

Prevention of Trauma and Stressor-Related Disorders: A Review

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Posttraumatic stress disorder (PTSD) is a common, frequently chronic, and disabling condition which, along with acute stress disorder (ASD), is categorized as a trauma- and stressor-related disorder by the DSM-5. These disorders are unique in requiring exposure to a severe stressor, which implies that potential sufferers could be identified and helped before developing a disorder. Research on prevention strategies for stress-related disorders has taken a number of avenues, including intervention before and after trauma and the use of both psychosocial and somatic approaches. Despite advances in neurobiological understanding of response to trauma, clinical evidence for preventive interventions remains sparse. This review provides an overview of prevention approaches and summarizes the existing literature on prevention of ASD and PTSD, including clinical and preclinical studies. Given the potential benefits to trauma survivors and society, the development of effective preventive interventions should be given greater priority. Resources should be directed to adequately test promising interventions in clinical trials, and research should be conducted according to translational research principles in which preclinical research informs the design of clinical studies.

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a common, frequently chronic, and disabling condition that represents a major public health burden on par with other severe mental illnesses (Kessler, 2000). PTSD, along with acute stress disorder (ASD), is classified as a trauma- and stressor-related disorder by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). These disorders are unique in that diagnosis requires exposure to an extreme stressor such as threat of death, serious injury, or sexual violence. In the presence of such a clearly identifiable inciting event, clinicians may be positioned to intervene to prevent these disorders before they take hold. In light of the chronicity of PTSD and its associated suffering and impairment, successful prevention would clearly represent a major breakthrough benefiting trauma survivors and society. This opportunity has prompted research developing both psychosocial and pharmacologic approaches to prevent PTSD. Advances in neurobiological understanding could

engender tools both to identify trauma survivors at high risk of PTSD and to intervene before symptoms begin. However, despite the progress, clinical evidence for preventive interventions is distressingly underdeveloped (Stein and Lang, 2013). More efforts to leverage preclinical models to develop and test new prevention strategies are sorely needed.

ASD and PTSD are closely related. Many ASD patients later develop PTSD, although some individuals who go on to have PTSD do not meet ASD criteria in the aftermath of trauma (Bryant, 2011). In addition to exposure to a stressor, both disorders require additional symptoms, which may include intrusion, avoidance, changes in mood and cognition, and changes in arousal and reactivity. ASD requires symptoms to occur for at least 3 days and less than 1 month after the traumatic event, while PTSD requires symptoms to persist for at least 1 month. Studies have estimated that more than 80% of adults in the United States experience traumatic events that would qualify for ASD or PTSD diagnosis (Breslau, 2012). Categories of trauma that may result in ASD and PTSD include assaultive violence including military combat and sexual assault, other injuries such as motor vehicle accidents, and witnessing or learning of a sudden death or serious injury in another person. As a whole, assaultive violence is more likely to result in ASD and PTSD than other types of trauma and carries about a 20% risk for ASD and PTSD (Brewin *et al*, 2014). Overall, PTSD has an estimated 6.8% lifetime prevalence in the United States

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(Kessler *et al*, 2005). Importantly, efforts are underway to expand understanding of individual variability in posttraumatic responses based on different patterns of symptoms, time courses of symptoms, or underlying biological differences (Insel *et al*, 2010; Zoladz and Diamond, 2013). These investigations could lead to alternative classification systems beyond the DSM categories of ASD and PTSD.

In this review, we summarize research on the prevention of ASD and PTSD. We begin with a general overview and classification of approaches to prevention, along with special considerations for prevention of stress-related disorders. We consider alternative classification systems that account for variability in posttraumatic responses not captured by categorical DSM diagnoses, which may prove useful in individualized preventive interventions. We then briefly discuss primary prevention approaches including prevention of traumatic events as well as pretrauma interventions to improve resilience in the face of trauma. Then, we examine secondary prevention, including the targeting of interventions, psychosocial approaches, and somatic approaches. We conclude by discussing future directions in this important research area.

When the evidence for a particular intervention has been covered in detail in previous reviews, we will summarize the overall evidence rather than enumerate all studies. Interested readers are referred to the appropriate reviews for more detail. For example, two psychosocial interventions, psychological debriefing (PD) and cognitive behavioral therapy (CBT), have been the subject of numerous studies previously discussed in comprehensive reviews, and we do not describe each study in detail. In contrast, a larger number of separate somatic interventions have been tested in one or a handful of studies. For this reason, we discuss somatic approaches at somewhat greater length overall than psychosocial approaches, which is a consequence of our aim to address gaps in the current literature and maximize the overall utility of this review.

OVERVIEW OF PREVENTION APPROACHES

Historical Systems for Classifying Prevention Strategies

Discussions of disease prevention approaches need to contend with the question of what constitutes the scope of preventive interventions and how these interventions should be classified. We will describe two major historical systems for classifying disease prevention. The first system comprises primary, secondary, and tertiary prevention based on the stage of disease pathophysiology. The second system consists of universal, selective, and indicated prevention based on the population or group being targeted for prevention.

An early approach to classify preventive interventions was initially introduced in 1957 by the Commission on Chronic Illness and later broadened (Caplan, 1964; Commission on Chronic Illness, 1957). This classification scheme consists of

primary, secondary, and tertiary prevention and is based on a mechanistic account in which biologic disease onset precedes presenting symptoms. Primary prevention occurs before the biologic onset of disease and seeks to reduce disease incidence. Primary prevention efforts could take the form of general health promotion (eg, promotion of good nutrition) or attempts to prevent a specific disease (eg, vaccines). Prevention efforts could also focus either on reducing exposure to environmental risk factors or on improving individuals' resilience in the face of risk factors (Rose, 1992). Secondary prevention occurs after a disease has originated but before it becomes symptomatic. Pre-symptomatic diseases can be identified by screening programs. Finally, tertiary prevention refers to prevention of further decline or disability after a disease has already manifested, and overlaps substantially with treatment.

