Etiology of Depression Comorbidity in Combat-Related PTSD: A Review of the Literature

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Etiology of depression comorbidity in combat-related PTSD: A review of the literature☆

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HIGHLIGHTS

- This paper reviews two decades of research on combat-related PTSD-depression comorbidity.
- We examine 3 types of explanations for comorbidity: causal paths, common factors, and confounds.
- We review longitudinal and twin studies, which are well designed to test developmental hypotheses.
- Diversity in study constructs and design present important challenges in this research domain.
- Issues uniquely relevant to combat-related PTSD-depression comorbidity are discussed.

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ABSTRACT

Posttraumatic stress disorder is often diagnosed with other mental health problems, particularly depression. Although PTSD comorbidity has been associated with more severe and chronic symptomology, relationships among commonly co-occurring disorders are not well understood. The purpose of this study was to review the literature regarding the development of depression comorbid with combat-related PTSD among military personnel. We summarize results of commonly tested hypotheses about the etiology of PTSD and depression comorbidity, including (1) causal hypotheses, (2) common factor hypotheses, and (3) potential confounds. Evidence suggests that PTSD may be a causal risk factor for subsequent depression; however, associations are likely complex, involving bidirectional causality, common risk factors, and common vulnerabilities. The unique nature of PTSD–depression comorbidity in the context of military deployment and combat exposure is emphasized. Implications of our results for clinical practice and future research are discussed.

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1. Introduction

Posttraumatic stress disorder (PTSD) can be a debilitating consequence of severe or life-threatening trauma (Breslau, Chase, & Anthony, 2002). The disorder is associated with a number of symptoms that can broadly interfere with personal functioning and quality of life, including social withdrawal, anger and aggression, and sleep disturbance (Begic & Jokic-Begic, 2001; Carroll, Rueger, Foy, & Donahoe, 1985; Hoge, Terhakopian, Castro, Messer, & Engel, 2007; Kehle, Reddy, Ferrier-Auerback, et al., 2011). Furthermore, PTSD is often complicated by other mental health problems (Kehle, Reddy, Ferrier-Auerback, et al., 2011; Kilpatrick et al., 2003). Given a diagnosis of PTSD, epidemiological studies have documented elevated risk for a broad spectrum of disorders, including depression, anxiety disorder, panic disorder, conduct disorder, personality disorders, and multiple types of substance abuse (Axelrod, Morgan, & Southwick, 2005; Scherrer et al., 2008; Wolf et al., 2010).

As depression is the disorder most commonly comorbid with PTSD, this review focuses on the etiology of comorbid PTSD and depression. In part, depressive disorders are frequently comorbid with PTSD because of their high population prevalence overall (Breslau, Davis, Andreski, & Peterson, 1991). There also is some obvious overlap in symptomology between PTSD and depression, confounding the two diagnoses (Ferrada-Noli, Asberg, & Ormstad, 1998). However, despite the prevalence of PTSD–depression comorbidity and the amount of empirical literature that has accumulated on the topic, surprisingly few reviews have focused specifically on this subject (Ducrocq, Vaiva, Cottencin, Molenda, & Bailly, 2001; Quarantini et al., 2009; Solomon & Bleich, 1998). Further, only one of these reviews examined PTSD and depression comorbidity in a military population (e.g., Israeli war veterans; Solomon & Bleich, 1998).

1.1. PTSD comorbidity among military personnel

Although PTSD has been documented across disparate populations and in reaction to multiple types of trauma (Breslau, 2002; Kilpatrick et al., 2003; Norris, 1992), historically it often has been studied among military personnel in relation to combat trauma (Beckham, 1999; Brewin, Andrews, & Valentine, 2000; Keane, Gerardi, Lyons, & Wolfe, 1988). This is not surprising given that the diagnosis evolved in an environment of activism on behalf of Vietnam-era veterans (Breslau, 2004). Furthermore, the spectrum of problems associated with PTSD is of particular concern to military leadership, who are responsible for the health and readiness of their personnel (Solomon, 2001). The U.S. government also takes long-term responsibility for the well-being of military veterans, especially those who have experienced service-related trauma (Kimerling, Gima, Smith, Street, & Frayne, 2007; Ramaswamy et al., 2005).

The total emotional and economic burden of PTSD on individual military members, their families, and on the armed services as institutions is difficult to quantify, but it is likely greater for those with comorbid conditions (Brown, Stout, & Mueller, 1999; Kramer, Booth, Han, & Williams, 2003; McCrone, Knapp, & Cawkill, 2003). As in the general population, PTSD is commonly associated with depression among veterans (Boman, 1986; Green, Grace, Lindy, Gleser, & Leonard, 1990; Kehle, Reddy, Ferrier-Auerback, et al., 2011; Seal et al., 2009). Furthermore, the last decade has seen a flurry of research in this area, including some landmark studies that can inform our understanding of PTSD–depression comorbidity among veterans. These include the U.S. Department of Defense Millennium Cohort study, the study of Readiness and Resilience in National Guard Soldiers (RINGS), the U.S. Army and Department of Veterans Affairs Neurocognition Deployment Health Study (NDHS), The King's Center for Military Health Research study of TELIC era British veterans, and the University of Utrecht Medical Center study of mental health among Dutch veterans (Goodwin et al., 2012; Jacobson et al., 2012; Kehle, Reddy, Ferrier-Auerbach, et al., 2011; van Zuiden, Heijnen, et al., 2012; Vasterling et al., 2012). In this review, we present an in-depth synthesis of this emergent literature.

1.2. Etiological hypotheses for PTSD comorbidity

Mental health disorders co-occur more often than would be expected by chance given their relative population prevalences (Breslau et al., 1991; Kessler, 1995), and this has spurred theory and research on the developmental underpinnings of comorbidity (Breslau, 2002; Brown & Wolfe, 1994; Krueger & Markon, 2006). There has been considerable breadth and diversity among the major etiological hypotheses considered. However, in our review we have organized them broadly into three categories. The first category, “causality,” encompasses theories positing that depression is a causal risk factor for PTSD, or conversely, that PTSD is a causal risk factor for depression. Theories in the second “common factors” category suggest that associations among PTSD and depression are not directly causal. Rather, they are independent outcomes of a common set of risk factors or vulnerabilities. Here, a risk factor is defined as a potentially necessary or sufficient cause for the development of a disorder. By contrast, vulnerability factors increase the likelihood of the disorder only given the occurrence of a potentially causal risk factor. Finally, the third category of hypotheses, “confounding factors,” suggests that apparent associations among PTSD and depression are coincidental or even illusory. For instance, it is possible that comorbidity is an artifact of poor definitional distinction between different disorders and their criterion symptoms.

The complex nature of many etiological hypotheses, as well as the fine distinctions between them both conceptually and empirically, make research in this area challenging. The purpose of this review was to summarize research on the etiology of PTSD–depression comorbidity among combat-exposed military personnel and to highlight unique characteristics of these associations in military versus civilian populations. Using our three-category framework to organize the presentation of our results, we synthesize available research on the development of comorbid PTSD and depression, identify conclusions that can be drawn based on this existing information, and outline important directions for future research.

