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The Transformation of Post-Traumatic Stress Disorder: From Neurosis to Neurobiology

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1. Introduction

Lives can be severely disrupted after a momentous negative experience. Particularly potent are unexpected negative events, or "traumas," such as a near death experience, a severe injury, or being exposed to intense interpersonal violence or a natural disaster. Although most people recover from these traumatic events, many do not, and experience persistent fear, anxiety and/or depression following the event. In the past, these maladaptations after trauma were considered to be a reflection of personal weaknesses and were stigmatized. Now, after 30 years of research, the physiological responses to severe stress and trauma are being increasingly understood, as are the risk factors for a pathological response to trauma. These gains from the study of memory and neurohormonal reactivity and control systems hold forth the promise of improved, biologically-informed, psychotherapeutic and pharmacologic interventions for the prevention and treatment of post-traumatic stress disorder (PTSD) in the future.

2. History and development

2.1 Origins of PTSD

That the severe stress of military combat exposure could cause disabling psychiatric symptoms among soldiers had long been recognized, and was identified by a variety of names across wars, such as *shell shock*, *battle fatigue*, and *traumatic war neurosis.* These reactions are characterized by a period of emotional numbness, depersonalization or derealization in the days after the trauma, followed by a longer period of anxiety, insomnia, nightmares, painful memories and phobic avoidance. However, these symptoms were considered to be time-limited responses to combat or other sudden, unexpected trauma, much as grief was a time-limited reaction to personal loss (McHugh & Treisman, 2007). In 1952, with the creation of the first edition of the DSM (DSM-I), the American Psychiatric Association included the diagnosis of '*gross stress reaction*' in its nosologic classification system and defined it as a response to an extreme physical or mental stressor by an otherwise normal person. By definition, the response needed to be short-lived in nature, and if persistent, required the diagnosis of another, more enduring diagnosis unrelated to trauma (Andreasen, 2010). PTSD became a formal psychiatric diagnosis with its inclusion in the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-III

(American Psychiatric Association [APA], 1980). The diagnosis emerged from the work of American psychiatrists opposed to the Vietnam War, who documented symptoms of severe stress among war veterans that continued for years after having returned home (Scott, 1990).The emergence of PTSD in DSM-III, involved two key changes to the classic stress reaction construct: 1) eliminating the time frame as a temporary reaction; and 2) eliminating the requirement that the individual experiencing symptoms after a traumatic event had to be 'otherwise normal.'

The DSM-III defined a traumatic event as a catastrophic stressor experienced by an individual that was outside the realm of normal human experience, be it natural, such as hurricanes or floods, or man-made, such as war, torture, rape or plane crashes. By design, commonly occurring stressful experiences for individuals, such as divorce, loss of employment and illnesses were excluded as traumatic events due to the assumption that these experiences were relatively common and ordinary stressors (APA, 1980). Initially, motor vehicle accidents as well as traumatic experiences in childhood, such as sexual or physical abuse, were not thought to elicit a traumatic stress response of an intensity warranting the diagnosis. This distinction was altered in the fourth version of the DSM (DSM-IV). The traumatic stressor required for a diagnosis of PTSD in the DSM-IV is defined in the "A"-criterion: the experience of an event that involves an actual or threatened death or serious injury, or threat to the physical integrity of oneself or another person, or learning about the unexpected or violent death, serious harm or threat of death or injury to somebody close to oneself (Criterion A1). In addition, the individual response must involve fear, helplessness or horror (Criterion A2) (APA, 1994).

Although the concept of PTSD has received broad acceptance in psychiatry, there continues to be ongoing controversy about the diagnosis, particularly regarding the breadth of experiences and phenomenology it encompasses (McHugh & Treisman, 2007; McNally 2003). The expansion of the events considered as 'stressors' for the "A1" criterion from the DSM-III to DSM-IV has been criticized for weakening the criterion from traumatic exposure to oneself (e.g. rape) to simply hearing about something traumatic happening to another person. No longer does the stressor need to be "outside the range of normal human experience." By grouping such distinct types of events under one "trauma" rubric, the potential to identify biological substrates of PTSD may be weakened, and the potential for misuse of the diagnosis for political or personal benefit is increased.

