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The Effect of Concurrent Depression on PTSD Outcomes in Trauma-Focused Psychotherapy: A Meta-Analysis of Randomized Controlled Trials

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The co-occurrence of depression with posttraumatic stress disorder (PTSD) is common and associated with greater severity and impairment than PTSD alone, but the effects on PTSD treatment outcomes are unclear. This study investigated the impact of baseline depression on PTSD symptom change and dropout in a meta-analysis of 44 randomized controlled trials (N = 4,866) of trauma-focused psychotherapies for PTSD. Analyses included 107 active (k = 71) and control (k = 36) conditions. Baseline depression was indexed within samples as (a) continuous symptom severity (e.g., Beck Depression Inventory), standardized across depression measures and (b) proportion of patients with comorbid depressive disorder diagnosis. Among active conditions reporting continuous depression scores (k = 62), greater depression severity predicted smaller PTSD treatment effect sizes (ß = -.36, p = .002), but not dropout (ß = .25, p = .18). Categorical depressive diagnosis rates (k = 29)—reported less frequently—were not associated with treatment effects or dropout in active conditions. Greater depression severity may reflect a risk factor for attenuated response in PTSD psychotherapies, potentially demanding complementary strategies within trauma-focused interventions. Variability between trials in baseline depression symptoms may suggest the need to consider this sample characteristic when comparing treatment outcomes across studies.

Keywords: PTSD; meta-analysis; depression; comorbidity; psychotherapy

DEPRESSION COMMONLY CO-OCCURS WITH posttraumatic stress disorder (PTSD), with more than half of all patients with PTSD also meeting diagnostic criteria for major depressive disorder (MDD; Rytwinski et al., 2013). Understanding the comorbidity between these two disorders is complicated by factors such as heterogeneity within each diagnosis (e.g., Zoellner et al., 2014) and shared symptoms (e.g., Flory & Yehuda, 2015; Post et al., 2011), yet there is evidence of significant, clinically relevant differences between individuals with PTSD alone and those with co-occurring depression. Individuals with co-occurring PTSD and MDD tend to experience more severe symptomatology (Bedard-Gilligan et al., 2015; Campbell-Sills et al., 2012; Kessler et al., 2005; Post et al., 2011), lower

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global functioning and quality of life (Bedard-Gilligan et al., 2015; Raab, Mackintosh, Gros, & Morland, 2015), increased risk of completed suicide (Oquendo et al., 2005), a more chronic course of impairment (Breslau et al., 1991), and increased health care utilization (e.g., Kramer, Booth, Han, & Williams, 2003) relative to those individuals with PTSD alone. Thus, compared to PTSD alone, co-occurring PTSD and depression appears to be characterized by increased impairment, greater psychopathology, and increased likelihood of negative health outcomes.

Despite its prevalence and association with more severe symptomatology, the impact of comorbid depression on PTSD treatment is not well understood. There are a range of efficacious options for PTSD (e.g., Watts et al., 2013), with trauma-focused cognitive behavioral therapies effective in reducing symptoms of both PTSD (Cusack et al., 2016; Kline et al., 2018) and depression (Ronconi et al., 2015). Optimal implementation of current PTSD treatments for patients with comorbid MDD has stimulated debate (Angelakis & Nixon, 2015; Flory & Yehuda, 2015) and a corresponding interest in the development of modified treatment protocols targeting this specific treatment combination (e.g., Nixon & Nearmy, 2011). Suggested strategies have included augmenting trauma-focused therapies with cognitive behavioral components, such as behavioral activation early in treatment to overcome depressive symptoms (Angelakis & Nixon, 2015), or integrating elements of transdiagnostic interventions (Gros et al., 2012). The presence of comorbid depression has also been shown to affect clinical decision-making surrounding implementation of exposure therapy for PTSD, shifting bias towards antidepressant medication even among trauma therapists (van Minnen et al., 2010), despite a lack of empirical evidence supporting this approach (Lee et al., 2016). However, current knowledge regarding how to best treat co-occurring depression and PTSD—as well as the efficacy of existing treatments among patients with this comorbidity—remains limited.

Indeed, empirical evidence of the effect of comorbid MDD symptoms on PTSD treatment outcomes specifically is mixed, as some studies have reported that initial levels of depression predict worse outcomes (e.g., Taylor et al., 2001; Stein et al., 2012; Walter et al., 2012), whereas others have not (e.g., Asamsama et al., 2015; Hagenaars et al., 2010; van Minnen et al., 2002). There is less evidence with respect to the purported link between comorbid depression and risk of dropout from PTSD treatments, despite commonly cited concerns regarding whether depressed patients will experience greater difficulty in engaging with aspects of trauma-focused treatment (e.g., van Minnen et al., 2015). The speculative link between baseline depression burden and increased dropout risk is particularly relevant given relatively high dropout rates in treatments for PTSD and the pressing need to identify reliable factors associated with poor retention (e.g., Steenkamp et al., 2015). Once again, the literature yields mixed findings, with some studies finding that more depressed patients are more likely to drop out from PTSD treatments (e.g., Levi et al., 2019), while others have failed to detect an association (e.g., Goodson et al., 2012; van Minnen et al., 2002). Overall, it remains unclear whether depression severity impacts PTSD treatment response and retention in the most widely used, efficacious treatments for PTSD.

Inconsistent findings from this literature highlight some of the complexities inherent to this issue. Baseline rates of comorbid depression or continuous measures of depressive severity are not uniformly reported in clinical trials, and few studies explicitly test for potential moderating effects of these variables on clinical outcomes. Moreover, because depression severity can vary substantially across samples (Rytwinski et al., 2013), its effect on outcomes may be difficult to gauge within a single study. Consider two PTSD treatment studies examining the same intervention, with similar populations except for the rate of comorbid depression. If the rate is low in one sample (10%) and high in another (90%), the ability to detect relationships between depression and outcomes will be limited in both cases. However, such an effect will be detectable by comparing the relationship between baseline depression and clinical outcomes *across* studies, assuming some degree of variability in both these variables.