Gordon (1983) advanced a critique of the distinction between primary and secondary prevention on the basis that this distinction requires a mechanistic biologic understanding of disease and that it is often difficult to identify a specific origin in multifactorial, complex diseases that may have several preexisting risk factors. He proposed an alternative system in which prevention approaches are classified according to the population or group to which they are targeted. Universal prevention is targeted toward the entire population. Selective prevention is targeted toward a subgroup of the population, which has been shown to be at higher risk for the disorder. Subgroups could be distinguished by age, gender, occupation, family history, or other characteristics. Finally, indicated prevention is targeted toward individuals with a condition or abnormality that identifies them as being at high risk for disease, although they remain asymptomatic.

Special Considerations for Prevention of Trauma- and Stressor-Related Disorders

There are several special definitional considerations when discussing classification of preventive interventions for stress-related diseases (American Psychiatric Association, 2013). First, both ASD and PTSD require exposure to one or more traumas. Second, ASD and PTSD are defined in part according to the duration of symptoms after trauma exposure. ASD can be diagnosed when the duration of the disturbance is 3 days to 1 month after a trauma, while PTSD requires persistence of symptoms for more than 1 month. Finally, like other mental illnesses, ASD and PTSD are defined according to a set of symptoms, and the presence of asymptomatic disease might be considered a contradiction in terms (unlike for many physical health problems). The definitions of these disorders therefore present a challenge for the application of the distinction between primary and secondary prevention. Prior approaches to the prevention of stress-related diseases have considered any intervention before trauma exposure to be primary prevention, while any intervention after trauma exposure but before development of PTSD (ie, before 1 month of symptoms) to be

secondary prevention (Skeffington *et al*, 2013; Stein and Lang, 2013). For the purposes of this review, we will adopt the same convention. Primary prevention includes any intervention designed to prevent trauma exposure as well as attempts to improve resilience before a trauma. Primary prevention approaches could be either universal or selective. Secondary prevention could occur for asymptomatic individuals, but also for those who have symptoms but do not yet meet criteria for PTSD (eg, those having symptoms for less than 1 month). Secondary prevention could be targeted toward individuals meeting criteria for ASD. The distinction between ASD treatment and PTSD prevention may not always be clear, but we will focus on studies that assessed subsequent development of PTSD rather than merely change in ASD symptoms. Tertiary prevention (interventions after onset of PTSD which overlap with PTSD treatment) will not be considered in this review.

Categorical and Dimensional Approaches to Posttraumatic Symptoms

Recent perspectives on mental disorders including trauma and stressor-related disorders have emphasized the importance of individual heterogeneity within DSM diagnoses in terms of symptoms, time course, underlying biological dysfunctions, and other factors. In particular, patients meeting criteria for PTSD may differ in terms of underlying biology, symptom profile, course of illness, and response to interventions. To optimize prevention strategies for all trauma survivors, it may be necessary to account for variability that is not captured by a categorical DSM diagnosis. Recognizing this problem, the National Institute of Mental Health (NIMH) has launched the Research Domain Criteria (RDoC) project. RDoC aims to create a framework to develop improved classification schemes based on new pathophysiological findings, including discoveries in genomics and neuroscience, rather than solely based on symptoms (Insel *et al*, 2010). While a full overview of alternatives to the DSM classification scheme for trauma and stressor-related disorders is outside the scope of this review, we will briefly introduce a handful of approaches that may prove useful in developing and targeting preventive interventions.

Alternative approaches to classification of posttraumatic pathology have begun yielding insights that may be useful when developing and targeting preventive interventions. Such studies have used a number of statistical methods to identify patterns in posttraumatic symptoms, both in cross-sectional and in longitudinal designs. Confirmatory factor analysis (CFA) is used to uncover underlying factors that reflect the latent structure of diagnoses such as PTSD. Application of this method has yielded two prominent four-factor models of PTSD (King *et al*, 1998; Simms *et al*, 2002). This research influenced the change in criteria from DSM-IV (which includes three PTSD symptom clusters) to DSM-5 (which includes four) (American Psychiatric Association, 2000, 2013). However, recent competing models

have also been proposed, ranging from two factors to seven factors (Forbes *et al*, 2015a; Zelazny and Simms, 2015).

Latent class analysis (LCA) is a method that uses observed symptoms to identify subgroups in a population, which are not directly observable. Unlike CFA, which identifies underlying dimensional factors, LCA can be used to assign individuals to discrete groups. LCA has been used to characterize PTSD presentation in terms of severity (Steenkamp *et al*, 2012), personality profiles of PTSD patients (Forbes *et al*, 2010), a dissociative subtype of PTSD (Wolf *et al*, 2012), PTSD comorbidity (Galatzer-Levy *et al*, 2013), and psychopathology after trauma (not limited to PTSD) (Forbes *et al*, 2015b). A related method, latent transition analysis (LTA), has been used to examine the movement of trauma-exposed individuals between subgroups over time (Forbes *et al*, 2015b).

Another type of method categorizes trauma-exposed individuals based on their trajectory of symptoms over time. Rather than characterizing the overall mean level of symptoms at each time point, these methods separate individuals into groups following different trajectories over time. For example, a 6-year study using latent growth mixture modeling (LGMM) identified five distinct trajectories of PTSD symptoms after injury, including resilient (representing a majority of individuals), chronic, recovery, worsening/recovery, and worsening (Bryant *et al*, 2015). Improved understanding of different time courses of symptoms after trauma could help elucidate the influence of preventive interventions on different individuals.

As reviewed above, new approaches to classification of posttraumatic symptoms may improve prevention efforts by tailoring interventions based on factors specific to an individual. Nevertheless, most research to date has relied on DSM criteria, and progress has been made in the identification and evaluation of preventive interventions using these criteria. For this reason, the majority of studies reviewed here use DSM criteria. Future research will likely evince an expansion of efforts to more fully account for variability in trauma-exposed individuals, potentially resulting in better preventive efficacy through targeted interventions.

