A Meta-Analysis of Depressive Symptom Outcomes in Randomized, Controlled Trials for PTSD

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Abstract: Posttraumatic stress disorder (PTSD) often co-occurs with depression. Current PTSD practice guidelines lack specific guidance for clinicians regarding the treatment of depressive symptoms. We conducted a meta-analysis of all randomized, placebo-controlled trials for PTSD therapies focusing on depression outcomes to inform clinicians about effective treatment options for depressive symptoms associated with PTSD. We searched literature databases for randomized, controlled clinical trials of any treatment for PTSD published between 1980 and 2013. We selected articles in which all subjects were adults with a diagnosis of PTSD based on the Diagnostic and Statistical Manual of Mental Disorders criteria, and valid PTSD and depressive symptom measures were reported. The sample consisted of 116 treatment comparisons drawn from 93 manuscripts. Evidence-based PTSD treatments are effective for comorbid depressive symptoms. Existing PTSD treatments work as well for comorbid depressive symptoms as they do for PTSD symptoms.

Key Words: Posttraumatic stress disorder, PTSD, depression, psychotherapy, medications

Several professional groups have created clinical guidelines that address comorbid PTSD and depression. The International Society for Traumatic Stress Studies (ISTSS) identified 4 treatment approaches when treating any psychiatric disorder that co-occurs with PTSD: a) integrated treatment in which comorbid disorders are treated by the same treatment, b) sequential treatment in which the comorbid condition is treated after PTSD, c) parallel treatment in which both disorders are treated with separate treatment approaches, and d) single diagnosis treatment in which only 1 disorder is targeted by treatment (Foa et al., 2009). Most PTSD clinical guidelines recommend integrated treatment for depression and PTSD (American Psychiatric Association, 2004; Department of Veterans Affairs and Department of Defense, 2010). The British National Institute for Health and Care Excellence guidelines are unique in recommending PTSD treatment first, with the rationale that depression symptoms often improve with effective PTSD treatment (National Institute for Health and Care Excellence, 2005), and ISTSS guidelines also state that this strategy may be effective (Foa et al., 2009). Beyond the sequencing of treatments, the existing guidelines do not recommend specific interventions for comorbid PTSD and major depressive disorder.

Previous reviews have not comprehensively examined the question of how best to treat depressive symptoms comorbid with PTSD. Studies have examined the efficacy of individual PTSD treatments on depression outcomes (Brady et al., 2000a; Schnurr et al., 2003; Tucker et al., 2001) but have not systematically examined depression outcomes for PTSD treatments. Many PTSD meta-analyses do not assess depressive symptom response to PTSD treatments at all (Benish et al., 2008; Davidson and Parker, 2001; Deacon and Abramowitz, 2004; Hofmann and Smits, 2008; Norton and Price, 2007; Pae et al., 2008; Seidler and Wagner, 2006; Stein et al., 2000; Watts et al., 2013). Other PTSD meta-analyses examine depression outcomes but only for a limited number of PTSD treatment modalities. Among those meta-analyses that examined depression outcomes, 3 focused only on effectiveness of medications (Adamou et al., 2007; Stein et al., 2006; Van Etten and Taylor, 1998), whereas 3 others focused exclusively on psychotherapies (Bisson and Andrew, 2007; Seidler and Wagner, 2006; Sherman, 1998). A comprehensive review of all PTSD treatments and their effect on comorbid depressive symptoms has not been conducted.

We sought to conduct a meta-analysis of all randomized controlled trials (RCTs) for PTSD therapies with a goal to specifically evaluate depression outcomes. Our primary aim was to inform clinicians about effective treatment options for PTSD and comorbid depression. We hypothesized that effective treatments for PTSD are also effective for comorbid depressive symptoms. Our secondary aim was to determine the overall relationship between change in depressive symptoms and change in PTSD symptoms in clinical trials for PTSD.