Furthermore, while a majority of patients improve after receiving evidence-based interventions for PTSD, a meaningful proportion of patients fail to respond (Larsen et al., 2019; Steenkamp et al., 2015), signaling the need to identify factors associated with attenuated response. In light of the established pattern of overall greater severity and worse functioning in co-occurring depression and PTSD, it is plausible that comorbid depression reflects a risk factor for attenuated response to treatments for PTSD, a finding in line with several studies that have examined this question (e.g., Stein et al., 2012; Taylor et al., 2001; Walter et al., 2012). Accordingly, we conducted a systematic review and meta-analysis of trauma-focused psychotherapies for adults with PTSD in randomized controlled trials (RCTs) to examine whether baseline depressive symptoms impact PTSD symptom reduction and treatment dropout.

Methods

SEARCH STRATEGY

Our systematic search process involved several stages. First, we searched the PsycINFO database (Ebsco) for all relevant articles published between 1980 and 2019. Search terms included: "PTSD" OR "post traumatic stress disorder" OR "posttraumatic stress disorder" OR "post-traumatic stress disorder" and "psychotherapy" OR "therapy" and "treatment" OR "trial" OR "randomized." Studies were limited by publication year (1980–2019), language (English), and age group (adults 18 years and older). We also reviewed references from recent comprehensive meta-analyses on RCTs for PTSD treatments (e.g., Cusack et al., 2016; Jonas et al., 2013; Lee et al., 2016; Watts et al., 2013) for articles not identified by our initial search. Finally, we reviewed the PTSD Trials Standardized Data Repository, a database created by the National Center for PTSD and the Agency for Healthcare Research and Quality (AHRQ) of over 300 randomized clinical trials for PTSD (O'Neil et al., 2019).

INCLUSION CRITERIA

Inclusion criteria were designed to provide a focused review of the highest quality, most representative treatment research on trauma-focused psychotherapies for adults with PTSD. Studies were required to be (a) randomized controlled treatment trials with the primary aim of reducing PTSD symptoms for (b) adults with PTSD involving (c) at least one face-to-face trauma-focused, standardized individual or group psychotherapy treatment conducted primarily in outpatient settings, of at least four sessions duration. For studies meeting these preliminary criteria, additional requirements were (d) the use of a validated clinical assessment to establish full PTSD diagnosis, (e) reporting of posttreatment PTSD symptom outcomes with validated measures, and (f) information about baseline depression characteristics of the sample, using a validated clinical interview (binary depressive disorder diagnosis) or depression-specific measure (continuous depressive symptoms). Based on meta-analytic guidelines and standards used in other contemporary reviews of the PTSD literature (e.g., Cusack et al., 2016), we also included only studies that (g) met a minimum sample size at the study level ($N = 30$) and (h) were rated as having "low" or "moderate" risk of bias to enhance the confidence in and precision of findings (Cuijpers et al., 2010; Higgins et al., 2011; Turner et al., 2013; Viswanathan et al., 2012). Recent contemporary meta-analyses have imposed inclusion criteria based on sample size (e.g., Morina et al., 2014; Rytwinski et al., 2013) and ratings of study quality or bias (Cusack et al., 2016; Jonas et al., 2013) given their impact on effect size estimates. We used the risk of bias (ROB) assessment rubric described by Cusack and colleagues (2016), excluding studies rated as "high" ROB (low quality). This assessment is based on 12 items originally developed in a Guide for Comparative Effectiveness Review published by the Agency for Healthcare Quality and Research Methods (Viswanathan et al., 2012) to assess potential selection, confound, performance, detection and attrition biases. Binary questions assessed adequacy of randomization and treatment concealment, group comparability at baseline, blinding of outcome evaluators, overall and differential attrition rates, analytic strategy, method of handling missing data, quality of outcome assessment methods, and treatment fidelity checks. ROB ratings of the majority of studies included in this meta-analysis were previously published (Cusack et al., 2016) and thus treated as a primary criterion for exclusion. The remaining studies were independently rated for ROB by the first, second, and third authors, with strong agreement for quality scores and related inclusion/exclusion decisions; any disagreements were resolved by discussion among the first three authors until reaching consensus.

CODING PROCEDURE AND DATA EXTRACTION

The first and second authors extracted data separately for each treatment condition. Reliability of extracted data was based on ratings made independently by a trained undergraduate research assistant and was extremely high for main variables of interest (ICCs > .95). Dropout rate (%) was recorded separately for each treatment condition, where dropouts were classified as patients who were randomized but failed to complete treatment as prescribed, except those who were removed administratively (i.e., for protocol violations, medical complications or death). Dropout rates were uniformly increased by 1% to address analytic complications associated with the occurrence of zero values in proportion data (Trikalinos et al., 2013). We also extracted treatment and study details to better characterize the sample. We extracted condition-level data when possible; if a study reported information at the study level only (e.g., BDI average in an entire study sample, rather than BDI average within each treatment condition), these study-level data were used in analyses. Studies were classified on the basis of target trauma type (mixed, assault, military/combat, or motor vehicle accident), population type (civilian/mixed or all military), and type of primary analyses (intent-to-treat [ITT] or completer). We also coded the intended duration of sessions and weeks for active

treatment conditions. Psychotherapies were classified closely mirroring Cusack et al. (2016), where interventions with active, trauma-focused components were coded as active conditions. These included interventions such as: cognitive behavioral therapy–mixed (CBT-M) for interventions using one or a combination of components of CBT, such as cognitive restructuring and *in vivo* exposure exercises; cognitive processing therapy (CPT; Resick & Schnicke, 1993); cognitive therapy (CT); eye movement desensitization and reprocessing (EMDR); and exposure, including prolonged exposure (Foa et al., 2007), virtual reality, or other interventions primarily emphasizing exposure to the trauma memory. Control conditions were those without an active treatment ingredient, categorized as waitlist control (WLC) or nondirective, non-trauma-focused conditions (NDC) intended to serve as an inactive therapy control, such as those with elements of relaxation, psychoeducation, present centered therapy, or nondirective supportive counseling.