PRIMARY PREVENTION

Prevention of Traumatic Incidents

One approach to prevention of stress-related disorders is the prevention of exposure to trauma. Traumatic events that can lead to PTSD include assaultive violence (including military combat trauma, rape, and physical assault), other injuries (including motor vehicle accidents and other accidents), and learning about sudden death or injuries of loved ones. Assaultive violence is more likely to result in PTSD than other traumas (Breslau, 2012). Efforts to prevent injuries and assaults include a large variety of public health and policy interventions, which are beyond the scope of this review. Injury prevention strategies include recall of defective motor

vehicles, implementation of blood alcohol limits for drivers, and addition of separation barriers to freeways, among many others (Kraus *et al*, 1998). Interventions to reduce assaultive violence include educational programs, strengthening of community-based support services, laws limiting access to firearms, and attempts to improve identification of victims of violence by medical personnel to prevent further victimization (Rosenberg *et al*, 1998). Strategies to prevent trauma include universal measures and selective measures (such as those targeting low socio-economic status families).

Pre-Trauma Resilience Building

Hourani *et al* (2011) reviewed studies of predeployment interventions meant to mitigate the impact of combat-related stressors in military populations. Approaches included psychoeducation programs to educate military personnel about reactions to trauma as well as stress inoculation training, which aims to improve ability to cope with stressors. However, most studies were descriptive and did not include a control group for comparison of outcomes. A controlled, non-randomized, parallel group study compared mental health outcomes between military personnel deployed to Iraq who received pre-operational stress briefing and those who did not and found no difference in PTSD, other mental health disorders, or alcohol misuse (Sharpley *et al*, 2008).

Skeffington *et al* (2013) performed a review of primary prevention of PTSD, which was not restricted to studies in military populations. The literature was extremely limited, with only seven studies identified as meeting eligibility criteria. Studies of pretrauma psychoeducation were non-randomized and were insufficient to make any determination concerning efficacy. A handful of studies examining interventions combining psychoeducation and skills building either used non-randomized design or did not measure PTSD symptoms at follow-up. Finally, two very small studies of police officers showed that stress management training could reduce physiologic arousal in response to a simulated stressor, but did not measure response to actual stressors and did not measure actual PTSD symptoms. Overall, the authors concluded that there is currently insufficient evidence for any primary prevention strategy for PTSD and that more research is needed in this area.

SECONDARY PREVENTION

Targeting Interventions

Overall, fewer than 10% of individuals exposed to a traumatic event go on to develop PTSD, although the rate for assaultive violence is approximately 20% and for rape is as high as 50% (Breslau, 2012). If techniques are available to identify individuals at highest risk for developing PTSD after a trauma, then preventive interventions could be targeted to those individuals. There is an extensive body of research on risk factors for PTSD, and a full summary is outside the

scope of this review. We will therefore only provide a very brief introduction to the topic. It should be emphasized that the risk factors reviewed here have poor sensitivity and specificity in identifying individuals that will develop PTSD, and as yet the only clinically useful factor in targeting intervention has been the emergence of symptoms (eg, ASD) in the aftermath of trauma. However, future risk prediction tools that incorporate an array of risk factors may be more successful in identifying individuals most likely to benefit from intervention.

Research has indicated that risk factors for PTSD include female gender, preexisting psychiatric disorders, family history of psychiatric disorders, lower IQ, personality traits such as neuroticism, and low social support (Breslau, 2012). In addition to these risk factors, a recent review also identified psychophysiological predictors of PTSD, most of which were related to arousal (DiGangi *et al*, 2013). These included startle reactivity, salivary elevations in the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), alterations in the glucocorticoid system, attentional bias away from fearful faces, and reduced extinction of a conditioned emotional response. Research has established that the development of PTSD after trauma is moderately heritable, and a growing number of studies have attempted to identify genes associated with PTSD. Candidate gene studies, in which genes are selected for study based on biological pathways thought to have a role in PTSD, have identified a number of genes possibly associated with risk of PTSD. These include genes involved in the hypothalamic-pituitary-adrenal (HPA) axis, the noradrenergic, serotonergic and dopaminergic systems, memory consolidation, and other biological systems (Almli *et al*, 2014; Logue *et al*, 2015). However, some of these candidate gene studies have failed to replicate. Another approach to identify genetic variants associated with PTSD is a genome-wide association study (GWAS), in which genetic variation is examined without any prior hypotheses about particular genes. To date, four GWAS of PTSD have been published, which have identified five loci associated with PTSD (Logue *et al*, 2015). It should be noted that each identified genetic variant likely accounts for only a small proportion of variance in the disorder (Nievergelt *et al*, 2015).

In addition to pre-trauma risk factors, risk for PTSD could also be stratified based on reactions in the immediate aftermath of trauma. Bryant (2011) reviewed 22 studies that assessed for ASD within 1 month of trauma and later assessed for PTSD. Positive predictive power was fairly high, with most studies finding that more than half of individuals who met ASD criteria went on to develop PTSD. However, sensitivity was low, as indicated by the fact that the majority of trauma survivors who went on to develop PTSD did not meet full ASD criteria. It should be noted that subsequent to this review, DSM-5 removed the requirement for dissociative symptoms for ASD diagnosis, thereby making the diagnosis less stringent (American Psychiatric Association, 2013). Several studies have shown that removal of the requirement for dissociative symptoms improves the sensitivity in

predicting subsequent PTSD (Bryant, 2011). A recent study confirmed that ASD diagnosed based on DSM-5 criteria compared with DSM-IV has greatly improved sensitivity with comparable specificity in predicting subsequent PTSD (Bryant *et al*, 2014).

Research has suggested that measures of biological and cognitive mechanisms in the acute aftermath of trauma may offer more accurate prediction of PTSD than any constellation of acute symptoms (Bryant, 2003). Markers in the acute period after trauma that predict development of PTSD include elevated resting heart rate and respiration rate (Bryant *et al*, 2008), low plasma levels of gamma amino-butyric acid (GABA) (Vaiva *et al*, 2004), and maladaptive cognitive factors including negative appraisals (Dunmore *et al*, 2001).

