested in the extent to which RCTs to test treatments for PTSD have been highly selective or representative of the broader PTSD population with respect to substance use. Specifically, we addressed five research questions: 1) How commonly do published articles from RCTs of PTSD treatments report exclusion criteria related to substance use status? (2) How commonly do these reports include descriptive findings regarding participants' substance use? (3) Are RCTs that report excluding participants based on substance use status associated with differential PTSD treatment outcomes than those that do not? (4) Are RCTs that report exclusion based on substance use status associated with differential study retention rates than those that do not? (5) Among RCTs that report substance use findings, how, if at all, does PTSD treatment affect substance use? Finally, we developed recommendations for treatment and future research directions based on our findings.

While prior findings suggest frequent exclusion of those with SUD in RCTs for PTSD, the extent to which those with SUD have been excluded from these studies, and the potential impact of these exclusions have not been addressed systematically. Should strict exclusion criteria be common, this might call into question the representativeness of these study samples, and therefore, the applicability of findings to the broader population of PTSD patients.

2. Methods

2.1. Basis for review

Our review was based on a recent meta-analysis of the efficacy of PTSD treatments by Watts et al. (2013). We selected this meta-analysis because it 1) included pharmacotherapy and psychotherapy RCTs; 2) utilized broad inclusion criteria; 3) was published in a peer-reviewed journal with distinguished impact according the Thompson-Reuters' *Journal Citation Reports*; and 4) was methodologically rigorous in its use of databases and search terms.

2.2. Data extraction

We began by considering the 112 RCTs in Watts and colleagues' meta-analysis. We examined each paper to ascertain whether participants were excluded based on their substance use status and recorded all relevant details. Nicotine was excluded from our review because nicotine use tends not to be associated with exclusion from RCTs for PTSD. After extracting exclusion criteria related to substance use, the first two authors evaluated these exclusions and determined whether the criteria were described clearly or ambiguously. Criteria were considered clear if: 1) exclusion was based on diagnostic criteria, assessment scores (e.g., Alcohol Use Disorders Identification Test [AUDIT]), or specific levels of substance use (i.e., frequency and/or quantity of use); and 2) the relevant timeframe for substance use and/or diagnosis was stated explicitly (e.g., lifetime). The same two raters then recorded two main types of substance use-related results: 1) descriptive data regarding substance use status at study entry; and 2) study outcomes: either relationships between substance use status and PTSD outcomes or treatment retention or changes in substance use status *following* treatment for PTSD. Disagreements between raters were resolved through discussion.

2.3. Updated review

Publications in the original meta-analysis (Watts et al., 2013) were published between January 1, 1980 and April 1, 2012. We then searched the literature for additional recent papers published between 2012 and May 2015. We implemented the same search strategies as Watts et al. (2013), using the same databases (PILOTS, PsycINFO, PubMed and MEDLINE and Cochrane), with the goal of locating English-language reports of RCTs for PTSD treatments among adult samples. These search terms were used: “Combat disorders”, “posttraumatic stress disorder”, “post-traumatic stress disorders”, “PTSD”, and “stress disorders, post-traumatic.” We also reviewed reference lists of relevant meta-analyses and literature reviews. See Watts et al. (2013) for additional search strategy details.

The updated search was conducted by the first two authors. After the initial pool of papers was obtained, two raters evaluated each paper for adherence to inclusion criteria from Watts and colleagues' meta-analysis: 1) RCT methods (i.e., one or more control conditions with random assignment to conditions); 2) sample of