ANALYTIC STRATEGY

The primary dependent variable used throughout the meta-analysis was pre-post within-group improvement in PTSD symptoms, which was calculated by subtracting the posttreatment mean in PTSD symptoms from pretreatment mean in PTSD symptoms, divided by pretreatment standard deviation, per the recommendations of Morris and DeShon (2002). When multiple measures or results were reported, we favored interviewer-based over self-reported PTSD symptom assessments (Möller, 2000) and statistics from ITT analyses over completer sample analyses. We collected both continuous and categorical data related to baseline depressive symptoms in each condition. For each condition, we calculated a continuous depression score based on the *mean* plus 1 *standard deviation* divided by the highest possible score on the measure used in the study. This allowed us to compare scores across different measures and to capture variability in scores not reflected in mean values (Cohen & Cohen, 1983). To account for differences between measures, this value was transformed into a ratio by dividing by the highest possible score on each measure.[1] Categorical depression values were typically based on percentage of patients diagnosed with comorbid major depressive disorder. In trials where current or lifetime bipolar disorder were exclusion criteria from the study, rates of mood disorder or depressive order were coded, and these trials were included in the meta-analysis. Treatment conditions were weighted by sample size at randomization (Hunter & Schmidt, 2004). Preliminary analyses were conducted to assess sample heterogeneity via the Q and I^2 statistics (Higgins et al., 2003). Heterogeneity among all conditions for pre-post effect sizes was high when examining all conditions (Q = 3495.18, $p < .0001$, I^2 = 96.97); random-effects models were utilized for all analyses (Lipsey & Wilson, 2001). All analyses were implemented in SPSS 26 using macros developed by Wilson (2005).

Results

Figure 1 documents the process of identifying studies for inclusion in this meta-analysis. The initial search yielded 4,323 articles, which on the basis of abstract and title review led to 319 articles selected for further evaluation. A review of recent meta-analyses and the National Center for PTSD/AHRQ clinical trials database identified a further 69 articles that were included at this stage. After a detailed review of these studies by the first two authors (AAC and ACK), 344 were removed for failure to meet inclusion criteria, leaving 44 trials for meta-analysis inclusion. The most common reason for exclusion was diagnostic makeup of sample (e.g., not all patients met full PTSD diagnostic criteria), although studies commonly met multiple criteria.[2]

Table 1 lists descriptive characteristics for all 44 studies and 107 constituent conditions included in this meta-analysis. Studies included in the current meta-analysis were published between 1998 and 2019. A total of 4,866 patients were included in our analyses, with condition sample sizes ranging from 10 to 180 (median = 33, M = 45.48, SD = 33.87). Of 107 conditions included in our analyses, 71 were active treatments, predominantly delivered in individual format (k = 66, 93.0%). Over half of all active treatment conditions were classified as exposure therapy (k = 39; 54.9%). Control conditions were split fairly equally between waitlist (k = 17; 47.2%) or nondirective control, such as relaxation or supportive counseling (k = 19; 52.8%). Index trauma types were diverse; studies with mixed index trauma was most common (k = 21, 47.7%), while remaining studies treated solely one type of index trauma, including physical or sexual assault (k = 13; 29.5%), military- or combat-related trauma (k = 8; 18.2%), or motor vehicle accident trauma (k = 2; 4.5%). A subset of studies

[1] For example, a sample-level mean of 10 and standard deviation of 3 on the PHQ-9 (range: 0-27) would correspond to a value of 0.48, or moderate depression severity.

[2] In a small number of studies (k = 6), some treatment conditions were omitted because they failed to meet specific inclusion criteria; specifically, one condition each in Liu et al., 2019; Markowitz et al., 2015, Morland et al., 2014, and Nidich et al., 2018 was not a trauma-focused, face-to-face treatment, and three conditions between van der Kolk et al., 2007 and Zoellner et al. 2019 involved only pharmacological interventions.