METHODS

Data Sources and Search Strategies

We searched PubMed, MEDLINE, PILOTS, PsychINFO, and the Cochrane databases for papers published between January 1, 1980 (the year the diagnosis of PTSD was established) (Association AP, 1980), and July 1, 2013. For PubMed and MEDLINE, we used the medical subject headings (MeSH) post-traumatic stress disorders,
Depressive Symptoms in PTSD

We limited results to articles indexed by a MeSH term as a clinical trial or those that included the terms treatment trial, randomized, or controlled trial in their title or abstract. We searched the entire Cochrane database by hand. For PILOTS, we used the thesaurus terms clinical trial and adults and limited our search to English language publications since 1980. In addition, we systematically reviewed references of all included studies as well as previous review articles and meta-analyses to locate additional references.

Study Selection

Included studies had to a) be a clinical trial in which participants were randomly assigned to 1 or more active PTSD treatments and to a control group; b) involve only adult participants (age 18 or older), all of whom met PTSD diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition; Third Edition, Revised; or Fourth Edition (DSM-III, DSM-III-R, DSM-IV); and c) present pretreatment and posttreatment measures of PTSD and depression.

Treatment Classification

Treatment classification followed the hierarchy of treatment types described by Watts et al. (2013). In this classification system, treatments were classified into their smallest group of similar modalities.

Data Extraction

One author (JMR) extracted data. All authors checked the work to ensure accuracy. The primary outcome was change in the depression measure. If more than 1 depression measure was used in a study, we extracted data according to a hierarchy developed before the data extraction. Clinician-reported measures were given first priority, followed by self-reported measures. We recorded the mean and SD of pretreatment and posttreatment measures for the treatment groups and the control group. If multiple posttreatment assessments were completed, we used the first assessment performed after the end of treatment. We excluded studies for which needed information was not provided.

If a study had more than 1 possible control group for comparison, we used the most robust control group available, according to FIGURE 1. Flow diagram of study identification and selection.
the following hierarchy: a) active control (for psychotherapy studies) or placebo (for drug studies), b) nonspecific comparison treatment such as treatment as usual, or c) wait-list control.

**Statistical Analysis**

To determine depressive symptom efficacy, we pooled depression effect sizes for each treatment group classification. The primary outcomes used to calculate the effect size was a continuous measure of depression symptom severity. Effect sizes and pooled estimates for the studies were calculated with the Comprehensive Meta-Analysis software package (Biostat, Inc, 1999). We calculated effect size as the between-groups difference in pretreatment-posttreatment change using Hedges G correction for small samples (Hedges and Olkin, 1985). To inform clinicians about treatments that would reduce both PTSD and depressive symptoms, we limited our reporting to effect sizes for depressive symptoms associated with known effective treatments for PTSD. Two recent meta-analyses show that effective treatments for PTSD include cognitive processing therapy, eye movement desensitization and reprocessing, fluoxetine, narrative exposure therapy, paroxetine, prolonged exposure, risperidone, sertraline, simulator exposure, and venlafaxine (Jonas et al., 2013; Watts et al., 2013).

To determine the overall relationship between change in depressive symptoms and change in PTSD symptoms in clinical trials for PTSD, we completed the same series of steps to determine the PTSD effect size of each treatment arm included in the meta-analysis. We compared depression and PTSD effect sizes for each treatment arm using a pairwise correlation coefficient.