In this review we focus on studies that represent the state of the art in addressing questions of etiology and causality. Although most of the research on PTSD comorbidity has been correlational and retrospective, these study designs are not well suited for testing etiological hypotheses, because these designs cannot shed light on the temporal precedence of different disorders. Longitudinal studies are necessary in establishing potentially causal chains of events. Although experimental studies are the ultimate gold standard in evaluating causality, in general these cannot ethically be conducted in this topic area. Human beings cannot be randomly assigned to groups involving combat exposure as a treatment condition. Twin studies, however, offer a natural experiment upon which research can capitalize. Twin pairs, in which one sibling has experienced combat while the other has not, offer a close analog to experimental study conditions that control for genetics as well as many potential environmental confounds. Therefore, this review focuses specifically on longitudinal and twin study designs.

2. Methods

The research included in this review was restricted to published empirical studies assessing both posttraumatic stress and depression among combat-exposed military personnel. Furthermore, studies meeting these criteria were included in the present review only if they provided empirical evidence relevant to one or more etiological hypotheses regarding the development of PTSD–depression comorbidity. The selection of studies was further constrained to those published during the 22-year period between 1990 and 2012 and to those employing a longitudinal or twin study design. Studies primarily evaluating the impact of clinical treatments or pharmaceutical therapies and cross-sectional studies were not reviewed.

To identify potentially relevant studies, we conducted searches using several different electronic databases (Biomedical Reference, Nursing & Allied Health, Psychological and Behavioral Sciences, PsycARTICLES, PsycINFO, PsycEXTRA, MEDLINE, and Military & Government). Within each database, we searched for all articles with at least one keyword from each of the following three sets: (a) combat, deployment, military, Army, Navy, Marine Corps, Air Force, armed, or defense; (b) PTSD or posttraumatic stress disorder; and (c) depression or dysthymia. The bibliographies of studies identified through electronic search then were reviewed for additional relevant publications. Finally, we electronically searched for the names of the first authors of each of the studies previously identified for inclusion to locate other relevant research they may have published. Articles identified using these strategies were initially evaluated to determine whether they met all relevant criteria for inclusion in this review. A summary table of all of the studies included in this review is available from the first author upon request.

2.1. Longitudinal studies

Our search procedures yielded 68 publications reporting results of longitudinal research bearing on the nature of the associations between PTSD and comorbid depression. Of these reports, 52 presented results from one of 37 unique longitudinal studies. Sixteen more involved secondary analysis of archival data such as military personnel files or Department of Veterans Affairs (VA) medical records. Collectively, the military personnel in these studies were drawn from six countries (i.e., United States, Australia, Great Britain, Netherlands, Israel, and Sweden), and they had served in at least 10 different military conflicts (World War II, Vietnam, Persian Gulf, Lebanon, Yom Kippur, Iraq, and Afghanistan Wars, as well as Somalia, Cambodia, and recent European peacekeeping missions).

2.2. Twin studies

We located 13 twin studies meeting our inclusion criteria, all of which were sampled from the Vietnam Era Twin (VET) Registry. The VET Registry is a compilation of military service records and self-report data from the 1987 Survey of Health for 4774 male–male twin pairs (Henderson et al., 1990). All members of the VET Registry served in the U.S. military during the Vietnam era, with 77% reporting some level of combat exposure. Two research projects relevant to this review have collected additional data from subsamples of twins participating in the VET Registry. One is the Harvard Twin Study of Substance Abuse conducted in 1992. This study collected considerable information about current and preexisting psychopathology (including PTSD) from 1874 twin pairs, and 7 of the 13 reports reviewed here were based on those data (Fu et al., 2007; Koenen, Lyons, et al., 2003a,b; Koenen et al., 2002, 2008; Scherrer et al., 2008; Wolf et al., 2010). Six additional articles were reviewed from a Harvard/Veterans Affairs collaborative study of PTSD, cognition, and psychophysiology (Gilbertson et al., 2002, 2006, 2010; Kasai et al., 2008; Shin et al., 2009, 2011). These data included 102 twin pairs solicited from the Vet Registry and an additional 27 twin pairs solicited separately from Veterans Benefits Administration rosters (Orr et al., 2003).

Data from twin studies can be analyzed using several different strategies. One strategy uses traditional data analysis techniques such as regression, but includes information regarding familial mental health history from both twins as predictors (Koenen et al., 2002). Another approach examines the relative risk of comorbid disorders between twin siblings with different known levels of genetic and familial relationships (Koenen, Lyons, et al., 2003a,b). For example, if genetic vulnerabilities play a role in the development of PTSD, monozygotic twin pairs should be more likely than dizygotic twin pairs to be concordant (i.e., either both positive or both negative for disorder). Finally, modeling techniques can be used to partition the variance in phenotypic (observed) outcomes between a finite set of additive factors: (a) genetics, (b) shared environment such as familial or community contexts, and (c) unique, individual-specific environment including trauma exposure experienced by one sibling but not the other (Fu et al., 2007; Koenen et al., 2005, 2008; Scherrer et al., 2008; Xian et al., 2000). These domains can be further partitioned into variability predictive of disorder-specific outcomes (e.g., PTSD alone) or variability predictive of covariance between disorders (e.g., overlapping PTSD and depression).

3. Results

3.1. Causal influences

Hypothesis 1. Preexisting depression increases the risk of combat exposure.

Few studies have addressed the question of whether preexisting depression is a risk factor for deployment to a combat zone or exposure to combat trauma while in theater. Two longitudinal studies found no evidence to support the hypothesis (Larsson, Michel, & Lundin, 2000; Schnurr, Friedman, & Rosenberg, 1993). One twin study (Koenen et al., 2002) examined this question using more traditional analytic techniques, but included data regarding familial risk factors provided by combat veterans' cotwins as potential risk factors. In this study veterans' preexisting substance use problems and antisocial behavior were significant risk factors for combat exposure. Parental depression and cotwin mood disorder also were predictive of combat exposure. However, after controlling for these familial vulnerabilities, Koenen et al. (2002) found that combat veterans' own history of depression was actually protective. As depression had been a risk factor for trauma exposure in prior research among civilians (Breslau, Davis, Andreski, Federman, & Anthony, 1998; Breslau, Davis, Peterson, & Schultz, 1997), these authors suggested that the relationship between depression and combat trauma may be unique. However, another twin study of trauma among women that controlled for genetic vulnerabilities similarly found that depression was protective with respect to multiple types of civilian trauma (Kendler & Karkowski-Shuman, 1997).

Hypothesis 2. Preexisting depression is a risk factor for PTSD following combat exposure.