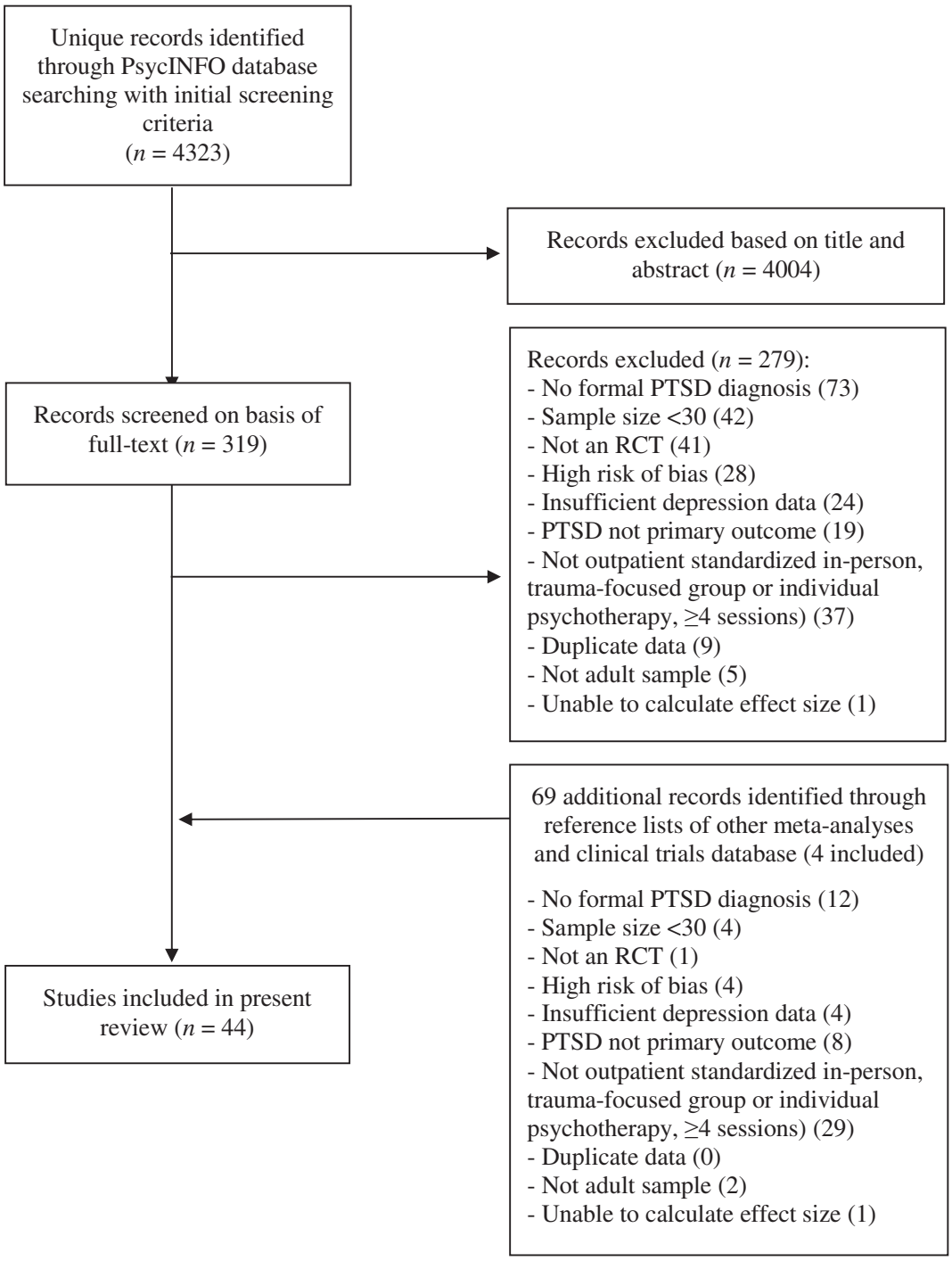

FIGURE 1 Flow diagram of study identification and selection process

exclusively involved veterans or active-duty service members (k = 16; 36.4%), while the remainder treated mixed or civilian samples. Most studies involved ITT analyses for primary outcomes (k = 36, 81.8%). Among active psychotherapy conditions, the average intended acute treatment duration was 9.29 weeks (SD = 4.77) and 11.07 sessions (SD = 3.71).

Among included studies (k = 44), most (k = 39, 88.6%) reported continuous depression baseline measures, while a smaller number (k = 18, 40.9%) reported categorical depressive disorder baseline data. Therefore, in all depressive disorder analyses, it is important to note the smaller sample size and thus statistical power compared to continuous depression

Table 1
Characteristics of Included Randomized Controlled Trials and Treatment Conditions

Study: Author, year, treatment conditions	*N*	Condition	Intended # Sessions (Weeks)	Population	Trauma type	PTSD measure	Depression measure	Comorbid MDD %
Bryant, Moulds, Guthrie, Dang, & Nixon, 2003	58			Civilian	Mixed	CAPS	BDI-II	–
IE	20	EX	8 (8)					
IE + CR	20	EX	8 (8)					
SC	18	NDC	8 (8)					
Bryant et al., 2008	118			Civilian	Mixed	CAPS	BDI-II	–
IE	31	EX	8 (8)					
IVE	28	CBT-M	8 (8)					
IE + IVE	31	EX	8 (8)					
IE + IVE + CR	28	EX	8 (8)					
Bryant et al., 2013	70			Civilian	Mixed	CAPS	BDI-II	
Emotion regulation training + CBT	36	CBT-M	12 (12)					67.0
SC + CBT	34	CBT-M	12 (12)					60.0
Carlson, Chemtob, Rusnak, Hedlund, & Muraoka, 1998	35			Military	Military	CAPS	BDI-I	–
EMDR	10	EMDR	12 (6)					
Biofeedback-assisted relaxation	13	NDC	12 (6)					
WLC	12	WLC	– (6)					
Chard, 2005	71			Female, civilian	CSA	CAPS	BDI-II	40.0
CPT-SA	36	CPT	17 (17)					
Minimal attention WLC	35	WLC	17 (17)					
Cloitre, Koenen, Cohen, & Han, 2002	58			Female, civilian	CSA, CPA	CAPS	BDI-I	45.0
STAIR + PE	31	EX	16 (12)					
WLC	27	WLC	– (12)					
Cloitre et al., 2010	104			Female, civilian	CSA, CPA	CAPS	BDI-I	–
STAIR + EX	33	EX	16 (16)					
SC + EX	38	EX	16 (16)					
STAIR + SC	33	CBT-M	16 (16)					
Ehlers et al., 2003	85			Civilian	MVA	CAPS	BDI-II	–
CT	28	CT	12 (12)					
Self-help booklet	28	NDC	1 (12)					
Repeated assessments	29	WLC	– (12)					
Ehlers et al., 2014	121			Civilian	Mixed	CAPS	BDI–II	–
7-day intensive CT	30	CT	12 (1)					
Standard weekly CT	31	CT	12 (12)					
SC	30	NDC	12 (12)					
WLC	30	WLC	– (14)					
Foa et al., 1999	96			Female, civilian	Physical assault, sexual assault	PSS-I	BDI-I	–
PE	25	EX	9 (4.5)					
SIT	26	CBT-M	9 (4.5)					
PE + SIT	30	EX	9 (4.5)					
WLC	15	WLC	– (5)					
Foa et al., 2005	190			Female, civilian	Physical assault, sexual assault, CSA	PSS-I	BDI-I	41.2
PE	79	EX	12 (12)					
PE + CR	74	EX	12 (12)					
WLC	26	WLC	– (12)					
Foa et al., 2018	370			Military	Mixed	PSS-I	BDI-II	–
Massed PE	110	EX	10 (2)					
Spaced PE	110	EX	10 (8)					
PCT	110	NDC	10 (8)					

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Table 1 (*continued*)

