Examining potential contraindications for prolonged exposure therapy for PTSD

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Although prolonged exposure (PE) has received the most empirical support of any treatment for post-traumatic stress disorder (PTSD), clinicians are often hesitant to use PE due to beliefs that it is contraindicated for many patients with PTSD. This is especially true for PTSD patients with comorbid problems. Because PTSD has high rates of comorbidity, it is important to consider whether PE is indeed contraindicated for patients with various comorbid problems. Therefore, in this study, we examine the evidence for or against the use of PE with patients with problems that often co-occur with PTSD, including dissociation, borderline personality disorder, psychosis, suicidal behavior and non-suicidal self-injury, substance use disorders, and major depression. It is concluded that PE can be safely and effectively used with patients with these comorbidities, and is often associated with a decrease in PTSD as well as the comorbid problem. In cases with severe comorbidity, however, it is recommended to treat PTSD with PE while providing integrated or concurrent treatment to monitor and address the comorbid problems.

Keywords: *PTSD*; *comorbidity*; *prolonged exposure*; *(contra)indications*

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Many controlled studies have demonstrated the efficacy of prolonged exposure (PE; Foa, Hembree, & Rothbaum, 2007), an exposure-based form of cognitive behavioral therapy focused on reducing PTSD and related psychopathology (see for a meta-analysis Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). PE includes components of psychoeducation, *in vivo* exposure to feared but safe trauma-related stimuli, imaginal exposure, and processing of trauma memories. PE is thought to work through fear extinction mechanisms, allowing the patient to emotionally engage and process the traumatic memories in the absence of feared outcomes (e.g., Foa et al., 2007). On the basis of the numerous studies demonstrating its efficacy, PE is considered a treatment of choice for PTSD (Ballinger et al., 2004; Nemeroff et al., 2006) and is recommended world-wide in official PTSD treatment guidelines, e.g.,

International Society for Traumatic Stress Studies (Foa, Keane, Friedman, & Cohen, 2009); National Institute for Health and Clinical Excellence Guidelines on PTSD (NICE, 2005). Indeed, in a report by the Institute of Medicine (2007), exposure therapy was considered the only form of PTSD treatment with a sufficient evidence base. Furthermore, gains made in PE are maintained in long-term follow-up (5–10 years post-treatment, Resick, Williams, Suvak, Monson, & Gradus, 2012). Despite its efficacy, the dissemination of PE to clinical practice has been challenging, as is illustrated by the underuse of this treatment by therapists. In a survey of psychologists in the USA, only 17% reported using imaginal exposure to treat PTSD (Becker, Zayfert, & Anderson, 2004). Similarly, a survey of European trauma experts found that imaginal exposure was the least used treatment for PTSD (Van Minnen, Hendriks, & Olff, 2010).

One of the primary reasons that clinicians report for not using PE techniques is a belief that the treatment is contraindicated for PTSD patients with various comorbid diagnoses and problems. In the study by Becker et al. (2004), for instance, many clinicians viewed imaginal exposure as contraindicated for patients with comorbid suicidality (85%), psychotic disorder (85%), dissociation (51%), any comorbid diagnosis (37%), or a comorbid anxiety disorder (32%). One of the main reasons for not employing PE was fear of exacerbation of symptoms (both of PTSD symptoms and comorbid symptoms). Similarly, the study by Van Minnen et al. (2010) found that clinicians believed PE was less indicated for patients with depression, especially when they had suffered multiple childhood traumas. In addition, the consensus among some PTSD experts (Cloitre et al., 2011) is that a treatment approach based primarily on memory processing (such as PE) is inappropriate for cases of "complex" PTSD (i.e., PTSD with associated features such as dissociative symptoms and dysregulation of affect and behavior, for definitions see also Sar, 2011). However, given the fact that PTSD has high rates of comorbidity (79–88.3%; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), these perceived contraindications would lead to the exclusion of the majority of PTSD patients from PE.

The PE manual (Foa et al., 2007) specifies several clinically determined contraindications for treatment: imminent threat of suicidal or homicidal behavior, recent (past 3 months) serious self-injurious behavior, and current psychosis. Substance abuse and dependence are not exclusion criteria per se, but it is recommended to address the substance use disorder simultaneously with PE. Patients with dissociative disorders are included, as long as the dissociative symptoms do not outweigh the PTSD symptoms. With regard to Axis II disorders, patients are only excluded from PE when the disorder is severe (e.g., in the case of borderline personality disorder (BPD) with current, serious self-injurious or destructive behavior).

Several studies have specifically addressed the question of whether comorbidity is a predictor of treatment outcome in PE (e.g., Feeny, Zoellner, & Foa, 2002; Speckens, Ehlers, Hackmann, & Clark, 2006; Van Minnen, Arntz, & Keijsers, 2002). No study found that comorbidity (including depression, dissociation, personality disorders, and substance use) predicted worse treatment outcome. Indeed, very few pretreatment variables were found to predict the outcome of PE. Therefore, patients should not be excluded from this highly effective treatment based on pretreatment characteristics such as comorbidity. However, some experts argue that these findings are not representative because patients with severe comorbidity are often excluded from randomized controlled trials (RCTs) of PE (e.g., Spinazolla, Blaustein, & Van der Kolk, 2005).