In the National Comorbidity Survey-Revised (NCS-R), a community survey of American adults, 60% of men and 51% of women had experienced at least one traumatic event in their lives; other surveys have found higher rates (Kessler et al., 2005; Breslau et al., 2009). The types of trauma experienced varies between genders, with men being exposed to more life-threatening accidents or events involving weapons, while women more frequently experience events involving sexual exploitation, such as rape or sexual assault (Kessler et al., 1995). Furthermore, the risk for PTSD varies across types of trauma. For example, development of PTSD after a natural disaster (men 3.7%, women 5.4%) is typically much less common than after rape (men 65%, women 46%) (Kessler, 2000).

2.2 Social repercussions resulting from the formal introduction of PTSD

The inclusion of PTSD as a formal psychiatric diagnosis has had substantial social impact. It has provided psychiatrically distressed patients a means for naming and conceptualizing how their lives have been altered by traumatic life events, thereby providing reassurance they are not "going crazy". However, the impact of PTSD on the larger culture is continuing

to evolve. Because the symptoms of PTSD are purely subjective, can overlap with other illnesses and are easily faked, malingering to obtain the diagnosis for secondary gains is a concern. For example, several investigators have identified over-reporting of symptoms or dishonesty among substantial numbers of Vietnam veterans, who can receive disability payments if diagnosed with life-impairments stemming from PTSD (Burkett & Whitley 1998; Frueh et al., 2000; Frueh et al., 2005). Similar concerns have arisen in the civilian arena, where diagnoses of PTSD have been increasingly used in litigation against employers (Guriel & Fremouw, 2003). Furthermore,, the potential loss of disability payments that would occur if a patient with PTSD recovers or improves function may act to perpetuate symptoms and maintain the disabled state. Another social consequence has been the widespread adoption of the practice of bringing counselors to sites of disasters or other traumas, with the aim of preventing the development of PTSD in those exposed to the event, although evidence of the benefit of these programs is scarce.

3. Diagnosis

Being exposed to a traumatic event does not inevitably lead to PTSD. Most people exposed to traumatic events experience a few psychiatric symptoms, such as insomnia or anxiety, but then re-adjust to their pre-trauma life as symptoms subside over a few weeks. Moreover, ongoing psychiatric symptoms following a trauma in some patients may be better characterized as major depressive disorder (MDD) or another anxiety disorder rather than PTSD. Maladaptation after the traumatic exposure with consistent re-experiencing and phobic avoidance symptoms which persist one month after the trauma justify consideration of a diagnosis of PTSD over other diagnoses. A comparison of diagnostic criteria for other potential post-trauma diagnoses is presented in **Table 1**.

3.1 Acute stress disorder, adjustment disorder and PTSD

3.1.1 Acute stress disorder

Re-experiencing of symptoms, avoidance and hyper-arousal are common and expected following a traumatic situation, and thus PTSD cannot be formally diagnosed until one month after the traumatic event. For the first month following a trauma, symptomatic patients may meet criteria for Acute Stress Disorder (ASD). The diagnosis of ASD requires the experience of three or more dissociative symptoms within 4 weeks of the traumatic event, together with re-experiencing parts of the trauma, avoidance of memories, increased arousal, and significant impairment in occupational and social functioning. These symptoms must not be better accounted for by another mental disorder (such as brief psychotic disorder). Important associated symptoms of hopelessness and despair are also often present. A co-morbid diagnosis of Major Depressive Disorder may be warranted (APA, 1994).

The diagnosis of ASD may change to PTSD if the symptoms do not resolve within 4 weeks and the criteria for PTSD are met. ASD was introduced into DSM-IV with the aims of improving prediction of PTSD and developing interventions to prevent the development of PTSD. Roughly 10-25% of people exposed to an interpersonal trauma or motor vehicle accident will develop ASD (Elklit, 2002; Harvey & Bryant, 1998). Of those who develop ASD and are not treated, roughly 80% will go on to meet criteria for PTSD. (Harvey & Bryant, 1998). However, many victims of trauma will later meet criteria for PTSD despite not meeting criteria for ASD. These patients often do not experience sufficient dissociative