Study: Author, year, treatment conditions	*N*	Condition	Intended # Sessions (Weeks)	Population	Trauma type	PTSD measure	Depression measure	Comorbid MDD %
Minimal contact	40	WLC	– (4)					
Forbes et al., 2012	59			Military	Military	CAPS	BDI-II	–
CPT	30	CPT	12 (6)					
TAU	29	NDC	– (6)					
Kubany, Hill, & Owens, 2003	37			Female, civilian	Battered women	CAPS	BDI-I	–
CTT-BW	19	CBT-M	11 (5.5)					
WLC, then CTT-BW	18	WLC	– (5.5)					
Kubany et al., 2004	125			Female, civilian	Battered women	CAPS	BDI-I	–
CTT-BW	63	CBT-M	11 (5.5)					
WLC, then CTT-BW	62	WLC	– (5.5)					
Liu et al., 2019	207			Military	Mixed	CAPS	PHQ-9	–
CPT in person	104	CPT	12 (12)					
CPT via telemedicine *	–							
McDonagh et al., 2005	74			Female, civilian	CSA	CAPS	BDI-I	–
CBT	29	EX	14 (14)					
PCT	22	NDC	14 (14)					
WLC	23	WLC	– (14)					
Markowitz et al., 2015	110							
PE	38	EX	10 (14)	Civilian	Mixed	CAPS	HRSD-24	53.0
Relaxation	32	NDC	10 (14)					47.0
IPT *								
Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998	87			Civilian	Mixed	CAPS	BDI-I (–)	
PE	23	EX	10 (10)					30.0
CR	19	CT	10 (10)					63.0
PE + CR	24	EX	10 (10)					65.0
Relaxation	21	NDC	10 (10)					38.0
Monson et al., 2006	60			Military	Military	CAPS	BDI-I	–
CPT	30	CPT	12 (6)					
WLC	30	WLC	– (10)					
Morland et al., 2014	125			Male, Military	Mixed	CAPS	–	
CPT-C in person	64	CPT	12 (6)					25.0
*CPT-C teletherapy**								
Mueser et al., 2008	108			Civilian, co-occurring SMI	Mixed	CAPS	BDI-II	
CBT	54	CBT-M	16 (–)					55.6
TAU	54	NDC	– (–)					66.7
Mueser et al., 2015	201			Civilian, co-occurring SMI	Mixed	CAPS	BDI-II	–
CBT with CR	104	CBT-M	16 (16)					
Brief CBT without CR	97	NDC	3 (3)					
Nacasch et al., 2011	30			Military	Military	CAPS	BDI-II	–
PE	15	EX	*M*=11 (–)					
TAU	15	NDC	– (–)					
Nacasch et al., 2015	40			Military	Mixed	CAPS	BDI-I	
PE (90 minutes)	20	EX	*M*=13.2 (–)					21.1
PE (60 minutes)	20	EX	*M*=13.6 (–)					25.0
Nidich et al., 2018	203			Military	Mixed	CAPS	PHQ-9	
PE	68	EX	12 (12)					50.0
PTSD health education	67	NDC	12 (12)					43.0
Transcendental meditation *								
Resick, Nishith, Weaver, Astin, & Feuer, 2002	171			Female, civilian	Rape survivors	CAPS	BDI-I	
CPT	62	CPT	12 (6)					43.5

Table 1 (*continued*)

Study: Author, year, treatment conditions	*N*	Condition	Intended # Sessions (Weeks)	Population	Trauma type	PTSD measure	Depression measure	Comorbid MDD %
PE	62	EX	12 (6)					47.5
WLC	47	WLC	– (6)					–
Resick et al., 2008	162			Female, civilian	IPV	CAPS	BDI-II	50.0
CPT	56	CPT	12 (6)					
CPT-C	51	CPT	12 (6)					
WA	55	CBT-M	7 (6)					
Resick et al., 2015	108			Military	Military	PSS-I	BDI-II	–
CPT-C	56	CPT	12 (6)					
PCT	52	NDC	12 (6)					
Rothbaum, Astin, & Marsteller, 2005	73			Female, civilian	Rape survivors	CAPS	BDI-I	–
PE	23	EX	9 (4.5)					
EDMR	25	EMDR	9 (4.5)					
WLC	24	WLC	– (4.5)					
Rothbaum et al., 2014	156			Military	Military	CAPS	–	
VR EX + DCS	53	EX	6 (6)					22.6
VR EX + ALP	50	EX	6 (6)					24.0
VR EX + PBO	53	EX	6 (6)					35.8
Sack et al., 2016	139			Civilian	Mixed	CAPS	BDI-II	–
EX + eye fixation, movement	47	EMDR	8 (8)					
EX + eye fixation, no movement	47	EMDR	8 (8)					
EX + no eye fixation	45	EX	8 (8)					
Schneier et al., 2012	37			Civilian	9/11 survivors	CAPS	HRSD-17	–
PE + paroxetine	18	EX	10 (10)					
PE + PBO	19	EX	10 (10)					
Schnurr et al., 2003	360			Military	Military	CAPS	–	
TFGT	180	CBT-M	30 (30)					58.6
PCGT	180	NDC	30 (30)					53.4
Schnurr et al., 2007	284			Military	Mixed	CAPS	BDI-I	–
PE	141	EX	10 (10)					
PCT	143	NDC	10 (10)					
Sloan, Marx, Bovin, Feinstein, & Gallagher, 2012	46			Civilian	MVA	CAPS	–	25.0
WET	22	EX	5 (5)					
WLC	24	WLC	– (5)					
Sloan, Unger, Lee, & Beck, 2018	198			Male, military	Mixed	CAPS	BDI-II	
CBT	98	EX	14 (16)					55.1
PCT	100	NDC	14 (16)					57.0
Suris, Link-Malcolm, Chard, Ahn, & North, 2013	86			Military	Military sexual trauma	CAPS	QIDS	–
CPT	52	CPT	12 (12)					
PCT	34	NDC	12 (12)					
Tarrier et al., 1999	72			Civilian	Mixed	CAPS	BDI-I	54.0
IE	35	EX	16 (16)					
CT	37	CT	16 (16)					
Thorp et al., 2019	87			Military	Military	CAPS	PHQ-9	
PE	41	EX	12 (12)					17.0
Relaxation	46	NDC	12 (12)					24.0
van den Berg et al., 2015	155			Civilian,	Mixed	CAPS	BDI-II	–

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Table 1 (*continued*)