A number of longitudinal studies have evaluated the importance of preexisting depression as a risk or vulnerability factor for the development of PTSD following combat trauma. Of those we identified, seven reported null results; preexisting depression did not longitudinally predict the development of PTSD (Benotsch et al., 2000; Ginzburg, Ein-Dor, & Solomon, 2010; Grieger et al., 2006; Lee, Vaillant, Torrey, & Elder, 1995; O'Toole, Catts, Outram, Pierse, & Cockburn, 2009; Schnurr et al., 1993; Wright et al., 2011). On the other hand, eight studies did find support for the hypothesis (Arbisi et al., 2012; Britt, Dickinson, Moore, Castro, & Adler, 2007; Dickstein, Suvak, Litz, & Adler, 2010; Erickson, Wolfe, King, King, & Sharkansky, 2001; Goodwin et al., 2012; Kelley

et al., 2012; Koenen, Stellman, Stellman, & Sommer, 2003; Skopp et al., 2011).

Most studies reporting positive results did so even after controlling for baseline PTSD, either by (a) including it with depression in multivariate prediction (Arbisi et al., 2012; Erickson et al., 2001; Koenen, Stellman, et al., 2003) or (b) grouping participants based on longitudinal patterns of PTSD symptom levels and verifying depression as a distinguishing risk factor (Dickstein et al., 2010; Goodwin et al., 2012). However, not all studies controlled for baseline PTSD, which is an important potential confound (Britt et al., 2007; Kelley et al., 2012; Skopp et al., 2011). Given the strong correlation between them, baseline depression could simply be serving as a stand-in for baseline PTSD. Britt et al. (2007) analyzed a path model that took this hypothesis one step further by testing whether depression mediated the relationship between traumatic life events and PTSD. Although their results supported the model, they did not control baseline PTSD, making it difficult to draw confidant conclusions.

Last, among twin pairs from the VET Registry, Koenen et al. (2002) confirmed preexisting anxiety and mood disorders as risk factors for subsequent PTSD. Again, these twin study results were based on more traditional data analysis techniques, and information regarding the onset of disorders was gathered in a retrospective manner. Overall, across both types of research, the results of studies evaluating preexisting depression as a predictor of subsequent combat-related PTSD were mixed. It also is noteworthy that perhaps the best designed study reporting results in support of Hypothesis 2 actually found bidirectional relationships (Erickson et al., 2001). These effects are elaborated further below for Hypothesis 5.

Hypothesis 3. Posttraumatic stress causes depression.

The hypothesis that PTSD leads to the development of other comorbid disorders is commonly evaluated. We identified eleven longitudinal studies evaluating whether preexisting PTSD predicts the development of depression among veterans (Erickson et al., 2001; Ginzburg et al., 2010; Grieger et al., 2006; Lee et al., 1995; O'Toole et al., 2009; Park, Kaiser, Spiro, King, & King, 2012; Polusny et al., 2011; Thompson et al., 2004; Wells et al., 2010; Wolfe, Brown, & Bucsela, 1992; Wright et al., 2011). Only three failed to support the hypothesis (Lee et al., 1995; Wolfe et al., 1992; Wright et al., 2011), and two of these involved fairly unique study populations (e.g., a sample of Harvard students with above-average academic performance; Lee et al., 1995; Wolfe et al., 1992).

With the exception of three papers (Park et al., 2012; Polusny et al., 2011; Thompson et al., 2004), studies reporting positive results for Hypothesis 3 supported PTSD as a longitudinal risk factor even after controlling for baseline symptoms of depression. Based on this pattern of results, it seems likely that PTSD may play a causal role in the development of comorbid depression. However, as in any non-experimental research, it remains possible that uncontrolled common risk factors or vulnerabilities—rather than any actual causal link between PTSD and depression—account for significant longitudinal associations (Wells et al., 2010). For instance, in a well-designed study, Wright et al. (2011) found no evidence that PTSD was a longitudinal risk factor for depression after controlling for baseline symptoms of insomnia. These results suggest that insomnia is a potentially confounding common vulnerability for both PTSD and depression.

Establishing mediation can strengthen arguments about causal associations. To support Hypothesis 3, PTSD should mediate the effects of combat exposure on depression. Unfortunately, few longitudinal studies have directly or even incidentally evaluated this relationship. In a rare study that did, Erickson et al. (2001) found that PTSD partially mediated the relationship between combat exposure and depression. Interestingly, in some studies deployment and combat exposure have not initially been significant risk factors for depression, effectively ruling out mediation; this issue is discussed further in the next section on common risk factors.

Studies based on VET Registry twin data provide another important type of evidence for Hypothesis 3 by parsing out variability in outcomes due to common genetic and family vulnerabilities versus unique environmental risk factors such as combat exposure (Gilbertson et al., 2002, 2006, 2010; Koenen, Lyons, et al., 2003b; Koenen, Stellman, et al., 2003; Scherrer et al., 2008). These studies verify that there are significant correlations between PTSD and depression independent of shared genetics and family history. This pattern still does not verify a causal relationship; but it does suggest that common vulnerabilities cannot completely account for comorbidity, which further supports the possibility of causality. Additionally, using conditional logistic regression to predict discordant diagnoses across twin pairs, the effects of combat exposure on depression were fully mediated by PTSD symptoms (Koenen, Lyons, et al., 2003a).

Analyzing data from a smaller subset of the Harvard study, Scherrer et al. (2008) quantified the amount of unique environmental variability (e.g., likely including traumatic experiences) explaining covariance among combat exposure, PTSD, and comorbid disorders. In twin modeling, this is the only variability that might represent causal associations. Unique environmental factors accounting for covariance were significant, but they explained only a small amount of variability in depression (9%). Also, in this analysis there were no genetic or environmental effects overlapping combat exposure and comorbid depression that were independent of PTSD, a pattern which suggests complete mediation.

These studies highlight some of the difficulties in interpreting twin studies. Although significant unique environmental effects accounting for covariance between comorbid disorders may identify a causal relationship, there are other possible interpretations. Such overlap may represent common measurement error or common environmental risk factors. Moreover, even if causality is assumed, the direction of the relationship is unclear (Fu et al., 2007). Additional analyses are necessary to verify the nature and directionality of the relationship (e.g., Koenen, Lyons, et al., 2003a). On the other hand, one of the advantages of twin modeling is the ability to estimate the relative contributions of genetic versus environmental effects. For instance, Scherrer et al. (2008) were able to estimate the maximum size of potential mediating effects of PTSD on trauma outcomes for comorbid depression in their sample. Estimates were minimal (e.g., 9% of the variability in depression). Much larger amounts of variability were due to unique environmental factors explaining disorder-specific variability (e.g., 58% for depression), indicative of experiences affecting individual disorders alone and/or measurement error associated with particular disorders.

3.2. Common factors

Hypothesis 4. PTSD and other mental health disorders share common risk factors.