To encourage the use of PE in clinical practice, it is important that clinicians are informed about valid indications and contraindications for PE. To that end, we review the research that has evaluated whether comorbid conditions and problems that are highly prevalent in PTSD patients are indeed contraindications for PE. These include dissociation, BPD, psychosis, suicidal and non-suicidal self-injury, substance use disorders, and major depression. We address the possible theoretical and clinical reasons why each particular comorbid condition or problem might interfere with PE. Also, we explore to what extent these comorbidities are indeed excluded in RCTs concerning PE using the studies included in the Powers et al.'s (2010) meta-analysis as a starting point (Table 1). In addition, we review the predictive value of comorbid problems in relation to PE treatment outcome. Lastly, we review the available research on PE for these patients, including results from RCTs as mentioned in the Powers et al.'s (2010) study, as well as effects derived from open and pilot studies of PE or modified PE treatment programs, specifically aimed at treating the above-mentioned comorbid populations.

Dissociation

Many patients with PTSD have at least some symptoms of dissociation. The DSM-IV describes dissociation as, "a disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment" (p. 477). Derealization and depersonalization are the most common dissociative symptoms among PTSD patients. A review showed that 30% of war veterans with PTSD reported elevated levels of derealization (Hunter, Sierra, & David, 2004). In addition, several dissociative symptoms, such as numbing, are among the diagnostic criteria of PTSD. In light of the Becker et al.'s (2004) study, in which 51% of clinicians considered *any* kind of dissociation a contraindication for PE, it would mean that many PTSD patients would be excluded. In the PE manual (Foa et al., 2007), severe dissociation and dissociative disorders were not considered contraindications for the use of PE unless the dissociation symptoms are much more prominent than the PTSD symptoms. Clinicians argue that they are concerned about exacerbations of dissociative symptoms as a result of PE (particularly recounting distressing trauma memories). Theoretically, one could argue that dissociation, especially emotional numbing, may hinder fear activation and thereby interfere with emotional processing, a necessary condition for PE to be successful. Although Taylor et al. (2001) found that numbing was negatively related to treatment outcome, other studies found no such relationship (Jaycox, Foa, & Morral, 1998; Speckens et al., 2006). However, most studies did not control for depression, a condition closely related to numbing (see Feeny, Zoellner, Fitzgibbons, & Foa, 2000). In addition, dissociation

Table 1. Co-morbidity exclusion criteria from the studies of Powers et al. (2010)

	Dissociation	Outline personality disorder	Psychosis	Suicidal and non-suicidal self-injury	Substance use disorders	Major Depression
Asukai, Saito, Tsuruta, Kishimoto, & Nishikawa (2010)	Severe dissociation	N/A	History of psychosis	Serious risk of suicidal behavior	Current substance dependence	Depression for which drug treatment was prioritized
Foa Rothbaum, Riggs, and Murdock (1991)	N/A	N/A	Current or previous diagnosis of schizophrenia, paranoid disorders, bipolar disorder, or depression with delusions, hallucinations or bizarre behavior	N/A	Current alcohol or drug abuse	Depression severe enough to require immediate psychiatric treatment
Foa et al. (1999)	N/A	N/A	Current schizophrenia, bipolar disorder	Severe suicidal ideation	Current alcohol or drug dependence	N/A
Foa et al. (2005)	N/A	N/A	Current diagnosis of schizophrenia or psychotic disorder. Unmedicated symptomatic bipolar disorder	High risk for suicidal behavior (i.e., with intent, plan or both). Recent history of serious self-injurious behavior (i.e., cutting)	Current substance dependence	N/A
Gilboa-Schechtman et al. (2010)	N/A	N/A	Current psychotic symptoms	Suicidal ideation posing imminent danger (suicidal thoughts were not excluded)	Current substance dependence	N/A
Marks et al. (1998)	N/A	N/A	Past or present psychosis	Suicidal intent	Use of 10 mg/day of diazepam (or equivalent), ingestion of 30 or more units of alcohol per week	Melancholia
McDonagh et al. (2005)	Dissociative identity disorder	N/A	Current diagnosis of mania, hypomania, schizophrenia, schizoaffective disorder, schizophreniform disorder, brief reactive psychosis, psychotic disorder NOS Bipolar disorder, depression with delusions, hallucinations or bizarre behavior	Presence of active suicidality or history of two or more suicide attempts/gestures in past year	Current alcohol or drug abuse, withdrawal from benzodiazepines, alcohol, heroin or other opiates in past 3 months	Depression severe enough to require acute psychiatric treatment

Table 1 (Continued)