As noted above, no individual risk factors for PTSD exhibit sufficient sensitivity and specificity to confidently identify individuals who will develop the disorder. An approach that may overcome this difficulty is the use of machine learning methods that integrate a number of clinical and biological risk factors to identify individuals at highest risk for developing the disorder. A recent study of 957 trauma survivors used machine learning methods to predict PTSD status at 15 months based on clinical and biological information collected within 10 days of trauma (Galatzer-Levy *et al*, 2014). The machine learning approach using a combination of factors outperformed ASD symptoms in predicting PTSD. In another study, machine learning methods were used to create a prediction algorithm for PTSD on the basis of retrospectively assessed risk factors (including trauma type, socio-demographics, prior history of trauma, and mental illnesses) for 9791 subjects (Kessler *et al*, 2014). Over 95% of all PTSD cases were associated with the 10% of trauma exposures classified by the algorithm as having the highest PTSD risk. The authors note that the approach will need to be applied in a prospective study to validate the findings. Taken together, research on PTSD risk factors suggests that prediction tools may be developed to stratify risk for PTSD and allow for targeted secondary prevention strategies.

Psychosocial Approaches

A number of psychosocial interventions have been tested for prevention of PTSD. Approaches differ in their components and theoretical grounding, the number of sessions, timing of the intervention, and targeting (eg, whether they are delivered only to patients with ASD symptoms or to all trauma survivors). The earliest approaches tended to be single-session interventions, often delivered in group settings to all survivors of a trauma. Later approaches used multi-session interventions based on cognitive behavioral therapy (CBT) principles and frequently targeted toward patients with full or subclinical ASD. In addition to these approaches, a number of other interventions have also been studied. The evidence for several psychosocial approaches to PTSD prevention, including single session and CBT-based

interventions, has been examined in depth in several reviews (Agorastos *et al*, 2011; Bryant, 2007; Forneris *et al*, 2013; Kearns *et al*, 2012; Rose *et al*, 2002). For this reason, we will summarize evidence for each approach but will not describe each study separately. Readers interested in a more comprehensive account of the evidence for these approaches are referred to the cited reviews.

Psychological debriefing (PD) is a single-session intervention provided to trauma survivors in the early aftermath of a traumatic incident. PD originated in the military, where commanders would meet with personnel after a battle to discuss their experiences with the intention of improving morale and preparing for future combat (Litz *et al*, 2002). There are several different forms of PD, with critical incident stress debriefing (CISD) being among the most widely used (Mitchell and Everly, 1993). CISD includes a number of components, including discussion of the traumatic event, sharing of thoughts and emotions about the event, and education about typical stress reactions and stress management strategies. While CISD was originally designed specifically for emergency service personnel and disaster workers, similar interventions have been used outside this context, such as in victims of violent crime (Rose *et al*, 1999). Despite widespread implementation, evidence has accumulated that PD is not an effective intervention in preventing PTSD. A systematic review of interventions to prevent PTSD by Forneris *et al* (2013) concluded that PD did not reduce PTSD incidence or symptom severity, while a Cochrane Review concluded that PD was either equivalent to or worse than control or psychoeducation in preventing or reducing PTSD severity (Rose *et al*, 2002). Overall, PD is not supported by the evidence as an intervention to prevent PTSD.

While single-session PD interventions do not appear effective at preventing PTSD, multiple session interventions using a CBT framework have received some support. These interventions are adapted from CBT approaches, which are known to be effective treatments for chronic PTSD (Harvey *et al*, 2003) and include psychoeducation, exposure, cognitive restructuring, and anxiety management (Bryant, 2007). These interventions occur in the first weeks or months after trauma and typically consist of 4–12 sessions (Kearns *et al*, 2012) with the most frequent length being about 5 sessions (Bryant, 2007). The largest trial is the Jerusalem Trauma Outreach and Prevention Study, which randomized a total of 242 trauma survivors with early PTSD symptoms to either 12 sessions of one of two forms of CBT (prolonged exposure or cognitive therapy), the selective serotonin reuptake inhibitor (SSRI) escitalopram or placebo, or to a waiting list (Shalev *et al*, 2012). Results indicated that both prolonged exposure and cognitive therapy were effective in preventing PTSD at 5 months (with approximately 20% of subjects meeting PTSD criteria compared with nearly 60% on the waiting list). Both therapy groups outperformed escitalopram, which was equivalent to placebo. A later study reanalyzed the same data using LGMM to assess different symptom trajectories of subgroups of patients (Galatzer-Levy *et al*, 2013). The

authors identified three subgroups based on symptom trajectories: rapid remitting, slow remitting, and non-remitting. Furthermore, the authors concluded that CBT accelerated recovery of the slow remitting group but did not affect the other two groups. The use of LGMM and similar methods may help clarify the influence of preventive interventions on specific subgroups of patients and may ultimately help target treatment to those most likely to benefit.

In addition to the Jerusalem Trauma Outreach and Prevention Study, smaller trials have also found evidence for the efficacy of CBT in patients who exhibit early symptoms. These studies are summarized in several reviews, which have concluded that CBT is effective at reducing subsequent PTSD incidence or severity in individuals with ASD (Agorastos *et al*, 2011; Bryant, 2007; Kearns *et al*, 2012). However, in another review, Forneris *et al* (2013) stated that the evidence in support of early CBT remains tentative due to limited evidence. A Cochrane Review has also concluded that CBT is an effective treatment for ASD (Roberts *et al*, 2010).

The utility of CBT in trauma survivors who do not meet criteria for ASD is less clear. Studies of psychological interventions administered to all trauma survivors irrespective of symptoms have typically utilized counseling interventions rather than CBT. A meta-analysis including eight such studies found no significant overall effect (Roberts *et al*, 2009). The same meta-analysis found that CBT interventions were effective at preventing PTSD when targeted to individuals exhibiting traumatic stress symptoms, with the greatest effect for individuals meeting full criteria for ASD or acute PTSD. A more recent RCT compared a three-session exposure-based intervention beginning in the emergency department with assessment only in 137 adult trauma survivors (Rothbaum *et al*, 2012). The intervention was delivered to all trauma survivors regardless of symptoms and was initiated as early as possible based on preclinical evidence suggesting that early extinction training can block fear memory consolidation. Participants receiving the intervention had lower levels of posttraumatic stress reactions at 4- and 12-week follow-up. Two follow-up studies by the same group examined predictors of PTSD symptoms and response to the exposure-based intervention. The first study found that dissociation after trauma predicted poor response to the intervention and also predicted greater PTSD symptoms in the control group (Price *et al*, 2014). The second study found that a group of genetic variants related to the stress response appeared to confer risk of increased PTSD symptoms in control subjects, but that this increased risk appeared to be mitigated by the exposure intervention (Rothbaum *et al*, 2014). More studies of CBT-based interventions in trauma survivors irrespective of symptoms are needed to draw definitive conclusions about their utility in this population. Overall, the balance of evidence indicates that CBT is effective at preventing PTSD for individuals with ASD, and possibly those with sub-threshold or no symptoms, although more research is needed.