**RESULTS**

The search results yielded 535 citations (Fig. 1). Two hundred sixty-two citations were duplicate studies. Review of the remaining 273 abstracts eliminated 124 studies because 76 were not clinical trials, 35 studied pediatric populations, and 13 were not PTSD treatment trials. We examined the remaining 149 studies in greater detail and excluded 8 because they did not require a PTSD diagnosis, 4 because they studied a pediatric population, 3 because they did not include a PTSD measure, 30 because they did not include a depression measure, and 11 because primary outcome data (depression or PTSD) were not available in the article. We found 93 eligible PTSD treatment studies with depression outcomes (Asukai et al., 2010; Bartzokis et al., 2005; Basoglu et al., 2005, 2007; Bass et al., 2013; Beck et al., 2009; Becker et al., 2007; Bichescu et al., 2007; Boggio et al., 2010; Brady et al., 2000a; Bryant et al., 2003, 2011; Carey et al., 2012; Carlson et al., 1998; Chard 2005; Church et al., 2013; Cloitre et al., 2002; Cohen et al., 2004; Cooper and Clum 1989; Davidson et al., 1990, 2001, 2003, 2006; Davis et al., 2004, 2008; de Kleine et al., 2012; Devilly and Spence, 1999; Difede et al., 2007a, 2007b; Duffy et al., 2007; Dunn et al., 2007; Dunne et al., 2012; Escherauru et al., 1997; Ehlers et al., 2003, 2005; Fecteau and Nicki, 1999; Feske, 2008; Foa et al., 1991, 1999, 2005; Forbes et al., 2012; Friedman et al., 2007; Gersons et al., 2000; Hamner et al., 2003, 2009; Herson-Levy et al., 2009; Hinton et al., 2005; Högborg et al., 2007; Hollifield et al., 2007; Kearney et al., 2013; Kent et al., 2011; Kosten et al., 1991; Krupnick et al., 2008; Kubany et al., 2004; Lindauer et al., 2005; Litz et al., 2007, 2012; Marcus et al., 1997; Marks et al., 1998; Marshall et al., 2001, 2007; Martenyi et al., 2007; Martenyi and Soldatenkova 2006; McDonagh et al., 2005; Miyahira et al., 2012; Monson et al., 2006; Mueser et al., 2008; Nacash et al., 2011; Neuner et al., 2004, 2010; Neylan et al., 2006; Pacella et al., 2012; Power et al., 2002; Ready et al., 2010; Reist et al., 1989; Resick et al., 2002; Rothbaum, 1997; Rothbaum et al., 2005, 2008; Schniefer et al., 2012; Schnurr et al., 2003, 2007; Shams et al., 2007; Shetatzyk et al., 1988; Taylor et al., 2003; Tucker et al., 2001, 2003; van der Kolk et al., 2007; Vaughan et al., 1994; Watts et al., 2012; Yeh et al., 2011; Zhang et al., 2013). The studies contain data from 116 comparisons because several studies compared more than 1 treatment with a control group.

Treatment groups differed to some degree in the extent which they were studied ranging from 4 studies that included 80 subjects for exposure using a simulator to 5 studies of 1132 subjects for paroxetine (see Fig. 2). RCT trauma populations were diverse and represented combat-related trauma, sexual violence, natural disaster, terror, motor vehicle accident, and medically related trauma. In many instances, an RCT included more than 1 trauma population.

We identified depression measures and their outcome. The most commonly used depression measure was the self-report Beck Depression Inventory (53%, n = 61), followed by the clinician-administered Hamilton Rating Scale for Depression (27%, n = 31). Eleven studies (9%) utilized the Montgomery-Asberg Depression Score. The remaining 13 studies utilized lesser-known scales and represented a mix of patient and clinician-administered measures. Categorical measures of depression were not used for outcome data in the studies. The Structured Clinical Interview for DSM Disorders (SCID) often established baseline diagnosis, but posttreatment assessment of depression diagnosis was not included in RCT for PTSD study design.