Another commonly tested hypothesis is that combat is a common risk factor for both PTSD and depression. We found evidence regarding this research question in papers from 15 different studies. However, only two longitudinal evaluations actually reported that both PTSD and depression were predicted by deployment history or combat exposure variables (Hoge, Auchterlonie, & Milliken, 2006; O'Toole et al., 2009). Seven distinct studies found that deployment or combat exposure histories significantly predicted PTSD but not depression (Booth-Kewley, Highfill-McRoy, Larson, & Garland, 2010; Duma, Reger, Canning, McNeil, & Gahm, 2010; Hourani et al., 2012; Larson, Highfill-McRoy, & Booth-Kewley, 2008; O'Toole et al., 2009; Seal et al., 2009; Sharkansky et al., 2000). Similarly a history of physical torture among former prisoners of war predicted PTSD but not depression (Park et al., 2012).

In a few longitudinal studies, deployment to a combat zone by itself has not been a risk factor for PTSD or depression (Grieger et al., 2006; Maguen, Litz, Wang, & Cook, 2004; Seelig et al., 2012). However, deployment is not necessarily a traumatic event, and there is evidence that deploying personnel are better adjusted prior to deployment than military personnel who do not deploy (i.e., health warrior effect; Haley, 1998). In the absence of combat exposure, deployers may continue to report better adjustment than nondeployers (Seelig et al., 2012). To flag trauma severity with objective measures, some studies have used various deployment characteristics as proxies (e.g., time in combat zone, military responsibilities during deployment, recognition for combat service; Frueh et al., 2005; Grieger et al., 2006). However, such attempts to better mine archival records still may result in poorly nuanced estimates of trauma exposure.

Few studies actually have evaluated self-reported combat exposure as a longitudinal risk factor for multiple disorders. One of the studies of deployment effects referenced above (Grieger et al., 2006) also included a self-report assessment of combat exposure severity and found the same null results using this operationalization. By contrast, O'Toole et al. (2009) and Hourani et al. (2012) both found a significant longitudinal association between self-reported combat exposure and PTSD although not depression. Unfortunately, even in longitudinal studies, the association between self-reported combat exposure and long-term mental health outcomes often has been analyzed in a cross-sectional manner (Larsson et al., 2000; Maguen et al., 2012; Seelig et al., 2012; Wright, Cabrera, Eckford, Adler, & Bliese, 2012). Logistically, a self-report measure of combat exposure can only be administered after return from deployment; in many studies this is also the time of final follow-up, precluding longitudinal analysis.

In three reports, depression symptoms actually declined from pre- to post-deployment (Larson et al., 2008; Maguen et al., 2004; Proctor, Heaton, Dos Santos, Rosenman, & Heeren, 2009). Two of these studies (Maguen et al., 2004; Proctor et al., 2009) involved peacekeepers, who may not have experienced significant levels of combat exposure. In those cases, the stress of preparing for deployment may have exacerbated mental health issues more than the deployment itself. One study also reported that PTSD symptoms decreased over time (Maguen et al., 2004).

Twin studies generally are not well designed to address Hypothesis 4, largely because it is not possible to distinguish the directionality of relationships from statistical models of additive effects. Twin modeling has verified that unique environmental influences (potentially including combat trauma) explain covariance between PTSD and depression (Fu et al., 2007; Koenen et al., 2008). However, these results potentially support Hypothesis 3, suggesting that combat causes PTSD, which subsequently causes comorbid disorders; they could also support Hypothesis 5 (common vulnerabilities), as discussed further in the next section of this review.

A well-designed study of monozygotic twins by the VA Research Service Psychophysiology Laboratory attempted to identify changes in brain structure and function following combat that may facilitate or mediate the effects of combat exposure as a common risk factor for PTSD and depression. In this study, one twin in each pair was a combat veteran, approximately half of whom had been diagnosed with PTSD. Results indicated that reductions in gray matter were uniquely associated with a history of combat experience and current PTSD severity (Kasai et al., 2008). However, comorbid depression was not consistently correlated with these same brain structures. Contrary to Hypothesis 4, this suggests that specific physiological changes may underlie the effects of combat trauma on PTSD, but not on depression.

Hypothesis 5. PTSD and other mental health disorders share common vulnerabilities.

Hypothesis 5 suggests that common vulnerabilities increase the likelihood of multiple mental health disorders in the event of a precipitating risk factor, increasing the likelihood of comorbidity. In longitudinal studies, this might manifest itself in equivalent bidirectional effects between comorbid conditions. If genetic or environmental factors create a vulnerability for the development of two separate conditions, then the diagnosis of one is equal proof of vulnerability and risk for the other and vice versa.

Few studies longitudinally tested bidirectional effects between PTSD and depression; of those that did, most failed to support Hypothesis 5 (Ginzburg et al., 2010; Grieger et al., 2006; Lee et al., 1995; O'Toole et al., 2009; Wright et al., 2011). In studies with null results, symptoms of depression always failed to predict PTSD. By contrast, PTSD only failed to reciprocally predict depression in the Harvard study of life success by Lee et al. (1995) and in the study of insomnia as a common vulnerability by Wright et al. (2011). In the best designed study, Erickson et al. (2001) found significant bidirectional effects, but the effect of baseline PTSD on follow-up depression was significantly stronger than the path from depression to PTSD.

Twin studies are well-designed to quantify the relative contributions of genetic versus environmental factors. It is important to remember that twin studies of combat-related PTSD have primarily been based on the same VET Registry population. However, results have consistently ruled out the likelihood of common environmental vulnerabilities (e.g., family characteristics such as poor parenting or high risk neighborhoods) for PTSD and depression (Fu et al., 2002; Koenen et al., 2008; Scherrer et al., 2008). By comparison, shared family environment may play a role in associations among externalizing problems (e.g., conduct disorder), combat exposure, and PTSD (Fu et al., 2002; Koenen et al., 2002; Wolf et al., 2010).

Twin studies based on the 1992 Harvard Study of Drug Abuse and Dependence have produced consistent evidence that some type of common genetic vulnerability contributes to PTSD and depression (Fu et al., 2007; Koenen, Lyons, et al., 2003b; Koenen et al., 2008; Scherrer et al., 2008). However, reports from the VA Research Service Psychophysiology Laboratory study (Gilbertson et al., 2002, 2006, 2010; Kasai et al., 2008; Shin et al., 2009, 2011) have not arrived at the same conclusion. In this program of research, although PTSD-positive veterans had higher rates of depression and other mental health problems than PTSD-negative veterans, there were no notable differences in mental health comparing their high- and low-risk cotwins respectively (Gilbertson et al., 2002, 2010). These authors point out that finding equivalent mental health across high- and low-risk co-twins undermines the argument of a general vulnerability to psychological problems. Furthermore, using these data, researchers examined a number of specific characteristics that could play a role as common genetic vulnerabilities. Several (e.g., low hippocampal volume, dorsal anterior cingulate activation, cerebral metabolic rate for glucose at rest) appeared to be vulnerability factors for PTSD but not depression (Gilbertson et al., 2002; Shin et al., 2009, 2011). For example, Gilbertson et al. (2002) examined the relationship between hippocampal structure and PTSD among twin pairs. Among study participants, low hippocampal volume appeared to be a preexisting genetic vulnerability for PTSD in the event of combat exposure (e.g., low volume was associated with PTSD symptom severity in combat-exposed twins, and it was highly correlated across PTSD-positive veterans and their high-risk co-twins). However, depression was elevated among PTSD-positive compared with PTSD-negative veterans, but not among their high-risk versus low-risk co-twins (Gilbertson et al., 2002, 2006, 2010; Kasai et al., 2008). This indicates that low hippocampal volume is not a vulnerability factor for depression independent of combat exposure and the development of PTSD.