Another multi-session intervention that is designed specifically to prevent PTSD in trauma-exposed youth is the Child and Family Traumatic Stress Intervention (CFTSI). In this approach, both child and caregiver undergo four sessions designed to improve caregiver support for the child and to improve coping behaviors. A study was performed in which 106 trauma-exposed youth reporting at least one new distressing posttraumatic symptom were randomized to receive CFTSI or a four-session supportive control intervention (Berkowitz *et al*, 2011). At 3 months, the CFTSI group had a lower rate of both full and partial PTSD diagnoses.

Another model for PTSD prevention is a collaborative care approach, in which trauma survivors are assigned a case manager and then possibly referred for CBT, pharmacologic management, or a combination on an individual basis depending on symptoms and patient preferences. One RCT has tested this approach in 207 acutely injured hospitalized patients and found that those receiving the collaborative care intervention had reduced PTSD symptoms over the year after injury compared with those who received care as usual (Zatzick *et al*, 2013). While more studies are needed to test this approach to PTSD prevention, the use of case management to identify individual trauma survivors who require psychological or pharmacologic interventions may represent a promising avenue to structure prevention efforts.

Several other psychosocial approaches to PTSD prevention have been tested, mostly in small studies. A memory structuring intervention that aims to shift processing of traumatic memories from uncontrolled affective processing to controlled cognitive and linguistic processing has shown mixed results in two small studies (Gidron *et al*, 2001, 2007). A limited body of evidence examining psychoeducation approaches does not currently support the efficacy of these interventions in preventing PTSD (Wessely *et al*, 2008). Battlemind, an intervention for military personnel exposed to combat trauma which was adapted from PD, found preliminary support from a study randomized at the platoon level but did not show an effect in another study (Adler *et al*, 2011; Mulligan *et al*, 2012). A study using an informational video designed for sexual assault survivors found reduced PTSD symptoms at 6 weeks only for women with a prior history of sexual assault, with the effect disappearing at 6 months (Resnick *et al*, 2007). Overall, more research is needed on these interventions before they can be considered effective at preventing PTSD.

In summary, the psychosocial intervention for PTSD prevention with the most evidence is brief CBT. Most studies have examined this approach in individuals either meeting ASD criteria or with subclinical traumatic symptoms. Due to the lack of evidence, no firm conclusions can be drawn about the efficacy of brief CBT in trauma survivors without significant symptoms. There is some evidence for a collaborative care approach in which acutely injured patients are assigned a case manager who can then refer patients for psychotherapy or medication management based on individual needs. However, more research is needed on this approach. PD appears to be ineffective in preventing PTSD

among trauma survivors. Finally, a number of other interventions have been developed, but currently lack enough evidence to conclude they are effective in preventing PTSD. More research is needed, both to further test various preventive interventions and to identify which individual trauma survivors are most likely to benefit from preventive interventions.

Somatic Approaches

Safe and effective pharmacologic interventions to prevent stress-related disorders after trauma could be widely implemented and result in a substantial public health impact. However, the current evidence base for such approaches remains very small. Only a handful of interventions have been tested in RCTs, and many of these clinical studies have been small. Most approaches tested in RCTs have not found clear and consistent support. Some interventions have been tested in observational studies but not yet examined in RCTs. Finally, rodent studies have identified a number of modulators of the stress response and memory consolidation which may be useful for PTSD prevention, but have not been tested in humans.

At this time, the pharmacologic intervention with the strongest evidence for PTSD prevention is glucocorticoid administration. Endogenous glucocorticoids function to orchestrate physiologic and behavioral responses to maintain homeostasis in the context of stressful events, and inadequate release of glucocorticoids in response to a stressor may interfere with information processing and disrupt long-term memory integration (Zohar *et al*, 2011). Human studies have found that lower cortisol levels immediately after a trauma predict future PTSD symptoms (Delahanty *et al*, 2000; McFarlane *et al*, 1997). Animal research has shown that rats with a hypoactive HPA axis are more prone to behavioral disruption after a stressor than rats with a hyperactive HPA axis, and also that administration of a glucocorticoid after a stressor reduces PTSD-like behaviors (Cohen *et al*, 2008).

Two studies in humans examined the effect of the administration of stress doses of hydrocortisone in critically ill patients or patients undergoing major surgery. The first study recruited 20 subjects from a larger RCT in which patients with septic shock were administered hydrocortisone or a placebo (Schelling *et al*, 2001). Patients who received hydrocortisone were less likely to meet criteria for PTSD at follow-up (median 31 months after hospital discharge). The second study was a RCT in which 91 patients undergoing cardiac surgery received either stress doses of hydrocortisone or standard treatment and found that patients receiving hydrocortisone had lower PTSD symptoms at 6-month follow-up (Schelling *et al*, 2004). These results are also supported by a retrospective case-control study in which patients with septic shock who had received high-dose hydrocortisone had lower incidence of PTSD several years after ICU discharge than those who had not (Schelling *et al*, 1999). These studies suggest that stress dose glucocorticoids

as an intervention to prevent PTSD in individuals undergoing critical illness or major surgery deserves more study, but by themselves cannot be generalized to contexts other than critical illness or major surgery.