	Posttraumatic Stress Disorder Symptoms	Acute Stress Disorder	Adjustment Disorder
Trauma exposure	**Cluster A (exposure): the individual has been exposed to a traumatic event and both of the following 2 conditions were present:** (A1): person experienced, witnessed or was confronted with 1 or more event(s) involving the actual or threatened death or serious injury or a threat to the physical integrity of self or others.	Identical to Posttraumatic Stress Disorder	The onset of the behavioral or emotional problems lay within 3 months of the onset of the stressor, irrespective of (A1) and (A2).
	(A2): The person's response involved intense fear, helplessness and horror	Identical to Posttraumatic Stress Disorder	Marked distress, in excess of what would be expected given the stressor
Cluster B Re-experiencing	**One** (or more) of the following experiences: (B1) recurrent and intrusive distressing recollections of the event, including images, thoughts or perceptions (B2) recurrent distressing dreams of the event (B3) acting or feeling as if the traumatic event was happening again, including flashbacks, reliving the experience, illusions or hallucinations (B4) intense psychological distress at exposure to internal of external reminders that symbolize or resemble an aspect of the traumatic event (B5) physiological reactivity on exposure to internal or external cues that symbolize or resemble	**One** (or more) of the following experiences: (B1) numbing (B2) reduction of awareness (B3) derealization (B4) depersonalization (B5) inability to recall important aspects of the trauma	Not applicable
Cluster C Avoidance	**Three** (or more) of the following experiences (C1) avoidance of thoughts, feelings or conversations associated with the trauma (C2) efforts to avoid activities, places, or people that trigger memories of the trauma. (C3) inability to recall an important aspect of the trauma (C4) marked reduced interest in previously important activities (C5) feeling of detachment of estrangement from others (C6) restricted range of affect (no loving feelings) (C7) sense of a foreshortened future (does not expect to have a career, marriage, family, or normal life span)	Marked avoidance of reminders of the traumatic event (number of experiences not specified)	Not applicable
Cluster D Arousal	**Two** (or more) of the following experiences: (D1) difficulty falling or staying asleep (D2) irritability or outbursts of anger (D3) difficulty concentrating (D4) hypervigilance (D5) exaggerated startle	Marked symptoms of anxiety and arousal (number of experiences not specified)	Not applicable
Criterion D	Duration of disturbance (Cluster B, C and D) is more than one month	Duration of disturbance is more the 2 days but less than 28 and occurs within 4 weeks of the traumatic event	Duration of disturbance does not exceed 6 months after the stressor has been removed/ended
Criterion F	The disturbances cause clinically significant distress or impairment in social, occupational or other important areas of functioning	The disturbance causes significant distress in social, occupational or other important areas of functioning	Significant impairment in social or occupational functioning

Table 1. Differential features of post-trauma diagnoses

symptoms after the trauma to warrant an ASD diagnosis, but do experience other ASD symptoms that put them at risk for PTSD. Thus, when present, ASD indicates a need for treatment intervention, but the absence of ASD does not eliminate the need for ongoing follow-up to monitor for the emergence of PTSD symptoms.

3.1.2 PTSD, current definition

As shown in **Table 1,** the diagnosis of PTSD requires multiple criteria. The two A-criteria that are required are: (A1) witnessing, experiencing or being confronted with the actual or threatened death of serious injury or violation of physical integrity to oneself or others, and (A2) the response consisted of intense fear, helplessness or horror.

The "B" symptom cluster involves the re-experiencing of the traumatic event identified by criterion A in at least one way. These include recurrent, intrusive memories of the trauma [including images, thoughts or perceptions that cause considerable distress, and/or recurrent distressing dreams of the event and/or reliving of the experience through illusions, hallucinations or flashbacks (including upon awakening and while intoxicated)], as well as experiencing psychological distress or physical reactions upon exposure to internal or external reminders of the trauma. The "C" symptom cluster incorporates avoidance symptoms, such as thoughts and feelings about the trauma, and places, people and situations that are associated with the trauma. A numbing of experienced emotions, a reduced interest in activities, and feelings of detachment and estrangement from others are also considered to be avoidance symptoms. Finally, the "D" symptom cluster incorporates symptoms of hyperarousal, such as insomnia, irritability and anger, concentration problems, hypervigilance, and increased startle responsiveness. The condition must be present at least one month after the occurrence of the criterion "A" event, and, as with all major disorders in the DSM, the illness must cause clinically significant distress or functional impairment.