3.3. Confounding relationships

Hypothesis 6. Secondary influences create artifactual associations among mental health disorders.

Potentially confounding secondary influences include a diverse array of factors (e.g., cultural expectations of the dynamics of mental health, the creation of patient subcultures in facilitating treatment, professional diagnostic guidelines and their implementation by clinicians, insurance policies, and the motivations of research funding institutions), any or all of which might bias estimates of the comorbidity of PTSD with other disorders. Given the wide spectrum of potential confounds, secondary influences are one of the more relevant threats to the validity of research on PTSD comorbidity. Given the likelihood that some of these factors can play a confounding role, more research should address these issues. Although few longitudinal studies have intentionally explored secondary confounds, we found a number with relevant results regarding: (a) the impact of service provider biases on archival medical data, (b) the influence of personal expectations on symptom manifestation, (c) the effect of motivational biases on data from treatment- or compensation-seeking populations, and (d) the impact of selective-memory and response bias on self-report data in general.

First, there is evidence that the expectations and biases of service providers may confound results in archival analyses of medical records for treatment-seeking samples (Carlson et al., 2010; Magruder & Yeager, 2008). For example, Carlson et al. (2010) concluded that the expectations of physicians at VA treatment facilities may have biased the results of their archival study of the chronological onset of TBI as a vulnerability for comorbid conditions. In 79% of cases, TBI was diagnosed after other mental health disorders. It is possible that this reflected developmental precedence. However, the authors surmised that it was equally likely to be a reflection of physicians' a priori expectations of the needs of their patient population and of the assessments they chose to conduct first. The results of Brewin, Andrews, and Hejdenberg (2012) also raise the possibility that service providers may be more attuned to looking for substance dependence than depression comorbidity among military veterans diagnosed with PTSD.

Personal expectations about the impact of combat exposure may become a self-fulfilling prophecy, skewing perceptions of the effects of combat trauma. This type of bias may also confound research on PTSD–depression comorbidity. In one investigation of post-deployment adjustment, Grieger et al. (2006) assessed an inpatient sample of veterans suffering from combat injuries. Among these personnel, subjective injury severity appeared to be more important than combat exposure in predicting mental health outcomes such as PTSD and depression. There was also evidence that ongoing difficulty dealing with the aftermath of combat injury was a more important predictor of adjustment outcomes than the experience of the trauma itself.

Personal expectations may come into play particularly during transition to and from deployment. Before deployment anticipatory fears may heighten perceptions of stress and poor mental health. In some studies of peace-keeping missions, this may have contributed to greater symptomology prior to than during or after deployment (Maguen et al., 2004; Proctor et al., 2009). Similarly, personnel returning from deployment may tend to have rose-colored expectations about being home, and this may contribute to an immediate “honeymoon phase” marked by suppressed perception of mental health symptoms. Bliese, Wright, Adler, Thomas, and Hoge (2007) suggested that this could have contributed to apparent patterns of delayed PTSD and depression symptom development in military post-deployment screening assessments. Alternatively, some returning personnel may purposefully fake-good in order to avoid interventions that might interfere with their post-deployment plans. This alternative explanation is similar to the possibility discussed next, that treatment- and compensation-seeking veterans exaggerate their symptoms (fake-bad) to qualify for better benefits.

For some time investigators have been concerned about the impact of compensation-seeking on the motivations and response biases of veterans participating in PTSD research (Charney et al., 1998; Frueh, Hamner, Cahill, Gold, & Hamlin, 2000). This is particularly an issue in archival studies using data from VA PTSD clinics, since an estimated 69% to 94% of veterans seeking care in that context may be compensation-seeking (Frueh et al., 2000). There is no question about the fact that many veterans suffer significantly from the effects of war trauma, and that they need and deserve compensation. However, empirical evidence does suggest that some compensation-seeking veterans may exaggerate either their exposure to criterion trauma (Frueh et al., 2005) or their mental health symptomology (Frueh, Gold, & De Arellano, 1997; Frueh, Smith, & Barker, 1996; Frueh et al., 2003; Grubaugh, Elhai, Monnier, & Frueh, 2004). As a result some experts have suggested excluding this group from PTSD studies entirely (Charney et al., 1998; Elhai & Palmieri, 2011; Frueh et al., 2005).

In our review, only two longitudinal studies with mixed results have evaluated the potential impact of response bias among compensation-seeking participants (DeViva & Bloem, 2003; Frueh et al., 2005). In the first (Frueh et al., 2005), results suggested that more than half of a group of veterans seeking treatment for combat-related PTSD could be falsifying or exaggerating claims of combat exposure; this calls into question their primary diagnosis of PTSD, at least with respect to combat. Furthermore, there were no differences in mental health symptom levels comparing groups with and without verifiable combat exposure. In discussion the authors of this study suggest that this may indicate that veterans who exaggerate combat experience also exaggerate mental health symptoms. However, in the only other study in our review that explored the effects of compensation-seeking on research results, scores on a measure of symptom exaggeration were not significantly different for compensation-seeking versus non-compensation-seeking participants (DeViva & Bloem, 2003). Ultimately, too few researchers consider the potential confounding influence of compensation seeking on their research. In studies of the etiology of PTSD–depression comorbidity, if some compensation-seeking veterans exaggerate either their combat exposure or their mental health symptoms, this could inflate mental health disorder comorbidity estimates and increase the likelihood that combat exposure erroneously will be identified as a common risk factor for multiple conditions.

Longitudinal surveys suffer from all of the potential confounds inherent in self-report research. In the studies we reviewed, an important concern was that reports of combat exposure might be unreliable, even for participants genuinely trying to provide accurate information. In particular, memories about deployment experiences may be colored by current symptom severity. Encouragingly, one study found that reports of combat exposure were quite reliable over time (Bramsen, Dirkzwager, van Esch, & van der Ploeg, 2001). In another, however, estimates of combat exposure increased over time, and increases in self-reported PTSD symptoms accounted for this shift in recollection (Roemer, Litz, Orsillo, Ehlich, & Friedman, 1998). In these studies, PTSD and depression did not demonstrate similar associations with recollection biases, making it unlikely that this confound results in exaggerated estimates of common associations with combat exposure. However, it is clear that self-reports of combat severity are somewhat subjective, and this must be taken into account in interpreting research.

Hypothesis 7. Comorbidity is an artifact of how mental health disorders are defined.