	Dissociation	Outline personality disorder	Psychosis	Suicidal and non-suicidal self-injury	Substance use disorders	Major Depression
Nacasch et al. (2011)	Severe dissociative disorder	N/A	Current psychotic symptoms Bipolar disorder	High risk for suicidal behavior (i.e., with intent, plan or both)	Current active substance dependence	N/A
Power et al. (2002)	N/A	N/A	Past or present psychotic illness	Suicidal ideation or intent	History of alcoholism or drug abuse in past 6 months	Severe depressive illness
Resick, Nishith, Weaver, Astin, & Feuer (2002)	N/A	N/A	Current psychosis	Suicidal intent Current parasuicidal behavior	Current dependence on drugs or alcohol. In case of history of substance dependence: <6 months abstinence	N/A
Rothbaum et al. (2005)	N/A	N/A	History of schizophrenia or other psychoses	Current suicidal risk Practiced self-mutilation	Current alcohol or drug dependence, cocaine use in past 60 days	N/A
Schnurr et al. (2007)	N/A	N/A	Current psychotic symptoms Mania or bipolar disorder	Prominent current suicidal ideation Self-mutilation in the past 6 months	Substance dependence not in remission for at least 3 months	N/A
Taylor et al. (2003)	N/A	N/A	Current psychotic disorder	N/A	N/A	N/A

is often addressed as a single, general construct, but is in fact a highly complicated construct, including a variety of symptoms (Bryant, 2007).

To address these issues, Hagenaars, Van Minnen, and Hoogduin (2010) studied the effect of dissociation on PE treatment outcome in 71 PTSD patients, discriminating among several dissociative phenomena and controlling for depression. Emotional numbing, depersonalization, and a general tendency to dissociate did not predict worse treatment outcome, nor treatment dropout, even in patients with high levels of these symptoms. On the contrary, patients with higher levels of dissociation (specifically numbing) had better outcome compared with patients with lower levels of numbing. Importantly, dissociation did not impede fear activation during exposure to the trauma memories. In this study, the presence of dissociative disorders was not assessed, but patients with clinical levels of dissociative symptoms were included and, when separately analyzed, the results were not altered. These findings are in line with the recent findings that adding exposure (in this study writing accounts, not PE) to cognitive therapy was indicated for patients with higher levels of dissociation (Resick Suvak, Johnides, Mitchell, & Iverson, 2012). Of interest, in the majority of the studies (10/13) included in the Powers et al.'s (2010) meta-analysis, dissociative symptoms or dissociative disorders were not an exclusion criterion, implying that results found in RCTs may apply to PTSD patients with (severe) dissociative symptoms.

Taken together, there is no evidence that dissociative symptoms are a valid contraindication for use of PE, even for patients with severe and clinical levels of dissociation. In fact, dissociation was associated with better emotional processing and enhanced treatment outcome. It is more likely that dissociation is a dysfunctional avoidance strategy (see Briere, Scott, & Weathers, 2005), preventing patients from fully processing their traumatic memories and thereby maintaining PTSD symptoms. Accordingly, patients with (severe) dissociative symptoms should not be excluded from PE, but rather should be encouraged to overcome their avoidance behavior, as is done in PE, so that their fear structure can be fully activated and emotional processing can take place. Consistent with this view, several studies have found that the symptoms of dissociation decrease significantly after PE along with the PTSD symptoms (Hagenaars et al., 2010; Harned, Korslund, Foa, & Linehan, 2012; Rothbaum, Astin, & Marsteller, 2005; Taylor et al., 2003).

Borderline personality disorder

Research has indicated that 24.2% of individuals with PTSD also have BPD (Pagura et al., 2010), and comorbid BPD is particularly common among women with PTSD related to childhood sexual abuse (37%; Heffernan & Cloitre, 2000). Individuals with BPD are often viewed

as inappropriate for exposure therapy for PTSD, including PE. These concerns are based on the belief that BPD patients are unable to tolerate exposure, particularly imaginal exposure to traumatic memories, and may even get worse (e.g., become increasingly suicidal, require psychiatric hospitalization) during such treatment. Theoretically, patients with BPD possess a number of characteristics that may interfere with achieving effective emotional engagement and fear reduction during PE. A core feature of BPD is pervasive emotion dysregulation, which includes intense emotional reactivity and avoidance of emotional experiencing (Linehan, Bohus, & Lynch, 2007). In addition, patients with BPD often use a variety of maladaptive emotion regulation strategies (e.g., intentional self-injury, dissociation, substance use) that may both interfere with fear activation and cause safety concerns during PE.