Full PTSD symptom criteria lasting for less than 3 months is considered "Acute" PTSD, while "Chronic" PTSD refers to duration of PTSD symptoms for more than 3 months. It is important to note that the onset of PTSD may not start immediately after the traumatic experience and thus the sub-classification 'with delayed onset' is given if symptoms started 6 months or longer after the event occurred. A several-year delay of symptom-onset is possible in some cases.

A potential subtype that is not part of DSM-IV, but is worthy of clinical consideration is "PTSD with psychotic symptoms." Some severely ill patients with PTSD experience frank hallucinations, despite never having had psychotic symptoms prior to their trauma. Just as MDD can become sufficiently severe to develop psychotic symptoms, a similar process may occur in PTSD patients. Under current DSM-IV criteria, PTSD patients experiencing psychotic symptoms after a traumatic event would be diagnosed with PTSD and co-morbid "Psychotic Disorder, not otherwise specified."

3.1.3 Adjustment disorder

Adjustment Disorder is a diagnosis designed to capture the presence of clinically significant psychiatric symptoms that fall short of a more definitive diagnosis, such as MDD or PTSD. Adjustment disorders occur following a stressful life event, cause significant impairment or distress, and may require treatment. Unlike ASD and PTSD, the stressful events qualifying for an adjustment disorder need not be traumatic; for example, events such as divorce, sudden unemployment or involuntarily dropping out of college are considered non-

traumatic stressors. Per definition, an Adjustment Disorder is a temporary impairment that must resolve within 6 months of the stressor onset, unless the stressor persists (e.g. an ongoing severe medical condition).

3.1.4 Anxiety disorder not otherwise specified (NOS)

Patients who, after the resolution of a traumatic event, still experience ongoing clinically significant anxiety symptoms falling short of ASD or PTSD criteria per the DSM-IV definitions should be diagnosed with Anxiety Disorder NOS. Such "sub-syndromal" PTSD patients may still be substantially impaired and/or distressed by their symptoms and usually require a treatment intervention. Furthermore, subsyndromal ASD increases the risk of later developing PTSD.

3.2 Complex PTSD

Although not part of DSM-IV, "Complex PTSD" (also referred to as Disorders of Extreme Stress Not Otherwise Specified, or DESNOS) has increasingly become a focus of research (Herman, 1997; Ford, 1999). The concept of Complex PTSD reflects the variety of psychological consequences of being emotionally or physically controlled by others, under the belief that such long-term captivity (literal or figurative) changes the person's sense of self and reactions to stress. Examples of such situations include prisoner of war camps, a prostitution brothel, or situations of long-term child abuse or domestic violence. In addition to classic PTSD symptoms of avoidance, re-experiencing and hyper-arousal, Complex PTSD is proposed to include distorted perceptions of both the self and the perpetrator, and a tendency to pursue a pattern of chronic victimization. Greater than 90% of people who meet criteria for Complex PTSD also meet criteria for DSM-IV-defined PTSD, which led to its exclusion from the DSM-IV. However, the concept has clinical utility in differentiating between PTSD patients who may need broader or more intense forms of treatment.

3.3 Differential diagnosis of PTSD symptoms, and the problem of comorbidity

Symptoms resembling PTSD can be attributed to other psychopathologies as well. Of crucial importance in differential diagnosis is clarifying which, if any, symptoms preceded rather than followed the traumatic event. For instance, recurrent intrusive thoughts can occur in Obsessive-Compulsive Disorder (OCD). The differentiating characteristic of intrusive thoughts in PTSD is that these thoughts and memories relate to the traumatic event, whereas in OCD the intrusive thoughts are unrelated to a traumatic event and the patient at some point in their life should have recognized the thoughts as being inappropriate. Flashbacks (i.e., highly vivid sensory experiences of the trauma occurring while awake) reflect re-experiencing the traumatic event, and differ from sensory hallucinations of non-existent stimuli, such as occur in substance-abuse or psychotic disorders. Also, PTSD Cluster C symptoms, such as loss of interest in activities, can also occur in Major Depressive Disorder as well as other anxiety disorders. The overlap of PTSD symptoms with MDD, bipolar disorder or other anxiety disorders is especially problematic for the Cluster D symptoms (particularly sleep disturbances, irritability, and concentration difficulties). It is important to note that the DSM permits the simultaneous diagnosis of PTSD with MDD, OCD, or other mood, anxiety or psychotic disorders if they also meet criteria for those disorders.