Two RCTs have tested hydrocortisone in adults exposed to traumatic events who are not critically ill. In one trial, 25 patients with symptoms of ASD received either a single high dose of hydrocortisone or placebo within 6 h of exposure to a traumatic event (Zohar *et al*, 2011). Patients receiving hydrocortisone had significantly lower PTSD symptoms at 3 months. In another trial, 64 traumatic injury patients received a 10-day course of low-dose hydrocortisone or placebo initiated within 12 h of trauma, and those receiving hydrocortisone had lower PTSD symptoms at 3 months (Delahanty *et al*, 2013). Overall, while glucocorticoids for PTSD prevention need more study, preliminary studies have shown promise that they may be effective for some trauma survivors.

Another pharmacologic intervention that has been tested for prevention of stress-related disorders is propranolol, a beta-adrenergic antagonist. Preclinical studies have shown that the adrenergic system is involved in memory enhancement in the context of stress and hyperarousal, and that administration of propranolol can block memory consolidation after a stressful learning task (Cahill *et al*, 2000; Southwick *et al*, 1999). An early small non-randomized study that compared 11 trauma survivors with tachycardia who received a course of propranolol with eight similar patients who refused propranolol found that patients receiving propranolol exhibited lower levels of PTSD symptoms at 2 months (Vaiva *et al*, 2003). However, several RCTs have not found an effect of propranolol in preventing PTSD. Three RCTs consisted of adults who had experienced a traumatic event and presented to an emergency department or were admitted to a trauma center. In two studies, propranolol was compared with placebo (Hoge *et al*, 2012; Pitman *et al*, 2002), and in another study propranolol was compared with both placebo and gabapentin (Stein *et al*, 2007). None of these trials found significant differences in PTSD incidence or PTSD symptoms between patients receiving propranolol or placebo. However, Pitman *et al* (2002) did find reduced physiologic reactivity to trauma-related imagery at 3 months in those who had received propranolol. Another RCT compared a course of propranolol with placebo in pediatric injury patients and also failed to find an overall difference in PTSD symptoms, although girls receiving propranolol actually exhibited higher PTSD symptoms than those receiving placebo (Nugent *et al*, 2010). A retrospective chart review of 363 pediatric burn patients who had received propranolol or placebo as part of an earlier RCT found no significant difference in rates of ASD between patients receiving propranolol vs placebo (Sharp *et al*, 2010). Differences in study population or time of administration may influence the outcome of studies of propranolol. For example, Pitman *et al* administered propranolol within 6 h of trauma, while other studies allowed for later administration. It should also be noted that in some

trials only a relatively small portion of eligible subjects consented to participate in medication studies. Overall, current evidence does not support propranolol as an intervention to prevent stress-related disorders.

Several SSRIs have shown efficacy in the treatment of chronic PTSD (Jonas *et al*, 2013). Two RCTs have examined the efficacy of early initiation of an SSRI in preventing PTSD. As part of the Jerusalem Trauma Outreach and Prevention Study (discussed above in the context of CBT interventions), 46 adult trauma survivors with PTSD symptoms were randomized to receive escitalopram or placebo beginning approximately 20 days after trauma (Shalev *et al*, 2012). There were no differences in PTSD symptoms at 5-month and 9-month follow-up. As noted above, prolonged exposure and cognitive therapy (two forms of CBT) were found to be effective and outperformed escitalopram in the same trial. Another RCT administered sertraline or placebo to 26 child and adolescent burn patients and found greater reduction in PTSD symptoms at 24 weeks among those receiving sertraline as assessed by parent report, but not by child report (Stoddard *et al*, 2011). Based on these two small samples, evidence for SSRIs in preventing PTSD remains equivocal.

Benzodiazepines are effective for anxiety and are frequently prescribed to chronic PTSD patients, although evidence does not support their efficacy for this disorder and there are a number of potential adverse reactions in this population (Lund *et al*, 2012). Preclinical studies have found that pre-administration of benzodiazepines before exposure to inescapable stress prevents the release of norepinephrine from the locus coeruleus, which has been posited to contribute to the development of PTSD (Bremner *et al*, 1993). Benzodiazepines also reduce arousal, decrease distress, and inhibit memory consolidation (Barbee, 1993). These findings led to the idea that benzodiazepines may prevent PTSD if administered in the acute aftermath of a trauma. However, two small clinical studies do not support benzodiazepines in preventing PTSD. A non-randomized study compared 13 trauma survivors exhibiting symptoms such as anxiety or insomnia who received a course of either alprazolam or clonazepam with 13 matched controls who did not receive a benzodiazepine, but found no difference in PTSD symptoms at 1-month and 6-month follow-up (Gelpin *et al*, 1996). At 6 months, 9 of 13 benzodiazepine subjects and 3 of 13 controls met PTSD criteria. Another study randomized 22 survivors of life-threatening injuries with PTSD symptoms to receive a 7-day course of temazepam or placebo and found no difference in PTSD severity at 6-week follow-up (Mellman *et al*, 2002). The risks of benzodiazepines should also be considered, given the potential for tolerance and dependency and concern for increased morbidity and mortality (Ashton, 2005; Kripke, 2009). Benzodiazepines are often used to treat insomnia, a common PTSD symptom, but are not recommended for long-term insomnia treatment (Riemann *et al*, 2015). Overall, there is currently no clinical evidence for the efficacy of benzodiazepines for the prevention of PTSD.

Several other pharmacologic interventions for PTSD prevention have been tested in prospective clinical trials. Trauma survivors treated with gabapentin, an anticonvulsant with some evidence as an anxiolytic, did not differ in PTSD symptoms from patients treatment with placebo or propranolol in an RCT (Stein *et al*, 2007). A study in which 137 adult patients requiring mechanical ventilation were randomized to receive light sedation or deep sedation found no significant differences in PTSD symptoms at 4 weeks (Treggiari *et al*, 2009). An open label study tested prevention of PTSD with omega-3 fatty acids, which have been shown in animal models to promote hippocampal neurogenesis, a process that may facilitate clearance of fear memories and thereby attenuate the development of PTSD (Kawakita *et al*, 2006; Kitamura *et al*, 2009). Eleven survivors of accidental injury were given a course of omega-3 fatty acid supplementation, and one patient met criteria for PTSD at 12-week follow-up, although there was no control group for comparison (Matsuoka *et al*, 2011). Overall, current evidence is not adequate to support any of these interventions for the prevention of PTSD.