Importantly, none of the PE studies in the Powers et al.'s (2010) meta-analysis excluded patients with BPD. However, all of the studies excluded patients with behaviors that commonly co-occur with severe BPD (e.g., acute suicidality, serious non-suicidal self-injury, substance dependence). This is consistent with recommendations in the PE manual (Foa et al., 2007), which states that patients should not be excluded from PE on the basis of any Axis II diagnosis, but individuals with severe degrees of personality disorders may be excluded for other reasons (e.g., cases of BPD with serious self-injurious behaviors). When these standard PE exclusion criteria are used, several studies have shown that patients with BPD or borderline personality characteristics (BPC) improve as much as those without BPD/BPC during standard PE (Clarke, Rizvi, & Resick, 2008; Feeny et al., 2002). In addition, four studies of modified PE treatments for childhood abuse-related PTSD have reported including BPD patients in their samples, including an RCT of a 16-week outpatient treatment involving skills training followed by modified PE (Cloitre et al., 2010), an RCT of a 14-week outpatient modified PE treatment (McDonagh et al., 2005), an open trial of a 3-month residential Dialectical Behavior Therapy (DBT) and modified PE program (Bohus, Kruger, Dyer, Priebe, & Steil, 2011), and case studies of a brief (5-day) intensive outpatient treatment based on PE (Hendriks, de Kleine, van Rees, Bult, & van Minnen, 2010). However, only one of these studies examined the impact of BPD on treatment outcome, finding that patients with and without BPD improved comparably (Bohus et al., 2011). All of these modified PE studies included patients with recent non-suicidal self-injury, but excluded patients with recent and/or acute suicidality.

To examine whether these results generalize to even more severe BPD patients, Harned et al. (2012) conducted an open trial of an integrated DBT and PE treatment for recently suicidal and/or self-injuring BPD

women with PTSD ($n = 13$). This one-year treatment uses standard DBT to target intentional self-injury and other forms of behavioral dyscontrol prior to implementing PE simultaneously with ongoing DBT. PE was modified by incorporating DBT skills and strategies (e.g., for monitoring and managing suicide risk) into the standard PE protocol and was implemented in an average of 13.5 weekly sessions during the year of standard DBT (for details see Harned, in press). From pre- to post-treatment, the patients with severe BPD in this study showed large and significant improvements in PTSD ($d = 1.4$, 70% reliable improvement, 60% remission), intentional self-injury, and a variety of secondary trauma-related outcomes (e.g., dissociation, trauma-related guilt, shame). No patients exhibited reliable worsening of PTSD or intentional self-injury. In addition, treatment dropout was low (23%) and occurred only before the initiation of PE.

Taken together, there is no empirical support for excluding patients with BPD from PE who meet the eligibility criteria specified in the PE manual. Indeed, several studies have shown that patients with mild BPD are effectively treated with standard PE. In addition, several studies examining modified PE treatments (delivered alone or in combination with DBT or DBT skills training interventions) have shown promising results among more severe BPD patients who are typically excluded from PE (e.g., those with recent serious self-injurious behaviors). Additional research is needed to further evaluate the efficacy of these modified PE treatments, to examine the potential impact of BPD on treatment outcome, and to determine how best to match these various treatment options to BPD patients with different levels of disorder.

Psychosis

Many patients with psychotic disorders have been exposed to traumatic events (see Read, Van Os, Morrison, & Ross, 2005, for a review), and the prevalence of PTSD in individuals with psychotic disorders is relatively high, ranging from 12% to 29% (Achim et al., 2011; Buckley, Miller, Lehrer, & Castle, 2009). Theoretically, active psychotic symptoms may interfere with the underlying working mechanism of exposure therapy. It may be more difficult for these patients to regulate their emotions, and, in the absence of adequate reality testing, adequate processing of traumatic memories may be hindered. In line, most clinicians see psychotic symptoms as a contraindication for trauma-focused treatments, such as PE, mainly because they are afraid that this will result in adverse events, such as exacerbation of psychotic symptoms, or an increase in crisis interventions or hospital admissions (Becker et al., 2004; Read, Hammersley, & Rudegeair, 2007; Young, Read, Barker-Collo, & Harrison, 2001).

Consistent with the exclusion criteria recommended in the PE manual (Foa et al., 2007), patients with current psychotic disorders were excluded from nearly all of the studies in the Powers et al.'s (2010) meta-analysis. In addition, five studies excluded patients with past (non-active) psychotic disorders. Consequently, these studies do not provide information as to whether PE can be applied to patients with either past or present psychotic disorders.

In an open trial, the effects of PE were studied in patients with a past year history of schizophrenia or schizoaffective disorder ($n = 20$; Frueh et al., 2009). Treatment consisted of a pre-exposure treatment phase (14 sessions containing psycho-education, anxiety management therapy and social skills training) followed by eight PE sessions. All patients received biweekly usual care of their case-manager during the trial and, when indicated, psychopharmacological management of their psychiatric symptoms. A significant reduction of PTSD symptoms was noted during and after PE. Nearly all completers (12 of 13) lost their PTSD diagnosis at post-treatment, and these effects were maintained at a 3-month follow-up. Importantly, no adverse events were noted during PE. These results suggest that patients with psychotic vulnerability can receive PE and benefit from it. However, seven (35%) of the patients dropped out before the start of PE, leaving the question open as to whether this rather long pretreatment phase is necessary. To address this question, De Bont, Van Minnen, and de Jongh (2012) applied standard PE to patients with (present) psychotic disorders ($n = 5$) using a randomized baseline controlled design. In this study, PE included a maximum of 12 sessions within 12 weeks and was delivered without modification except for one pretreatment session dedicated to the formulation of a crisis intervention plan. Patients also continued to receive concurrent care as usual, including pharmacological treatment and monitoring and case management, provided within the same service, but by another care-giver than the PE therapist. All four completers showed good treatment results and lost their PTSD diagnosis at the 3-month follow-up. Also no adverse effects (hospital admissions, suicidal behavior, non-suicidal self-injury, crisis interventions) were noticed, and active psychotic symptoms did not increase during treatment. On the contrary, symptoms of psychotic prone thinking style and general psychopathology decreased significantly during treatment.