Study: Author, year, treatment conditions	*N*	Condition	Intended # Sessions (Weeks)	Population	Trauma type	PTSD measure	Depression measure	Comorbid MDD %
PE	53	EX	8 (10)	comorbid				
EMDR	55	EMDR	8 (10)	psychotic				
WLC	47	WLC	– (10)	disorder				
van der Kolk et al., 2007	88			Civilian	Mixed	CAPS	BDI-II	–
EMDR	29	EMDR	8 (8)					
Fluoxetine *								
Pill PBO *								
Zoellner, Roy-Byrne, Mavissakalian, & Feeny, 2019	200			Civilian	Mixed	PSS-I	BDI-II	–
PE	116	EX	10 (10)					
Sertraline *								
Zoellner et al., 2017	42			Civilian	Mixed	PSS-I	QIDS	–
IE + methylene blue	15	EX	6 (1)					
IE + PBO	16	EX	6 (1)					
WLC	11	WLC	– (3)					

Note. ALP = Alprazolam; CAPS = Clinician-Administered PTSD Scale; CBT = cognitive behavioral therapy; CPA = childhood physical abuse; CPT = cognitive processing therapy; CPT-C = CPT without WA; CPT-SA = cognitive processing therapy for sexual abuse survivors; CR = cognitive restructuring; CSA = childhood sexual abuse; CT = cognitive therapy; CTT-BW = cognitive trauma therapy for battered women; DCS = D-cycloserine; EMDR = eye movement desensitization and reprocessing; EXP = exposure therapy; HRSD = Hamilton Rating Scale for Depression; IE = imaginal exposure; IPT = interpersonal psychotherapy; IPV = interpersonal violence; IVE = *in vivo* exposure; MDD = major depressive disorder; NDC = non-directive control; PBO = placebo; PCT = present centered therapy; PCGT = present-centered group therapy; PE = prolonged exposure; QIDS = Quick Inventory of Depressive Symptomology; SC = supportive counseling; SIT = stress inoculation training; SMI = severe mental illness; STAIR = skills training in affect and interpersonal regulation; TAU = treatment as usual; TFGT = trauma-focused group therapy; VR = virtual reality; WA = written accounts; WET = written exposure therapy; WLC = wait list control.
* = not included in meta-analysis.
– = specific number not provided or not applicable.

analyses. Using sample-level means and standard deviations from trials in the formula described above, baseline continuous depression scores showed good variability, ranging from moderate (.37) to severe (.82) depression severity, $M = .57$, $SD = 0.10$ (active conditions: $M = .56$, $SD = 0.10$; control conditions: $M = .58$, $SD = 0.10$). Rates of depressive disorder diagnosis ranged from .17 to .67, with $M = .44$, $SD = 0.14$ (active conditions: $M = .44$, $SD = 0.15$; control conditions: $M = .44$, $SD = 0.13$). Dropout rates at the study level ranged from 0 to .47, with $M = .21$, $SD = 0.11$ (active conditions: $M = .24$, $SD = 0.11$; control conditions: $M = .14$, $SD = 0.09$). The mean pre- to posttreatment effect size among all conditions was 1.45 (95% CI [1.29, 1.62]), with 1.88 (95% CI [1.69, 2.07]) for active conditions and 0.62 (95% CI [0.47, 0.76]) and for control conditions.

Data were closely inspected via scatterplots to confirm that there were no quadratic relationships between depression and PTSD treatment effect sizes. Results for analyses examining the relationship between baseline continuous depression severity and PTSD treatment effects and dropout are presented in Table 2. When examining all conditions,

Table 2
Impact of Continuous Comorbid Baseline Depression on PTSD Treatment Effects and Dropout Rates

	PTSD Treatment Effects				Dropout			
	k	B (SE)	ß	*p*	*k*	B (SE)	ß	*p*
All conditions	95	-3.03 (0.95)	-.32	.001	93	0.22 (0.16)	.20	.18
All active conditions	62	-3.00 (0.99)	-.36	.002	93	0.26 (0.20)	.25	.18
When comparison ≥1 active condition(s)	44	-2.75 (1.09)	-.36	.01	44	0.16 (0.25)	.15	.52
When comparison is NDC or WLC	18	-3.13 (2.29)	-.32	.17	18	0.33 (0.34)	.33	.33
All control Conditions	33	-1.01 (0.76)	-.23	.18	31	0.15 (0.30)	.19	.61
NDC conditions	17	-2.03 (0.80)	-.54	.01	16	0.03 (0.33)	.04	.94
WLC conditions	16	0.76 (1.17)	.17	.52	15	0.54 (0.93)	.35	.56

Note. NDC = non-directive control; SE = standard error; WLC = waitlist control.

greater baseline depression severity, as indexed by continuous measures, predicted smaller pre- to posttreatment PTSD effect sizes (k = 95, B = -3.04, SE = 0.95, ß = -.32, p = .001). This association was not observed for analyses using the proportion of sample meeting a depressive disorder diagnosis at baseline (k = 40, B = 0.00, SE = 0.01, ß = -.06, p = .70). Across all conditions, baseline depression in both continuous (k = 93, B = 0.22, SE = 0.16, ß = .20, p = .18) and categorical depressive disorder (k = 39, B = 0.00, SE = 0.00, ß = -.02, p = .92) analyses was not associated with dropout rates.

Within all active psychotherapy conditions, baseline continuous depressive symptom severity was associated with attenuated PTSD treatment effects (k = 62, B = -3.00, SE = 0.99, ß = -.36, p = .002), but this effect was not observed when examining the proportion of sample with categorical depressive disorder diagnosis at baseline (k = 29, B = -0.01, SE = 0.01, ß = -.11, p = .57).[3] Baseline depression was also not predictive of dropout rates within active psychotherapy conditions (continuous analyses: k = 62, B = 0.26, SE = 0.20, ß = .25, p = .18; categorical depressive disorder analyses: k = 29, B = 0.00, SE = 0.00 ß = -.03, p = .92). To examine whether type of comparison condition may have impacted the link between depression and PTSD treatment effect sizes and dropout, a test with a binary comparison moderator variable (≥1 active condition as comparison vs. control [NDC or WLC] condition as comparison) was run. Specifically, active conditions (k = 62) compared to at least one another active condition in the original trial comprised one category (k = 44), with the other (k = 18) made up of active conditions compared to a control condition (NDC or WLC). Given sample size constraints, these tests were only run among studies reporting continuous depression (k = 62). For both PTSD treatment effects (k = 62, ß = .02, p = .85) and dropout effects (k = 62, ß = -.08, p = .69), these interaction terms were nonsignificant, suggesting that the link between depression and PTSD treatment effects was not robustly influenced by the type of control condition used against active conditions. These results are presented in Table 2.