Several medications, including opioids, ketamine, and albuterol, have shown a possible connection with lower likelihood of PTSD in observational studies, but have not yet been tested in clinical trials. Preclinical evidence suggests that opioids may impair fear conditioning in the amygdala and could thereby reduce the likelihood of PTSD (Good and Westbrook, 1995). Two prospective observational studies have examined the correlation between morphine administration and subsequent PTSD in children with burns. The first study found a significant correlation between morphine dose in the hospital and decrease in PTSD symptoms over 6 months (Saxe *et al*, 2001). The second study, which had only 11 completers, found a non-significant correlation between morphine dose in the hospital and decrease in PTSD symptoms over 6 months, but a significant correlation between morphine dose and decrease in the arousal cluster of symptoms (Stoddard *et al*, 2009). Two chart reviews have examined the association between morphine and subsequent PTSD symptoms in adult trauma survivors. One study compared acute morphine dose in traumatic injury patients who later developed PTSD with those who did not and found that PTSD patients had received significantly lower doses of morphine (Bryant *et al*, 2009). A second study compared injured military personnel who received a diagnosis of PTSD with those who did not in terms of early administration of morphine and found that a lower proportion of those with PTSD had received morphine (Holbrook *et al*, 2010). While several observational studies have found evidence that administration of morphine after a trauma is associated with lower likelihood of developing PTSD, this has not been tested in RCTs and needs further study before a causal link can be confirmed.

Ketamine, an NMDA receptor antagonist used for anesthesia and analgesia, appears to have rapid antidepressant properties and may be beneficial for chronic PTSD

(Rasmussen, 2015). However, observational studies examining a possible link between ketamine administration and subsequent rates of PTSD have shown mixed results. Preclinical research is equivocal, with evidence showing that ketamine has anxiolytic effects but another study showing that administration of ketamine after a stressor does not prevent behavioral disruption (Juven-Wetzler *et al*, 2014; Zhang *et al*, 2014). A retrospective study of 56 injured accident victims found PTSD symptoms approximately 1 year post-accident were higher in those who had received (S)-ketamine during ambulance transportation, but were equal in those receiving racemic ketamine or opioids (Schönenberg *et al*, 2005). A chart review of 147 military service members who underwent surgery after a burn found that prevalence of subsequent PTSD was lower among those who had received intraoperative ketamine than those who had not (McGhee *et al*, 2008). However, a subsequent retrospective study by the same group that included 289 burned service members found no difference in incidence of PTSD among those who had received ketamine compared with those who had not (McGhee *et al*, 2014). It should be noted that intraoperative ketamine may or may not have similar effects to sub-anesthetic doses of ketamine administered to a conscious patient. More evidence is needed to resolve the inconsistent findings on the relationship between ketamine administration and subsequent PTSD.

Albuterol is a beta adrenergic agonist that is used for asthma, but has also been shown in animal models to impair avoidance learning, which is thought to be related to fear conditioning (Eliás *et al*, 2004). An observational study assessed 38 motor vehicle accident survivors who had received albuterol after the accident (for asthma attacks or respiratory insufficiency) and 337 who did not receive albuterol (Kobayashi *et al*, 2011). At 6 weeks and 1 year after the accident, patients who had received albuterol exhibited lower levels of PTSD symptoms than those who had not. No RCTs have tested the efficacy of albuterol for PTSD prevention.

A number of approaches to PTSD prevention have shown promise in preclinical studies but have not yet been tested in clinical trials. Some studies have focused on neuropeptide systems, which are involved in regulating anxiety and the stress response. Neuropeptide Y (NPY), a regulator of the HPA axis and noradrenergic system that alters stress-related behaviors, was shown in an animal model to prevent anxious behaviors when administered intranasally after exposure to a stressor (Sabban *et al*, 2014). Oxytocin, another neuropeptide that is involved in social bonding and the attenuation of anxiety in response to stress, was found to decrease subsequent anxiety-related behaviors when administered after a stressor in rats (Cohen *et al*, 2010). Nociceptin is an opioid-related neuropeptide, which has receptors expressed in the central amygdala. A study found that an agonist of the nociceptin receptor (NOP-R) interfered with fear memory consolidation after a severe stressor in mice (Andero *et al*, 2013). Corticotropin-releasing factor (CRF) is a peptide hormone that has a central role in activating the

HPA axis in response to stress. An animal study found that blockade of the CRF1 receptor prevents initiation and consolidation of anxiety-like behavior after a severe stressor (Adamec *et al*, 2010).

Other neurotransmitter systems have also been targeted in preclinical studies of prevention strategies for PTSD. The cannabinoid system is thought to be an important regulator of anxiety, stress, and emotional learning, and a rat study found that administration of a cannabinoid receptor agonist after a trauma prevented trauma-induced alterations in anxiety behaviors (Ganon-Elazar and Akirav, 2012). Adenosine is a nucleoside that has been found to decrease activity in the amygdala and noradrenergic system, exert anxiolytic effects, and to be neuroprotective. A mouse study found that administration of an adenosine derivative after trauma exposure alleviated anxious behaviors and memory deficits and also prevented cell death in the hippocampus (Huang *et al*, 2014).

Other strategies tested in preclinical studies do not target specific neurotransmitter systems but instead modulate immune responses to stress or memory consolidation processes. Based on evidence that T-cell recruitment to the brain may help maintain brain functions and improve coping in the context of stress, mice were immunized with a central nervous system-related peptide before exposure to a stressor, and were found to develop reduced stressor-related anxiety and acoustic startle response (Lewitus *et al*, 2008). Microinjection of anisomycin, a protein synthesis inhibitor, after stress exposure reduced subsequent anxiety-like and avoidant behavior, presumably by disrupting the process of traumatic memory consolidation (Cohen *et al*, 2006). Finally, a rat study found that sleep deprivation after exposure to a stressor ameliorated long-term PTSD-like behavioral disruptions, possibly by interfering with traumatic memory consolidation (Cohen *et al*, 2012).