The co-occurrence of 2 or more psychiatric conditions is referred to as comorbidity. When PTSD is comorbid, it may precede or follow the development of other psychiatric

conditions. On the one hand, pre-existing diagnoses, such as bipolar disorder and substance dependence, may increase the probability of traumatic exposure, thus increasing the risk for PTSD (Rakofsky et al., 2011). Conversely, data from the National Comorbidity Study (NCS) demonstrated that individuals with PTSD have an increased risk for developing substance use disorders, as well as mood and other anxiety disorders post trauma, compared to individuals with no PTSD diagnosis (Kessler et al., 2000).

3.3.1 Substance abuse

Patients with PTSD have a 3-4 fold increased risk of an alcohol or drug use disorder (Read et al., 2003). Most studies find that PTSD precedes the development of a substance abuse problem, and that experienced distress seems to serve as a key long-term risk factor for developing abuse (Read et al., 2004). Abuse of alcohol and other sedatives (e.g. benzodiazepines) may arise from an attempt to suppress the intrusion of distressing memories, so called "self-medication." Substantial research has identified connections between early-life traumatic experiences, such as childhood physical or sexual abuse, the development of PTSD, and subsequent drug abuse in adolescents (Kilpatrick et al., 2003). In one study of urban primary care patients, the number of traumatic events and a history of cocaine dependence both predicted current PTSD symptomatology, and this effect was independent of exposure to trauma during adulthood (Khoury et al., 2010). Comorbid PTSD has also been found to predict poorer outcomes of treatment for substance abuse (Ouimette et al., 1997). The clear implications for clinical practice are that all patients with a substance use disorder should be evaluated for PTSD, and vice versa.

3.3.2 Suicidality

Individuals with PTSD have a six-fold increased risk of attempted suicide (Kessler, 2000). The increased risk of both suicide ideation and attempts in patients with PTSD is present in both developed and developing countries (Nock et al., 2009). A well-designed prospective study examining suicidal ideation in women either with or without MDD and PTSD found that, after controlling for trauma history, MDD and PTSD independently predicted suicidal ideation, as did a history of interpersonal violence victimization. Women with PTSD alone reported more suicide attempts than women with MDD only. Among women with comorbid PTSD and MDD, 63% had experienced suicidal ideation and 14.4% had attempted suicide (Cougle, et al., 2009). Notably, thoughts of death or suicide are not a diagnostic criterion for PTSD, unlike for MDD. Nevertheless, inquiry and monitoring about suicidal thoughts is clearly of importance in the assessment and treatment of patients with PTSD.

4. Epidemiology

Lifetime exposure to traumatic events is estimated to range from 50-90% of the general population (Kessler et al., 1995; Darves-Bornoz et al., 2008; Breslau et al., 1998). There is substantial variability between countries, and even between cultures within countries, in terms of exposure to trauma and prevalence of PTSD. Chronic traumatic experiences, such as prolonged ethnic violence or civil wars increase the conditional risks of developing PTSD; thus, in less developed countries where these circumstances occur, rates of PTSD are higher. However, the likelihood of developing PTSD after specific types of traumatic exposure is relatively similar across countries (Wittchen et al., 2009). For example, professional Firefighters in the United States, Canada and Germany exhibit comparable conditional risks

for PTSD after traumatic experiences (Wagner et al, 1998; Corneil et al, 1999). Even after the most distressing events, the probability of developing PTSD is less than 50%, and for most traumas the risk is much lower (Wittchen et al., 2009; Breslau, 2009). Nevertheless, many victims of trauma who do not meet criteria for PTSD may still notice psychological changes after the trauma. For example, among survivors who were in the Twin Towers during the September 11, 2001 terrorist attacks, 15% had probable PTSD 2-3 years later, but 96% reported at least one post-trauma symptom, the most common being hypervigilance and increased startle reactivity (DiGrande et al., 2011).