When we compared the depressive symptom effect sizes of the specific treatments known to be effective for PTSD, we found that all effective PTSD treatments were also effective for depressive symptoms (Fig. 2). Most treatments had overlapping 95% confidence intervals (CIs) indicating that they were not significantly different (Fig. 2). Paroxetine had the highest effect size (1.18, 95% CI: 0.4–2.04), followed by cognitive processing therapy (1.12, 95% CI: 0.53–1.7), prolonged exposure (0.92, 95% CI: 0.64–1.19), eye movement desensitization and reprocessing (0.92, 95% CI: 0.43–1.42), simulator exposure (0.77, 95% CI: 0.32–1.22), narrative exposure therapy (0.67, 95% CI: 0.23–1.12), fluoxetine (0.42, 95% CI: 0.02–0.61), risperidone (0.3, 95% CI: 0.09–0.51), sertraline (0.23, 95% CI: 0.1–0.36), and venlafaxine (0.21; 95% CI: 0.06–0.36).

When we compared the effect size for depression outcome to the effect size for PTSD outcome for the 116 treatment arms (Fig. 3), the correlation coefficient for all studies was 0.56. Generally, there was a strong correlation, suggesting that a treatment’s efficacy for PTSD was similar to its efficacy for depressive symptoms.

**DISCUSSION**

PTSD is a debilitating condition that often co-occurs with depression. To improve clinical care for this population, we sought to conduct a meta-analysis of depression outcomes of RCTs of PTSD treatments. Our primary aim was to inform clinicians about effective treatment options for PTSD and comorbid depression. We determined that evidence-based PTSD treatments are also effective for comorbid depressive symptoms. In general, the efficacy of PTSD treatments for co-occurring depressive symptoms was similar between treatments.

Attempts to identify a single best treatment for comorbid depression in PTSD were impaired by the considerable differences in study design. For example, the medication trials had similar effect sizes ranging from 0.24 to 1.27. The psychotherapy trials had effect sizes ranging from 0.63 to 1.25. Overall, the CIs of the treatment modalities overlap. However, the psychotherapy trials compared wait list in 51 of 61 studies, whereas all of the medication studies compared with placebo. We believe most observed differences when comparing medication to psychotherapy are due to study design rather than real difference in treatment response. When comparing individual treatments within modalities, all psychotherapies have similar effect sizes, and most medications have similar effect sizes. The only exception is paroxetine, which appears to be superior to sertraline and venlafaxine. This suggests that there are not treatments specifically or particularly effective for the depressive symptoms associated with PTSD. Any noted differences should be considered preliminary findings. A reasonable next step might be to conduct a prospective comparative efficacy study of effective medications for PTSD on comorbid depressive symptoms.
Overall, we found a strong correlation between efficacy for PTSD symptoms and efficacy for comorbid depressive symptoms. Most treatments showed similar magnitude of effects for both depressive and PTSD symptoms. This was true within studies and across treatment types. In general, existing PTSD treatments are as effective for comorbid depressive symptoms as they are for PTSD symptoms. Therefore, the presence of associated depressive symptoms should not necessarily influence treatment choice.

The generalizability of our findings to all clinical PTSD populations is unclear. Recent data indicate that patients with PTSD marked by high levels of depressive symptoms (dysphoria) are more likely to engage in treatment for PTSD (Blais et al., 2014). As a result, RCTs of PTSD therapies may be more likely to enroll patients with depressive symptoms. If this is the case, our findings may not apply to all PTSD populations. Similarly, only 7 studies examined how specific PTSD symptom clusters responded to treatment. Thus, we cannot comment on the relationship of specific PTSD symptoms (re-experiencing for example) to depressive symptoms. Better understanding of how specific DSM-5 PTSD symptom clusters respond to treatment is an important topic for further research.

In addition, the sequence of improvement of PTSD and depressive symptoms during the course of PTSD treatment remains an open question. Although it would have been interesting to examine timing of response to treatment, most studies only reported end of treatment data. Therefore, we were unable to determine if depressive symptoms respond before PTSD symptoms or vice versa and we were unable to determine the speed with which symptom improvement occurred. Similarly, meaningful analysis of long-term depression outcomes was not possible due to limitation in reporting these outcomes in most studies.