In sum, there is some evidence that the standard protocol of PE (even without any modifications) can be effective and safe for PTSD patients with comorbid psychosis. However, most studies excluded currently psychotic patients and the positive data included only a few patients with only short-term follow-up, thus more research is needed.

Suicidal and non-suicidal self-injury

Individuals with PTSD are seven times more likely to attempt suicide and five times more likely to report suicidal ideation than those without PTSD (Cougle, Keough, Riccardi, & Sachs-Ericsson, 2009). Among suicide ideators, PTSD is the only Axis I disorder that predicts which individuals will go on to make a suicide plan and attempt suicide (Nock, Hwang, Sampson, & Kessler, 2010). Rates of non-suicidal self-injury (i.e., intentional self-injury without suicidal intent) are also high in clinical samples of PTSD patients (50–60%; Cloitre, Koenen, Cohen, & Han, 2002; Dyer et al., 2009; Zlotnick, Mattia, & Zimmerman, 1999). Expert consensus and PTSD practice guidelines recommend excluding individuals with acute suicidality (i.e., suicide ideation with intent to commit suicide) from PTSD treatments as clinically appropriate care requires a focus on reducing the suicide risk before addressing the PTSD (e.g., Department of Veterans Affairs/Department of Defense, 2004; Foa et al., 2009; Forbes et al., 2007). Similarly, the PE manual (Foa et al., 2007) recommends that individuals at imminent risk of suicide and those who have attempted suicide or engaged in serious non-suicidal self-injury in the past 3 months should be excluded from treatment until these behaviors are sufficiently stabilized. These clinical guidelines have been adopted in most studies of PE. Of the 13 studies in the Powers et al.'s (2010) meta-analysis, acutely suicidal patients were excluded in eleven studies and indirectly excluded in two studies (e.g., by requiring PTSD to be the primary or most severe presenting problem). In addition, four studies excluded individuals with recent non-suicidal self-injury. Of note, individuals with current suicidal ideation (without intent to commit suicide) and those with a history of attempting suicide (prior to the past 3 months) are included in most PE studies; however, these indices of elevated suicide risk predicted worse PTSD outcome in patients receiving cognitive therapy or imaginal exposure (Tarrier, Sommerfield, Pilgrim, & Faragher, 2000).

Harned et al.'s (2012) open trial is the first to specifically evaluate PE, in combination with DBT, for recently and/or imminently suicidal and self-injuring PTSD patients with BPD. This treatment uses standard DBT to target suicidal and non-suicidal self-injury and requires patients to achieve 2 months of abstinence from these behaviors and to not be at imminent risk of suicide prior to beginning the PE portion of the treatment (see BPD section above for a description). Urges to commit suicide and self-injure are monitored before and after each exposure task, and DBT is used to address any increases in urges as well as actual episodes of these behaviors that may occur. Results of the open trial indicate that it is safe to use PE within a DBT program in this high-risk population. Urges to commit suicide and self-injure rarely increased immediately after completing an exposure task (<7% of tasks), and the rate of relapse of these behaviors during PE was low (10%). Similarly, a study of a residential treatment for childhood sexual abuse-related PTSD that included actively self-injuring patients did not find an increase in non-suicidal self-injury during modified PE that occurred in the context of a DBT treatment (Bohus et al., 2011).

In sum, there is no empirical evidence to support the use of PE with patients with a recent (past 2 months) suicide attempt or patients who are acutely suicidal (suicidal ideation with intent to commit suicide). Further, although several PE or modified PE studies have not reported excluding patients with recent serious non-suicidal self-injury, only one study has reported results related to self-injury, making it difficult to determine the safety or efficacy of PE for actively self-injuring patients. Thus, there is currently insufficient evidence to support the use of PE with patients with recent (past 2 months) serious non-suicidal self-injury. However, research does support the use of PE after 2 months of abstinence from suicide attempts and serious non-suicidal self-injury and once suicide risk is no longer acute. For acutely suicidal and self-injuring patients, preliminary data suggests that DBT may be effective for achieving the stability necessary to begin PE as well as for concurrently monitoring and addressing these behaviors during PE; however, randomized controlled studies are needed to reach more firm conclusions.