In summary, no pharmacologic interventions to prevent PTSD currently have enough evidence to justify clinical use. The intervention with the most evidence at this time is hydrocortisone, which has shown promise in two RCTs of patients who were critically ill or undergoing major surgery as well as two RCTs in adult trauma survivors. Based on prospective clinical studies, the evidence for SSRIs in preventing PTSD is equivocal based on two small studies, while propranolol and benzodiazepines have not found support. Observational studies have found a link between opioid administration after trauma and lower rates of subsequent PTSD, although this has not been tested in RCTs. One small observational study found evidence of a link between albuterol administration and decreased PTSD, while findings on the effect of ketamine have been mixed. Preclinical research has identified a number of promising strategies for PTSD prevention, including modulators of the stress response and strategies to disrupt traumatic memory consolidation.

SUMMARY AND CONCLUSIONS

Overall, evidence for preventive interventions for ASD and PTSD is scarce. Some interventions have not been supported by the evidence, while others have shown promise but require further testing. Approaches to prevention of ASD and PTSD have taken a number of different avenues. While outside the scope of this review, public policy and public health interventions to reduce violence, traumatic injuries, and other traumatic events have a major role to play in reducing the incidence of ASD and PTSD. There may also be opportunities to bolster resilience in vulnerable individuals before trauma, although research in this area is lacking. To date, most clinical research has focused on secondary prevention of PTSD.

Optimal targeting of secondary prevention interventions remains largely unexplored. Most approaches have either targeted all individuals experiencing a trauma or have targeted individuals with acute stress symptoms. There is a growing body of research on predictors of PTSD (based on pretrauma factors and reactions after trauma), which may be useful in directing interventions to individuals at highest risk. However, the clinical utility of currently known risk factors for this purpose has not been tested.

The most studied psychosocial interventions to prevent PTSD are single-session PD approaches and multi-session CBT-based approaches. Evidence indicates that PD is not an effective intervention to prevent PTSD. On balance, research suggests that CBT is effective when ASD symptoms are present, but its usefulness in the absence of posttraumatic symptoms is unclear. Several other psychosocial interventions, such as a collaborative care approach, have shown promise but require more study.

Only a handful of medications have been tested in prospective studies, and many results have been disappointing. There is some evidence that hydrocortisone may be effective in preventing PTSD, but appropriate patient selection needs to be clarified in terms of risk/benefit tradeoffs. More research on this approach is needed. Other medications, such as propranolol, are not supported by current evidence. Observational studies have found a link between opioid administration and lower rates of subsequent PTSD, but opioids have not been tested in RCTs. If opioids are found to be effective, then risks and benefits will need to be considered when determining appropriate patient selection. A number of preclinical studies have identified medications that modulate the stress response, fear conditioning, and memory consolidation and appear to prevent PTSD-like behaviors in animal models. These promising strategies have not yet been tested in clinical trials.

FUTURE RESEARCH DIRECTIONS

The promise of preventive interventions for stress-related disorders has not yet been fulfilled. The clinical benefits of prevention can most likely be achieved by pursuing a translational research strategy in which the design of clinical

studies is rigorously based on neurobiological discoveries. It is crucial to direct resources to adequately test emerging interventions so that preclinical findings can enhance the lives of trauma survivors and alleviate the public health burden of stress-related disorders.

Proper patient selection will be an important consideration for any preventive interventions. Most studies to date have directed interventions either to all trauma survivors or to those with acute stress symptoms. However, advancing understanding of the factors underlying development of PTSD may result in more sophisticated targeting strategies. While a number of pretrauma factors as well as aspects of early response to trauma have emerged as risk factors for PTSD, most of these factors have not yet been shown to be clinically relevant for targeting interventions. It is possible that a clinical prediction tool which combines a number of factors could be accurate enough for this purpose, and development of such a tool could represent a useful research direction. In addition to predicting PTSD, research on individual variability in response to interventions could also be helpful in personalizing the treatment of trauma survivors and optimizing outcomes. The ability to select patients on a basis other than acute stress symptoms may also allow earlier intervention (hours rather than days or weeks after trauma), which may improve outcomes. New tools to aid in the development of alternative classification systems and dimensional approaches to PTSD may prove useful in this regard. These include confirmatory factor analysis, latent class analysis, and machine learning methods. Approaches to identify latent trajectories may also help clarify which individuals benefit most from preventive interventions.

In addition to identifying neural targets for intervention, preclinical research can also help identify the ideal timing of interventions. It is notable that many preclinical studies administer interventions within hours or days after stressor exposure, while some clinical studies do not intervene until weeks have elapsed after a trauma. A fuller understanding of processes involved in the development of PTSD including the stress response, fear conditioning, and memory consolidation could help guide the timing of different interventions. Again, using the principles of translational research by tying clinical study design to preclinical findings can ensure the best use of resources when testing clinical interventions.

Other aspects of clinical study design also require attention. In addition to adequate sample sizes, randomization, adequate controls, and other principles of rigorous design, outcome measurement is an important consideration. The studies reviewed here vary considerably in how outcomes are measured, whether PTSD incidence or level of symptoms is the primary outcome, and time to follow-up. This last point is particularly important given that some interventions may have short-term benefits that do not persist. Long-term follow-up studies are important to ensure that preventive interventions decrease PTSD beyond the first few weeks or months after trauma.

It is difficult to predict which types of interventions will be most effective in preventing stress-related disorders, and

multiple avenues should be pursued. This includes primary prevention strategies to enhance resilience in those at highest risk for trauma as well as secondary interventions administered after trauma. Likewise, both psychosocial and somatic approaches should be pursued. Each of these approaches may have advantages and disadvantages. Safe and effective medications may be easier to disseminate widely when compared with psychosocial interventions, and both types of interventions may differ in terms of risk profiles. As always, risk and benefits of intervention must be carefully considered before any intervention is used in a clinical setting.

Overall, the potential benefits of prevention of stress related disorders strongly argue for more research attention to this area. With sufficient resources and attention to the principles of translational research, there is reason to believe that successful interventions can be developed. Advances in neurobiological understanding of responses to trauma raise the exciting prospect that clinicians can intervene to prevent the extensive suffering and disability of PTSD and related disorders before they begin.

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