When applying these findings to clinical practice, our findings support most treatment guidelines for the treatment of PTSD and comorbid depression. Integrated treatment, treating both PTSD and depression simultaneously, is the most common recommendation (American Psychiatric Association, 2004; Department of Veterans Affairs and Department of Defense, 2010; Foa et al., 2009). Our results indicate that in most cases, a single evidence-based PTSD treatment is effective for comorbid depression. Stated another way, a clinician can knowingly choose an evidence-based PTSD treatment to treat...
depression and PTSD in an integrated fashion. In this respect, our findings support all PTSD treatment guidelines.

Our results do not differentiate depression effects based on severity of depression. However, the Department of Veterans Affairs and Department of Defense guideline suggestion that depression of mild severity may not require additional treatments outside those targeting PTSD (Department of Veterans Affairs and Department of Defense, 2010) is generally supported by our findings. We do not find evidence supporting the delay of PTSD psychotherapies in the presence of depressive symptoms, as suggested by the American Psychiatric Association (American Psychiatric Association, 2004).

There are several limitations to our findings. First, all data were obtained from studies utilizing DSM-III and DSM-IV diagnostic criteria. Although we anticipate that our findings apply to DSM-V PTSD criteria, research comparing depressive outcomes to DSM-V PTSD measures is warranted. Second, our findings are limited to RCTs of PTSD treatment. Novel treatments and treatments studied in open trials were not included in this meta-analysis and may yield different findings. Most patients included in the study had mild depressive symptoms. Although there were patients with more severe symptoms, we cannot comment on the effectiveness in patients with differing symptoms.

Differences in trial design between medication and psychotherapy studies prevent us from comparing medication and psychotherapy approaches in treating PTSD with comorbid depressive symptoms. All psychopharmacologic studies were placebo controlled. However, most psychotherapeutic studies used wait-list controls, potentially inflating psychotherapy effect sizes. Greater effort should be made to employ active control designs in psychotherapy studies to facilitate better between-treatment comparisons.

A final topic of consideration is the nature of depressive symptoms included in the PTSD diagnosis. A frequent criticism of the DSM-III and DSM-IV PTSD diagnostic criterion is their symptom overlap with major depressive episode (Bleich et al., 1997; Brewin et al., 2009; Simms et al., 2002). Critics state the inclusion of depressive-like symptoms generate a broad spectrum of PTSD presentation that could lead to inaccurate PTSD diagnosis (Brewin et al., 2009) and may reflect general dysphoria rather than PTSD (Simms et al., 2002). Writers of DSM-V PTSD diagnostic criteria weighed these criticisms, reviewed the literature, and determined that symptoms such as blame or guilt, negative appraisal of self, and negative emotional states were integral to the PTSD diagnosis (Friedman et al., 2011). The DSM-V creates a new diagnostic cluster, negative alterations in cognitions and mood (Criterion D), which highlights depressive symptoms in PTSD.

Our findings are particularly applicable to this new understanding of PTSD presentation. Although our results are exclusively from studies employing DSM-III and DSM-IV PTSD diagnostic criteria, we now know that existing PTSD treatments are effective for depressive symptoms. Because of the linkage between PTSD and depression responses to all forms of treatments, our findings support the inclusion of depressive symptoms (Criterion D) in DSM-V diagnosis of PTSD. Our findings also suggest that existing PTSD treatments should be effective when treating all PTSD symptoms including those newly included by the DSM-V.

CONCLUSIONS

In conclusion, comorbid depression appears to be effectively treated with existing PTSD treatments, and clinicians can use PTSD treatments as first-line treatment for comorbid depressive symptoms. Additionally, clinicians should not delay the administration of PTSD psychotherapies in the face of comorbid depression, as both will likely show improvement with treatment.

DISCLOSURES

Dr. Shiner is supported by a VA Health Services Research and Development Career Development Award (CDA11-263). This work was unfunded.

This is the work of the authors and does not necessarily represent the position of the Department of Veterans Affairs. The authors declare no conflict interests.

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