Substance use disorders

PTSD and substance use disorders (SUDs; i.e., abuse or dependence on alcohol or other drugs) frequently co-occur. Epidemiologic research has demonstrated that one-third of individuals with PTSD have a comorbid SUD (Mills, Teesson, Ross, & Peters, 2006). The most common SUDs among individuals with PTSD are alcohol, sedative, and cannabis use disorders; however, PTSD is most strongly associated with sedative, opioid, and amphetamine use disorders (Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Mills et al., 2006). It is important to note that approximately 45% of individuals with PTSD also smoke tobacco (Lasser et al., 2000); however, nicotine dependence is not included in our discussion of SUD here. Caffeine is also not included in our discussion; however, with the growing use of highly caffeinated energy drinks (Reissig, Strain, & Griffiths, 2009), it is also important to consider caffeine use among PTSD patients given its anxiogenic effects.

There is much controversy with regard to the use of PE in individuals with SUD. Traditionally, PE was considered inappropriate for use among patients with SUD (Foa & Rothbaum, 1998), as it was widely believed that these patients would be unable to cope with the intense emotions elicited during PE, placing them at increased

risk for relapse (Becker et al., 2004; Killeen, Back, & Brady, 2011). It has also been suggested that substance use may impair fear activation and processing of new information, thereby reducing treatment effectiveness, and that cognitive impairment associated with SUD may impair patients' ability to undertake imaginal exposure (Ouimette, Moos, & Brown, 2003). Therefore, historically it was recommended that PE should only be employed with SUD patients once a period of abstinence (typically between 3 to 9 months), or a substantial reduction in use, had been achieved (Back, 2010; Becker et al., 2004; Najavits, 2006; Ouimette et al., 2003).

On the basis of these assumptions, patients with substance dependence have been excluded from most trials of PE. Seven studies included in the Powers et al.'s (2010) meta-analysis explicitly excluded current substance dependence (but not abuse); however, only two studies provided definitions of what was meant by "current": 3 and 6 months. Conversely, some studies specified current substance abuse (but not dependence) as an exclusion criterion. Others included additional criteria such as not having used any cocaine within 60 days (Rothbaum et al., 2005) and not having experienced withdrawal in the past 3 months (McDonagh et al., 2005). The study by Marks, Lovell, Noshirvani, Livanou, and Thrasher (1998) appears to be the only study to have included individuals with substance dependence; 16% of the sample met criteria for alcohol abuse or dependence. The impact of these disorders on treatment outcome, however, was not examined. There is, however, some evidence to suggest that alcohol use during treatment is associated with drop-out from treatment, and that benzodiazepine use may also be associated with poorer treatment outcome (van Minnen et al., 2002).

A number of clinical researchers have begun investigating the efficacy of integrated treatment programs (i.e., programs that address PTSD and SUD simultaneously by the same clinician or service) that incorporate PE techniques. Typically this involves psycho-education regarding each disorder and their interrelatedness, coping skills training, relapse prevention, and trauma-focused PTSD treatment incorporating imaginal and/or *in vivo* exposure (Back, Dansky, Carroll, Foa, & Brady, 2001; Back et al., 2012; Najavits, Schmitz, Gotthardt, & Weiss, 2005; Triffleman, Carroll, & Kellogg, 1999). This combination of active PTSD treatment while engaging in concurrent substance use treatment is also recommended in the PE manual (Foa et al., 2007). Support for these programs is growing with an increasing number of studies providing evidence for their safety and efficacy. Patients in these studies did not get worse or demonstrate high rates of relapse; on the contrary, they demonstrated improvements in relation to both substance use and PTSD outcomes (Brady, Dansky, Back, Foa, & Carroll,

2001; Mills et al., 2012; Najavits et al., 2005; Triffleman, 2000).

However, the extant research is largely limited to small pilot studies, with only one large RCT completed to date. Mills et al. (2012) recently completed an RCT evaluating the efficacy of an integrated treatment called Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE). Compared to treatment as usual (TAU), individuals who received COPE plus TAU demonstrated a significantly greater reduction in PTSD symptom severity over the 9-month follow-up period.

Although the dearth of methodologically sound treatment trials makes it difficult to draw firm conclusions (van Dam, Vedel, Ehring, & Emmelkamp, 2012), findings from the aforementioned studies provide support for the use of integrated treatments that incorporate PE among individuals with SUD. For PTSD patients with a period of abstinence (3 or more months) or substance abuse only, standard PE without additional modifications is commonly utilized. Although treatment retention for patients with comorbid SUD is challenging, dropout rates for PE programs are similar to those observed in studies of non-trauma focused therapies (Hien et al., 2009; Najavits, Weiss, Shaw, & Muenz, 1998). Furthermore, as with studies of PE among non-SUD patients, dropout tends to occur prior to the onset of PE (Brady et al., 2001; Mills et al., 2012). In sum, while SUD may complicate PTSD treatment, it should not preclude it. While research on the use of PE in SUD clients is in its infancy, a growing number of studies are demonstrating the safety and efficacy of integrated treatment programs that utilize PE in this population.