Hypothesis 7 suggests that, at least to some extent, PTSD–depression comorbidity may be due to indistinct diagnostic criteria and poor differential diagnosis (Simms, Watson, & Doebbeling, 2002; Spitzer, First, & Wakefield, 2007). Some core symptoms of PTSD overlap the primary diagnostic criteria for other disorders, and this may inflate estimates of comorbidity. This is certainly the case for PTSD and depression, which share several key symptoms (anhedonia, sleep disturbance, trouble concentrating). These two disorders also share other nonspecific features (impaired memory for the trauma, emotional detachment, constricted affect, foreshortened future, and irritability) that are indicative of general distress or negative affectivity (Elhai & Palmieri, 2011). These common and nonspecific symptoms are, in fact, combined to

form a fourth symptom subcluster (dysphoria) in the well-known and widely used alternative structural model of PTSD proposed by Simms et al. (2002).

PTSD diagnostic criteria have changed over time, and the extent to which these changes either increase or decrease the number of common or nonspecific symptoms in its definition could artificially impact estimates of PTSD–depression comorbidity (Spitzer et al., 2007). Interestingly, however, some studies have suggested that eliminating common symptoms has little impact on comorbidity rates (Grubaugh, Long, Elhai, Frueh, & Magruder, 2010). Furthermore, it is possible that common underlying dimensions of PTSD and depression symptoms are actually manifestations of common vulnerabilities (Hypothesis 5) rather than definitional confounds. For example, structural analyses of combined PTSD and depression symptoms have suggested that the PTSD dysphoria symptom cluster may be a reflection of a general tendency toward negative affect shared across PTSD and depression, and nonspecific arousal symptoms (sleep disturbance, irritability, and difficulty concentrating) also may reflect a shared underlying factor of somatization (Biehn et al., 2013; Elhai, Contractor, Palmieri, Forbes, & Richardson, 2011). Results suggest that other shared underlying factors likely contribute to PTSD–depression comorbidity as well (Elhai et al., 2011).

Developmentally, if either artifactual symptom overlap or common underlying symptom factors are responsible for PTSD–depression comorbidity, these common and nonspecific symptoms should be the predominant features that predict comorbidity. In our review, we found only a few longitudinal studies that evaluated this in military populations, and overall results were mixed. For example, Erickson et al. (2001) observed that the PTSD symptom cluster most reliably predictive of comorbid depression was hyperarousal. Given that this cluster is more of a distinguishing than common feature of PTSD, this contradicts Hypothesis 7. By contrast, both Meis, Erbes, Kaler, Arbisi, and Polusny (2011) and Thompson et al. (2004) found that depression was best predicted by the PTSD symptom subclusters that are more overlapping and nonspecific, including dysphoria and emotional numbing. In an interesting study, Wright et al. (2011) considered the overlapping symptom of difficulty sleeping or insomnia. Although PTSD and depression were bivariately correlated, they were not significantly related after controlling for baseline symptoms of insomnia. This may indicate that predictive associations between PTSD and depression are dependent on this common symptom, which would support Hypothesis 7. However, considering prior research, these authors concluded that insomnia is actually a separate comorbid condition that presents a common vulnerability for PTSD and depression, supporting Hypothesis 5. Their conclusion was bolstered by the fact that the only individual PTSD subscale predicted by insomnia was intrusive experiences. This was the case even excluding the PTSD symptom of intrusive nightmares. Intrusive experiences are another unique feature of PTSD, supporting the distinctness of all three of these conditions as separate but interrelated disorders.

Hypothesis 8. Comorbid disorders are different aspects of a single spectrum of traumatic response.

The final hypothesis suggests that PTSD and depression are aspects of a larger spectrum of a posttraumatic stress syndrome rather than distinct disorders. If this were true, PTSD and depression should be difficult to empirically distinguish (e.g., developmental trajectories always highly correlated; risk factors, vulnerabilities, and predictive outcomes all overlapping; symptom severity and chronicity independent of comorbidity; and bidirectional effects always significant and equivalent). However, numerous studies conclude that PTSD and depression are empirically distinct. First, PTSD–depression comorbidity has been associated with greater symptom chronicity and severity than PTSD alone (Aversa et al., 2012; Ginzburg et al., 2010; Koenen, Stellman, et al., 2003). Furthermore, PTSD and depression do not appear to present equivalent bidirectional risks for one another in longitudinal research. As discussed for Hypothesis 5, PTSD is more often identified as a risk factor for depression than depression is for PTSD. Even where bidirectional effects have been observed, the link from PTSD to depression has been stronger and more consistent than the link from depression to PTSD (Erickson et al., 2001).

PTSD and depression may share some common predictive factors, but unique predictors are also likely. As discussed for Hypothesis 4, more longitudinal evidence indicates that combat exposure is a risk factor for PTSD than that it is a risk factor for depression (Booth-Kewley et al., 2010; Duma et al., 2010; Larson et al., 2008; O'Toole et al., 2009; Seal et al., 2009; Sharkansky et al., 2000). Also, a preexisting pattern of avoidant coping has been a vulnerability for PTSD but not depression in two longitudinal studies (Beevers, Lee, Wells, Ellis, & Telch, 2011; Sharkansky et al., 2000). Twin studies also lend evidence against Hypothesis 8; additive modeling of factors in the development of comorbid disorders (Fu et al., 2007; Gilbertson et al., 2010; Koenen et al., 2008; Scherrer et al., 2008; Wolf et al., 2010) has consistently pointed to genetic and environmental risks and vulnerabilities that uniquely influence specific disorders. For example, Koenen et al. (2008) estimated that only 24% of the variance in PTSD could be accounted for by the common risk and vulnerability factors it shares with depression. Furthermore, twin studies have identified some specific genetic characteristics that may play a role in vulnerability to PTSD (e.g., low hippocampal volume and high activation of the dorsal anterior cingulate of the brain; Gilbertson et al., 2002; Shin et al., 2009, 2011), which likely do not influence depression.

On the other side of the risk and vulnerability equation, PTSD and depression appear to differentially predict the development of some positive and negative adjustment outcomes. Among the studies included in our review, there was substantial variability in the outcomes addressed, again making it difficult to draw aggregate conclusions. However, differences in the association of PTSD and depression with longitudinal outcomes have been reported in relation to physical health, suicide, work functioning and posttraumatic growth (Aversa et al., 2012; Dekel, Ein-Dor, & Solomon, 2012; Erbes, Kaler, Schult, Polusny, & Arbisi, 2011; Kehle, Reddy, Ferrier-Auerbach, et al., 2011; Naragon-Gainey, Hoerster, Malte, & Jakupcak, 2012; Possemato, Wade, Andersen, & Ouimette, 2010; Ribeiro et al., 2012). These differences further contradict Hypothesis 8.