Among all control conditions, continuous (k = 33, B = -1.01, SE = 0.76, ß = -.23, p = .18) and categorical (k = 11, B = 0.00, SE = 0.01, ß = .07, p = .84) baseline depression were not linked to PTSD treatment effects. Similarly, baseline depression did not predict dropout rates among all control conditions (continuous analyses: k = 31, B = 0.15, SE = 0.30, ß = .19, p = .61; depressive disorder analyses: k = 10, B = 0.00, SE = 0.00, ß = .08, p = .89). To examine whether the relations between depression and PTSD treatment effect sizes and dropout may have differed among control conditions by type of control (i.e. WLC vs. NDC), a test with a binary control condition moderator variable (NDC vs. WLC) was run among conditions in studies reporting continuous depression. For PTSD treatment effects, this interaction term was at a trend level (k = 33, ß = .27, p = .09); specifically, continuous baseline depression was associated with smaller PTSD treatment effects among NDC conditions (p = .01), but not WLC conditions (p = .52). For dropout effects, this interaction term was nonsignificant (k = 31, ß = .21, p = .60). These results are presented in Table 2.

Publication bias was probed by calculating the fail-safe N (Rosenthal, 1979) as adapted by Orwin (1983). This calculation is an estimation of the number of nonsignificant or unpublished studies needed to reduce the aggregate effects observed across studies included in the meta-analysis to a specified criterion. Similar to recent meta-analyses (Kline et al., 2018; Sloan et al., 2013), this threshold was set at 0.01, reflecting an effect that is nearly null. For within-group effects on PTSD, the fail-safe N was 5,760 studies for our main within-group analyses. Calculations strongly suggest the absence of publication bias.

Discussion

We examined the connection between baseline depression and PTSD treatment efficacy in a meta-analysis focusing on RCTs involving one or more trauma-focused therapies. Our results suggest a connection between these two commonly comorbid features, such that greater pretreatment depression burden scores—when measured continuously (e.g., BDI)—were associated with attenuated pre-post PTSD symptom change. This association was not evident, however, among active treatment conditions when depression burden was estimated in the smaller subset of studies reporting percentage of patients with comorbid depression diagnosis. This discrepancy in findings—based on methodology of assessing depression—could be an effect of several factors. This may be due to decreased power in the categorical analyses, greater between-trial variation in assessing depressive diagnoses (e.g., major depressive disorder vs. "mood disorder"), or the limitations associated with categorical diagnoses rather than dimensional, continuous depression

[3] We also ran a series of exploratory moderator analyses to explore whether the impact of depression on PTSD effects in active conditions was moderated by various study level variables: year of publication, population type, trauma type, duration of treatment (weeks and sessions), and treatment type. Given the smaller number of studies reporting MDD diagnostic statistics at baseline, we exclusively used conditions with continuous depression data for moderator analyses, all of which were nonsignificant. These results can be found in the supplemental materials.

scores that are central to self-report measures. More specifically, it is possible that binary diagnostic categories—based on a clinical cutoff—did not have the level of sensitivity allotted by continuous data, as it is more difficult to capture a range in depressive severity when using a dichotomous index such as MDD. Contrary to our expectations, although comorbid depression has been commonly cited as a potential risk factor for dropout in treatments for PTSD (e.g., van Minnen et al., 2012), dropout rates in PTSD trials were not linked to baseline depression in our review. Findings have clear implications for ongoing research on the potential impact of comorbid depression on PTSD outcomes, as well as efforts to estimate treatment efficacy.

Results complement a substantial literature outside of treatment contexts connecting co-occurring depression with PTSD with greater chronicity, impairment, and complexity than PTSD alone (Bedard-Gilligan et al., 2015; Breslau et al., 1991; Campbell-Sills et al., 2012; Kessler et al., 2005; Post et al., 2011; Raab et al., 2015). Comorbid depression with PTSD, for example, has been identified as a key marker of clinical severity, more so than other commonly cited patient characteristics, such as childhood abuse and levels of trauma exposure (e.g., Bedard-Gilligan et al., 2015). Notably, close investigation of the PTSD-MDD comorbidity suggest these are distinct constructs, with their co-occurrence likely not simply a marker of greater PTSD severity (Post et al., 2011). Treatments for PTSD have proven effective in reducing symptoms of depression (Ronconi et al., 2015), which appear to change closely in conjunction with PTSD symptoms during the course of therapy (Brown et al., 2018; Liverant, Suvak, Pineles, & Resick, 2012). It is possible, however, that greater severity in depressive symptoms confers risk for attenuated response to even the most efficacious treatments for PTSD. Additionally, we note that depressive symptom severity was also associated with attenuated effects in nondirective control conditions as well. These comparison conditions typically included non-trauma-focused treatment conditions, such as present-centered therapy, treatment as usual, and supportive counseling. Thus, it is possible that baseline depression severity may inhibit optimal response globally across different types of psychotherapeutic interventions. Significant findings in the current meta-analysis reflect small effects, yet are clinically meaningful given the frequency with which depression and PTSD co-occur. Careful consideration of depression severity in the treatment of PTSD appears warranted given evidence of its link to treatment outcomes.

An important next step is to ascertain reasons for *why* comorbid depression might inhibit optimal response in treatments for PTSD. In addition to overlapping symptoms, PTSD and depression share similar maladaptive cognitive and behavioral processes that maintain each disorder, such as rumination and avoidance (e.g., Hayes, 2015), that may also negatively impact treatment outcomes (e.g., Angelakis & Nixon, 2015; Brady et al., 2015). Exposure to corrective information and experiences are integral features of trauma-focused treatments, yet the positive impact of these may be dampened by the overlapping maintenance processes that occur within depression and PTSD. Perhaps as key overlapping features and processes of PTSD and depression—such as anhedonia, rumination, numbing, hopelessness, avoidance, and diminished reward processing (e.g., Brady et al., 2015; Ehring & Watkins, 2008; Hayes, 2015; Nawjin et al., 2015; Zoellner et al., 2014)—increase in severity, the extent to which patients may be able to benefit from treatments for PTSD decreases in parallel.