Major depressive disorder

PTSD and major depression commonly co-occur, with approximately 40–50% of those in PE clinical trials reporting current major depressive disorder (MDD) and the majority of these patients showing elevated symptoms of depression severity (e.g., Foa et al., 2005; Resick et al., 2008; Schnurr et al., 2007). PTSD and MDD are significantly correlated with one another (.50) at levels similar to other anxiety disorders (.42–.60; Kessler, Chiu, Demler, & Walters, 2005). Most notably, PTSD with comorbid MDD is associated with greater disorder severity (e.g., Kessler et al., 2005), including higher PTSD, anxiety, and depression and worse functioning than individuals with either PTSD or MDD alone (see Post, Zoellner, Youngstrom, & Feeny, 2011). This greater disorder severity likely underlies clinicians' concerns about PTSD patients with co-occurring MDD being harder to engage in a behavioral treatment, having more difficulty tolerating exposure, and having more indelible negative beliefs such as hopelessness, guilt, low self-efficacy, and rumination. Comorbid depression,

however, is not an exclusion criterion for PE (Foa et al., 2007).

PTSD and depression not only share common observable symptoms (e.g., anhedonia, sleep problems, irritability, concentration difficulties), but also share underlying factors such as impaired emotion regulation and negative affect. Some have argued that the distinction between chronic PTSD and chronic PTSD with comorbid depression may be arbitrary and only reflects greater disorder severity (e.g., O'Donnell, Creamer, & Pattison, 2004). Extending this to therapeutic mechanisms, the mechanisms underlying fear extinction and depression-related behaviors show significant genetic, molecular, and neuroanatomical overlap (e.g., Tronson et al., 2008). Accordingly, it is not surprising to hypothesize that, through fear extinction occurring during *in vivo* and imaginal exposure in PE, depression symptoms would also improve due to a shared common mechanism for fear and mood regulation.

Indeed, this is the case. All of the PE trials in the Powers et al.'s (2010) meta-analysis included comorbid MDD, as long as PTSD was considered the primary diagnosis. Thus, patients with depression that was much more severe than their PTSD were routinely excluded from these trials. All but one large-scale clinical trial on PE measured depression as a secondary outcome, and, of these studies, all show clinically significant improvements in depression. In this meta-analysis, medium size effects for PE were found across all secondary outcome measures (post-treatment: Hedges' $g = 0.77$; follow-up: Hedges' $g = 0.41$). When depression is specifically examined, individual studies show consistent moderate-to-large PE effects (e.g., Cohen's $d = 0.96$; Foa et al., 2005), though smaller than for PTSD (e.g., Cohen's $d = 1.37$; Foa et al., 2005). This can easily be explained in that PTSD trials include individuals who are not depressed, resulting in attenuated effect sizes for depression. Individuals with more severe depression also show comparable reductions in PTSD severity with PE (Feeny, Zoellner, Mavissakalian, & Roy-Byrne, 2009; Hagenaars et al., 2010). In some studies with PE, *elevated* pre-treatment depression severity was associated with *reduced* post-treatment PTSD severity (Feeny et al., 2009; Rizvi, Vogt, & Resick, 2009). Negative beliefs about oneself, the world, and self-blame also show improvement with PE, corresponding strongly with changes in PTSD (Foa & Rauch, 2004; Hagenaars, van Minnen, & de Rooij, 2011), and, in one study, higher pre-treatment guilt predicted *better* treatment outcome (Rizvi et al., 2009). Finally, there may be a reciprocal relationship between changes in PTSD and depression in PE. Post-traumatic symptoms account for more variance of the change in depression than vice versa, suggesting that PE may work primarily by reducing posttraumatic stress, which in turn reduces depression (Aderka, Foa, Applebaum, Shafran, & Gilboa-Schechtman, 2011).

Taken together, evidence across randomized trials of PE consistently shows improvement in depression, and clinical improvement in PTSD occurs even for those who have higher pre-treatment depression severity. That said, patients with depression much more severe than their PTSD or patients with current suicidal intent and behavior, as discussed above, are routinely excluded from PTSD trials, as clinically appropriate care would require stabilizing these issues prior to addressing their PTSD.

Discussion

Given the high rate of comorbid disorders and problems among PTSD patients, it seems important to examine whether trauma-focused treatments, such as PE, can be effectively and safely applied to PTSD patients with severe comorbidity. Consistent with the inclusion and exclusion criteria described in the PE manual (Foa et al., 2007), and supported by RCTs that have utilized these criteria, PTSD patients with comorbid dissociation, depression, substance abuse, and/or mild BPD can be successfully and safely treated with standard PE and the outcome is comparable to that found in patients without these comorbidities. In addition, several recent studies have begun to evaluate the effects of PE in patient samples with severe comorbidity that have previously been excluded from RCTs and for whom cautiousness was recommended in the PE manual: patients with comorbid serious self-injurious behavior, acute suicidality, recent suicide attempt, current psychosis and substance dependence disorders. Although more and larger controlled trials are needed to draw firm conclusions, studies have found that PE can be effective and safe for these patients. These newer treatment programs have all included methods to simultaneously address PTSD (via PE or modified PE) and the comorbidity (via other treatments or strategies specific to those problems). These integrated or concurrent treatments may be the optimal approach when using PE with patients with these severe comorbidities. Of note, in each of these studies, trauma-focused treatment programs were dosed in the standard way despite the comorbidity; that is, PE sessions were scheduled once or twice weekly. In contrast, due to fear of adverse events, clinicians in routine practice may either postpone the trauma-focused treatment until the comorbid condition is less prominent (which may never occur) or start the trauma-focused treatment at a low frequency, alternating trauma-focused treatment sessions with treatment sessions aimed at addressing the comorbid conditions. There is no evidence for or against these as effective management strategies. However, the latter approach can be problematic as it may actually impair symptom improvement given that extinction mechanisms used in exposure therapy require repeated and prolonged exposure to the feared situations and the trauma-related memories.