There is some potential support for Hypothesis 8, in that PTSD and depression typically follow similar trajectories or patterns of symptom development over time (Bliese et al., 2007; Hourani et al., 2012; Milliken, Auchterlonie, & Hoge, 2007; Polusny et al., 2011; Skopp et al., 2011; van Zuiden, Geuze, et al., 2012; Wells et al., 2012). This would not necessarily establish comorbid disorders as indistinct, however. It may simply reflect a very strong association. Furthermore, some studies have identified unique symptom trajectories for PTSD and depression (Duma et al., 2010; Roemer et al., 1998; Wright et al., 2012).

4. Discussion

The purpose of this study was to conduct a systematic review of the literature regarding the development of PTSD and comorbid depression. Our primary goals were, first, to identify common research hypotheses about the etiology of PTSD and depression comorbidity from existing studies of military combat veterans. We identified 8 distinct hypotheses theorizing several potential causal relationships, common factors, and artifactual confounds. Our second goal was to determine what support exists for these hypotheses based on rigorous empirical evaluations (e.g., longitudinal and twin study designs).

In our review, we found a wide range of empirical support for the 8 hypotheses we identified. With respect to causal relationships in category 1, there was no evidence that depression is a risk factor for combat trauma (Hypothesis 1). Further, we found only inconsistent evidence that preexisting depression is a risk factor for PTSD following combat deployment (Hypothesis 2). In contrast, there was fairly consistent

evidence that PTSD is a risk for the subsequent development of comorbid depressive disorders (Hypothesis 3). Some level of bidirectional causality may be most likely, but the influence of PTSD on the development of comorbid depression appears more consistent and stronger than the reverse risk.

Based on our review of hypotheses from category 2, it is likely that common factors do influence the development of comorbid PTSD and depression. Twin study results, in particular, suggest both common risks (Hypothesis 4) and vulnerabilities (Hypothesis 5). Unfortunately, researchers have only begun to examine what those common risk and vulnerability factors might be. In particular, there is as yet only inconsistent evidence that combat exposure is a common underlying risk factor that ties these mental health problems together.

Last, on the basis of our review of hypotheses regarding potential confounds, it is unlikely that PTSD and depression are completely indistinct diagnoses (Hypothesis 7) or that they are simply subclusters of a larger syndrome of response to trauma (Hypothesis 8). Rather, conflating factors such as response bias among research participants or diagnostic bias among clinicians likely present the most viable artifactual threat (Hypothesis 6). Still, the empirical research evidence to date does not suggest that any particular secondary confound can account for the strong patterns of association observed among PTSD and depression.

The military is a unique context, and it is particularly important to understand the development of comorbid disorders among veterans. Many military volunteers enter the service with a history of prior trauma such as childhood abuse (Stander, Merrill, Thomsen, Crouch, & Milner, 2008; Stander, Olson, & Merrill, 2002; Wolfe et al., 2005), and during their service personnel continue to be at risk of experiencing multiple types of trauma, such as combat deployment and sexual assault, that are prominent risk factors for PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). In turn, PTSD presents one of the most significant risks/vulnerabilities for a number of other serious adjustment problems, such as depression (Polusny et al., 2011).

The results of this review highlight a number of ways that combat deployment may be relatively unique as a criterion event for PTSD. First, combat deployment may not be perceived as traumatic by all veterans, but rather as important work experience and an opportunity for personal growth. Furthermore, the experience may be very different based on combat role and military occupational specialty. Combat is further unique as a criterion stressor because it may not be a single event but rather an extended high-stress timeframe or a series of traumatic events. This makes it challenging to identify the actual timeline of PTSD symptom development. Also, preparing for deployment and returning home can be stressful life changes which may exacerbate symptoms, further confusing the study of symptom onset and development. One of the studies we reviewed suggested that PTSD symptom structure may evolve over the course of the deployment cycle, with different symptoms predominating and different associations emerging at different times (Meis et al., 2011). Further, unique stressor events are likely to have unique predictors, which may be more or less relevant to specific adjustment outcomes. Deployment and combat exposure, for instance, may be more strongly predicted by externalizing problems such as antisocial behavior than by internalizing symptoms like depression.

Unique military demographics, including marked overrepresentation of men, may impact comorbid associations, in part because men are less likely than women to experience depression. However, demographic factors will likely evolve as more women serve in the military and in combat roles. Possible service provider biases in the types of comorbid conditions attended to and diagnosed also may evolve if these are gender-related as well. Additionally, in the context of the all-volunteer force, both military- and self-selection factors appear to result in a deploying population with relatively good mental health (e.g., healthy warrior effect; Haley, 1998), which may weaken or obscure some potential associations among disorders in military populations.

Many of the confounding factors discussed for Hypothesis 6 are context specific. Military members anticipate and train for deployment, and their expectations may influence both their actual experience of the event and their reactions to it. Military policies, the attitudes of leaders, and other cultural characteristics (e.g., requirements for compensation; stigma regarding help-seeking; military fitness standards) also likely confound the presentation of comorbidities to the extent that they motivate people to present themselves as either more healthy or more symptomatic than they actually are. Twenty-two of the longitudinal studies we reviewed (32%) either collected data from treatment-seeking populations or analyzed archival military medical and health screening data, heightening the potential impact of these types of biases.

4.1. Limitations and important considerations

In interpreting the results of this review, important limitations should be considered. First, this is a descriptive review rather than a meta-analysis. However, the breadth and diversity in the body of literature available on PTSD–depression comorbidity is a challenge for meta-analysis (e.g., disparities in the operationalization of key constructs such as PTSD and combat trauma, wide variability in statistical methodology). Also, in conducting this study we focused solely on peer-reviewed publications, which may not be representative of all the studies that have been conducted. However, the number and complexity of hypotheses regarding the etiology of comorbidity in conjunction with the paucity of research currently available on many of them makes the present review an important step forward in understanding this body of research.

Another important issue that should be noted in interpreting the results of this review is that many study findings were relevant to more than one hypothesis. Perhaps the best example of this was evidence regarding directional effects among PTSD and comorbid disorders. Many findings cited in support of unidirectional causal effects for Hypotheses 2 and 3 were also cited in support of bidirectional effects for Hypothesis 5. These same study results also have some bearing on Hypotheses 8, evaluating the equivalent strength of bidirectional effects. Finally, there has been substantial overlap in study samples across different published reports and we have tried to point this out throughout the review. Most notably, all twin studies completed to date on veteran populations have relied primarily on the same subject pool (the VET Registry).

In a literature review, the quality of available research presents another limitation. All of the longitudinal research and the twin studies we reviewed employed reasonably good study designs. However, researchers seeking to determine the causal etiology behind comorbid PTSD and depression face difficult challenges. To verify a causal association, three conditions must be established. First, variables hypothesized to be causally related must be correlated. In the case of PTSD and depression, the results of this review sufficiently support this conclusion. Second it is necessary to eliminate all plausible alternative “third variables” that could explain correlations. Meeting this condition is much more of a work in progress. This standard is a high bar for longitudinal studies that are fundamentally correlational. Without being able to experimentally control research conditions, any number of third variables may confound associations. Twin studies are a much more efficient approach to ruling out many possible third variables (i.e., those associated with common genetic and environmental factors), particularly when they are analyzed using sophisticated modeling procedures, partitioning variability into separate components reflecting unique and common environmental and genetic sources of variance.