Findings raise the possibility that between-study differences in PTSD treatment efficacy may be associated with pretreatment sample differences that are often unmeasured, unreported or unexamined. There is growing recognition of the potential for such "hidden moderators" to exist (Van Bavel et al., 2016), and also of the inherent limitations of any particular trial in terms of the ability to detect such effects (DeRubeis et al., 2014). We contend that concurrent depression may be worthy of further investigation as a potentially hidden moderator. There is a robust literature on the neuropsychobiological and social factors linking depression and PTSD (e.g., Flory & Yehuda, 2015), which in turn provides a strong theoretical foundation for the potential negative impact of depression on the efficacy of PTSD treatment. Nevertheless, when examined individually, RCTs are unlikely to be able to provide decisive information as to the potential link between baseline depression burden and PTSD treatment outcome. Indeed, investigating patient-level differences while ensuring representative variability in depression burden may only practically be achievable with "mega-analytic" approaches (e.g., Fournier et al., 2010), studies which require access to participant-level data from multiple sources. Investigations using this approach could yield additional information regarding the link between baseline depression and PTSD treatment outcomes, thus assisting in ongoing efforts to modify existing treatments (Nixon & Bralo, 2019), enhance the efficacy of transdiagnostic approaches, or develop new treatments (Nixon & Nearmy, 2011). This could also

help inform guidelines surrounding clinical practice and treatment design, such as helping articulate expected attenuation of efficacy linked to different levels of depression comorbidity.

A greater understanding of how depression may impact PTSD treatment at the patient level is likely to enhance the ability to ameliorate deleterious effects and improve existing treatments for PTSD. It is possible, for example, that intentionally integrating evidence-based depression-related treatment components may boost response to PTSD interventions among patients with greater baseline depression severity. However, augmentations such as these to address comorbid depression within PTSD treatment have not been systematically investigated. Integration of depression-focused treatment ingredients into PTSD treatment protocols also introduces the possibility of increasing the number of sessions needed for specific patients (Stein et al., 2012). For some patients with PTSD, brief interventions, whether in terms of sessions (e.g., Zoellner et al., 2017) or duration (e.g., Foa et al., 2018), are effective; however, among the subset of patients with more severe depression, it is possible that a stronger, wider-reaching "dose" of treatment is necessary to achieve optimal outcomes. Consistent with this, the optimal dose of sessions for patients in psychotherapy appears to be broad, as patients respond to treatment at variable rates (Robinson et al., 2019). This finding has also been found in treatments for PTSD specifically; for instance, in a recent trial involving flexibly implemented CPT, a meaningful minority of patients did not reach optimal end-state criteria until after Session 12 (Galovski et al., 2012). Notably, greater baseline depression severity was associated with a greater number of attended sessions in this trial. Such work reflects the necessity to tailor treatments to individual patients, a flexibility that is afforded in manuals for first-line PTSD interventions.

Regarding strengths of the current study, this meta-analysis was conducted closely in concert with current guidelines for systematic reviews and meta-analyses (e.g., Preferred Reporting Items for Systematic Reviews and Meta-analyses; Moher et al., 2009). We conducted a systematic search of randomized trials using inclusion and exclusion criteria designed to minimize bias and boost the precision and interpretability of findings. We included trials that were methodologically rigorous and used validated PTSD outcome measures, with further requirements that studies be of sufficient sample size and minimal risk of bias as per independent raters via established criteria (i.e., Cusack et al., 2016).

Our findings should also be considered in the context of several limitations. First, as we have noted, there is considerable diagnostic overlap between symptoms of depression and PTSD, and item-level data from measures identifying nonspecific versus specific symptoms were not reported in the included trials. Despite this, prior studies have suggested that symptom overlap between depression and PTSD does not explain their common comorbidity, which appear to be two separate and distinct disorders (e.g., Franklin & Zimmerman, 2001; Post et al., 2011; Post et al., 2015). Second, we did not include unpublished data in our analyses. Fail-safe *N* calculations do not suggest potential publication bias, though we acknowledge the myriad ways of assessing publication bias and their respective limitations (Thornton & Lee, 2000). Third, definitions of dropout are not always uniform across studies, and reported information was variable across trials regarding how dropout rates were calculated. Additionally, examination of a continuous index of treatment engagement—such as average sessions attended—was not possible due to variable reporting of these data. In the current meta-analysis, we were consistent in adhering to authors' definitions of dropout in each trial. In future research, examining potential links between depression and a continuous rather than dichotomous measure of attendance may be beneficial to provide a more nuanced understanding of this relationship. Finally, we acknowledge the challenges associated with setting inclusion and exclusion criteria for meta-analyses, which ultimately impact findings (e.g., Mayo-Wilson et al., 2017). We emphasized criteria in a manner to maximize our confidence in the interpretability and precision of findings, focusing on RCTs of the most evidence-based, commonly used treatments for PTSD with sufficient sample size and minimal bias according to established methods for assessing bias (Cusack et al., 2016; Kline et al., 2018; Viswanathan et al., 2012).

Overall, when indexed via continuous depressive symptom measures, sample-level depression severity predicted attenuated average treatment response to trauma-focused therapies for PTSD. Similar findings were observed when examining NDC conditions—which typically included treatment components such as supportive counseling or present-centered interventions—suggesting these effects may occur globally across different types of psychotherapy interventions for PTSD. Contrary to its link to PTSD treatment response, no relationship was established between any index of baseline depression and dropout from either active or control conditions, complementing literature suggesting that patients with comorbid depression are still able to optimally engage in and attend trauma-focused treatments. Findings point to the need for consistent reporting

and comprehensive evaluation of baseline depression burden as a potential hidden moderator of PTSD treatment outcomes, which in turn may help enhance the efficacy of existing and novel approaches to treat this common comorbidity.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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