Importantly, clinicians' concern that patients with severe comorbidities will show an exacerbation of symptoms after starting PE was not confirmed. On the contrary, across studies it was consistently found that patients showed a decrease of comorbid symptoms along with a decrease in PTSD symptoms. Also, patients with severe comorbidity did not show an elevated rate of dropout from PE, and, if dropout occurred, it most often happened *before* the implementation of PE. Moreover, no studies reported reliable worsening of PTSD or comorbid problems. These findings indicate that PE is not only effective in reducing PTSD for patients with severe comorbidity, but is also a tolerable and safe treatment that is likely to have positive effects on the comorbid conditions as well. That said, clinically, these comorbidities should not be ignored during PE, but rather carefully monitored and addressed as needed.

In line with the research findings, a meta-analysis of the effects of comorbidity on treatment (in most cases cognitive behavioral treatment) outcome for anxiety disorders found that comorbidity had a *positive influence* on PTSD treatment outcome (Olatunji, Cisler, & Tolin, 2010). A possible explanation could be that PTSD often precedes or maintains the comorbid conditions and can therefore in most cases be considered the primary condition. Further, patients with comorbidities are often more severe; thus, when they make comparable gains to those without the comorbidities, treatment effects are larger.

Despite the fact that standard and modified PE was found to be effective and safe in patients with severe comorbidities, treating these patients in clinical practice may be challenging, especially when a patient has more than one comorbid condition (which is actually more common than uncommon). In such cases, clinicians may make adjustments to tailor PE to the specific needs and complexities of the patient. For example, when working with depressed patients, clinicians may have to work harder to engage the patients with the treatment, as they may lack interest in psychotherapy (Feeny et al., 2009). Also, as recommended in the PE manual (2007), clinicians may add *in vivo* exposure tasks to address specific comorbid symptoms, such as anhedonia and avoidance by increasing activity levels and targeting areas of previous enjoyment (e.g., Echiverri, Jaeger, Chen, Moore, & Zoellner, 2011; Foa, Huppert, & Cahill, 2006). Some patients with limited emotion regulation skills may need more help from the clinician to carefully modulate emotional engagement with the trauma memory (e.g., Jaycox, Zoellner, & Foa, 2002), and strategies for helping patients achieve optimal emotional engagement are suggested in the PE manual (Foa et al., 2007). Lastly, clinicians may need to increase patients' adherence with homework assignments through between-session phone contact and incorporation of others in the *in vivo* homework assignments. Moreover, these multi-morbid patients often have severe psychosocial stressors, making it more difficult for patients to plan and attend treatment sessions and complete homework assignments. For these patients, it may be helpful to enhance the treatment process by, for instance, providing PE in an intensive and brief format instead of traditional weekly sessions. In a pilot study (Hendriks et al., 2010), patients with PTSD with multiple comorbid disorders ($n = 4$) received 15 sessions of modified PE within one week. This intensive treatment was effective in decreasing PTSD symptoms, was tolerable for patients, had no serious adverse effects, and none of the patients dropped out. Another way to enhance PE is to use D-cycloserine, a cognitive enhancer of extinction learning, in combination with PE. In a randomized placebo-controlled trial (de Kleine, Hendriks, Kusters, Broekman, & van Minnen 2012), it was found that, in a subgroup of patients with more severe PTSD, 50-mg D-cycloserine significantly enhanced the exposure effects. Because patients with comorbidities may have more severe PTSD symptoms, this enhancing effect could be especially of clinical relevance for them. This extinction enhancement approach has been shown to accelerate gains and produce generally comparable outcome in other anxiety disorders (Norberg, Krystal, & Tolin, 2008). Also, other biological treatment approaches show promise in combination with PE, including paroxetine (Schneier et al., 2012) and cortisol (Yehuda, Bierer, Pratchett, & Malowney, 2010). Possibly, these combination therapies could especially be effective for co-morbid patients, because of their assumed complimentary mechanisms of action.

In conclusion, the existing research on PE for PTSD patients with severe comorbidity is encouraging. It seems that even severely comorbid PTSD patients can profit from PE in a tolerable and safe way. Typically, in individuals with dissociation, moderate-to-severe depression, mild BPD, and substance abuse, standard PE can be applied. In the case of comorbid substance dependence, psychosis, severe BPD, acute suicidality, and recent suicidal or serious non-suicidal self-injury, PE can also be effectively and safely applied within a treatment program monitoring and addressing the comorbidity.

Conflict of interest and funding

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