The third and final condition for establishing causality is temporal precedence; that is, the putative cause must precede the effect. This has been quite difficult to establish for PTSD and depression, and

typically twin studies are not helpful with this issue. Longitudinal studies that assess symptoms of both PTSD and depression at multiple points in time, both before and after combat exposure, may provide the strongest evidence on this point. Having assessments prior to trauma exposure and controlling for baseline symptomology is critical here. Ideally, there would be many observations relatively close in time to reduce the impact of retrospective biases on results; diary studies, though resource intensive, are ideally suited to accomplish this.

The strongest evidence for causal associations comes from experimental research. Randomly assigning individuals to different study conditions ensures that comparison groups are initially equivalent. Although experimental designs are not ethically possible with respect to trauma exposure, experimental treatment outcome studies do offer an opportunity to explore causal connections between PTSD and depression. Of course, this research approach still requires all of the ingredients of strong longitudinal study design.

4.2. Clinical and research implications

In this review, we did not consider clinical trials or treatment outcome studies, but unfortunately there appears to be very little literature on PTSD–depression comorbidity in this genre. In a broad review of treatments for PTSD and comorbid disorders, Najavits et al. (2009) pointed out that depression is prevalent enough that PTSD treatment samples will always include participants with depressive symptoms. However, clinical studies typically do not report the prevalence of mood disorders, and at the time of this review none had evaluated differential treatment outcomes for participants with comorbid mood disorders versus PTSD alone.

Meyer, Kimbrel, Tull, and Morissette (2011) reviewed research on the treatment of PTSD with other comorbid disorders among military populations and found only a handful of studies related to comorbid depression. Despite this paucity of evidence, they did conclude that treatments for PTSD tend to reduce symptoms of depression, while treatments for comorbid conditions such as depression do not necessarily reduce symptoms of PTSD. These results would be expected if PTSD treatment protocols affect symptoms unique to multiple disorders or symptoms common across disorders as well. They also are consistent with the possibility that PTSD is a causal risk factor for depression. It will be important for future clinical research to further evaluate treatment effects on comorbid PTSD and depression, to identify the critical mechanisms that may mediate outcomes across disorders, and to specify the symptom clusters that may best respond to treatment. Unfortunately, none of the clinical studies in these reviews evaluated integrated treatments that target both PTSD and depression. Najavits et al. (2009) and Meyer et al. (2011) conclude that this strategy may be most effective. Future efforts should focus on developing more integrated treatment approaches and evaluating their efficacy.

The newly released Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association, 2013), includes revised PTSD diagnostic criteria, and many experts have questioned how these changes will affect differential diagnosis and comorbidity prevalence rates (Friedman, Resick, Bryant, & Brewin, 2011). In addition to reclassifying PTSD in a new section titled "Trauma- and Stressor-Related Disorders," the new criteria refine what qualifies as a traumatic event, and expand the symptom structure from three to four clusters, including: re-experiencing (Cluster B), avoidance (Cluster C), negative cognitions and mood (Cluster D), and arousal symptoms (Cluster E). Compared to the DSM-IV-TR, in the DSM-V cluster C has become more limited and now excludes numbing symptoms.

There is uncertainty as to whether the new criteria will improve or degrade PTSD–depression differential diagnosis. Over time, it will be important to empirically evaluate the actual net effect of important changes under the new guidelines. For example, there is still substantial overlap in the symptoms included in the criteria for both PTSD and depression. However, using the DSM-IV-TR, a clinician could identify an elevation in avoidance/numbing PTSD Criterion C based solely on numbing symptoms common to depression; whereas under the DSM-5 at least two avoidance symptoms more unique to PTSD will be necessary for the diagnosis. This should improve the distinction between these two disorders (Forbes et al., 2011). On the other hand, the DSM-5 includes new symptoms that may not be very unique to PTSD (i.e., persistent distorted blame of self or others; pervasive negative emotional state; negative expectations about one's self, others, or the world; reckless or self-destructive behavior; irritable, angry, or aggressive behavior). Using data from the Multiphasic Personality Inventory, Koffel, Polusny, Arbisi, and Erbes (2012) evaluated the differential diagnostic utility of the new PTSD symptoms of anger, aggressive behavior, and negative expectations. Of the three, anger was the most associated with current PTSD, and was the only symptom that predicted the development of PTSD in their sample of deploying personnel. Negative expectations were more aligned with depression and aggressive behavior was more associated with substance dependence. These authors concluded that as a set, the newly proposed symptoms degrade differential diagnosis.

There are many other understudied aspects of PTSD–depression comorbidity, which should receive greater attention in future work. In particular, there have been very few evaluations of the relative impact on military personnel of multiple types of trauma, including childhood abuse, sexual trauma, and other civilian trauma as well as general life stress (Arbisi et al., 2012; Black et al., 2011; Gilbertson et al., 2002; Goodwin et al., 2012; Hourani et al., 2012; Kasai et al., 2008; Maguen et al., 2012; Seelig et al., 2012; Shin et al., 2009, 2011; van Zuiden, Geuze, et al., 2012; van Zuiden, Heijnen, et al., 2012). Given the high risk for multiple trauma exposure in military populations, clinicians and researchers alike need to be more attuned to considering their synergistic effects among military personnel. Military research has made an immeasurable contribution to our knowledge of PTSD, through pioneering research on combat stress reaction and broadening our understanding of psychological reactions to extreme stress. In the future, military research programs should continue to make important contributions to the broader literature as they examine the synergistic impact of multiple types of traumas and stressors, many of which are also common in civilian populations.

Ultimately, future research on the etiology of PTSD–depression comorbidity must emphasize the identification of modifiable risks and vulnerabilities that can be targeted with new prevention and treatment programs. In particular, more longitudinal studies need to get beyond examining associations between PTSD and depression at the macro level and move toward specifying the time-sensitive mechanisms that facilitate and mediate comorbidity at the level of specific symptom clusters. More twin studies need to get beyond simply validating the fact that common risk and vulnerability factors exist, and also work on verifying specific genetic vulnerabilities that reliably increase risk for multiple mental health disorders. Finally, clinicians and researchers must collaborate in translating research into practical prevention and intervention programs and in evaluating their efficacy for PTSD–depression comorbidity.

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14. ABSTRACT

Posttraumatic stress disorder (PTSD) is often diagnosed with other mental health problems, particularly depression and substance dependence. PTSD comorbidity has been associated with more severe and chronic symptomology, however the relationships among these commonly co-occurring disorders are not well understood. The purpose of this study was to review the literature regarding the development of PTSD, depression, and substance abuse comorbidities. We summarize research results for commonly tested hypotheses about the etiology of PTSD comorbidity, including (1) causal hypotheses, (2) common factors hypotheses, and (3) potential confounds. Recommendations are made for future work in this area of research.

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