The first National Comorbidity Survey, which conducted interviews of a nationally representative sample of about 8,000 American adults in the 1990's found the lifetime prevalence of PTSD to be 7.8%. The prevalence among women (10.4%) was twice that of men (5%) (Kessler et al., 1995). These estimates were confirmed in the US National Comorbidity Survey – Replication (NCS-R), conducted about 10 years later, in which the lifetime prevalence of PTSD was 6.8%, with 9.7% of women and 3.6% of men affected. (Kessler et al., 2005).

Important unresolved issues in the epidemiology of PTSD are the rates of recovery and recurrence of the disorder. As occurs in MDD and several anxiety disorders, such as GAD and panic disorder, symptoms of the illness typically wax and wane over time. They tend to worsen at times of stress, particularly with the occurrence of a new traumatic event. For example, among patients who experienced active PTSD symptoms over many years, the majority experienced extended periods of times with only limited symptom severity or impairment (Breslau et al., 1998). Thus, it appears that patients with chronic PTSD often do not meet full criteria for the illness continually, but rather enter periods of remission or partial remission from their symptoms, even without treatment.

4.1 Risk factors for the development of PTSD

A broad range of factors have been identified to predict greater risk of PTSD, though there is great variability between studies regarding the relative importance of these factors. Although earlier work suggested that mere exposure to prior trauma was a risk factor for developing PTSD, longitudinal data indicate that only prior traumas that result in PTSD increase the risk of PTSD from subsequent traumatic events (Breslau et al., 2008). Pre-existing (i.e. pre-trauma) risk factors include female gender, pre-existing psychiatric disorders, substance use disorders, low socioeconomic status, lower intelligence, and adverse early life experiences. Risk factors associated with the traumatic event itself and its associated context are probably more significant predictors for PTSD than pre-trauma factors, and include the severity of the trauma, social support post-trauma, physical injuries, and the development of ASD (Berwin et al., 2000). Additionally, psychological factors such as humiliation, guilt and self-blame for actions taken during the event may arise in the aftermath of trauma, and may increase risk for developing PTSD (Yehuda, 2002).

A "dose-response" model postulates that PTSD symptoms increase with the severity of the stressor (March, 1993). This model is supported by some studies (e.g. greater proximity to the epicenter of an earthquake increases risk for PTSD symptoms) but not others (e.g. greater severity of motor vehicle accidents do not increase PTSD, (Pynoos et al., 1993; Schnyder et al., 2001). In accordance with the dose-response theory, the risk of a comorbid psychiatric disorder does appear to increase with the intensity and severity of the PTSD symptomatology. A non-linear dose model posits that the most significant risk for developing PTSD occurs once a certain threshold of trauma severity occurs, but

greater trauma severity beyond that threshold adds little to increased risk (Harvey & Yehuda, 1999).

4.2 Recent disasters and PTSD

Improvements in survey methodology have allowed for initial evaluation and follow-up for PTSD surveillance among survivors exposed to traumas in recent years. **Table 2** presents findings from some more notable recent disasters. The consistent finding is that symptoms of PTSD are common in the days to weeks after an event, but for the majority of those exposed, return to normal functioning occurs. Notable in Table 2 is that mass disasters appear to induce higher rates of PTSD (25-50%) than smaller scale natural disasters that were previously found to carry PTSD rates of about 5% (Kessler, et al., 1995). Although most people are resilient to trauma, particularly for non-interpersonal events, when the scale of destruction is immense, and produces social breakdown and mass casualties, greater rates of PTSD can be expected. One shortcoming to these data is the limited amount of detailed surveillance data from disasters occurring in poorer nations.

The World Trade Center terrorist attacks on September 11, 2001 have been the focus of several investigations into the psychiatric effects of mass trauma. Consistent with the dose-response model, likelihood of having PTSD 2-3 years after the attacks was directly correlated with the number of types of trauma experienced by the victims during the attacks, and with presence on a higher floor of the buildings at the time of the attacks (DiGrande et al., 2011). Nearly 6 out of 10 people living in lower Manhattan at the time of the attacks experienced at least one PTSD symptom, most commonly insomnia and intrusive memories (Galea et al., 2002). One unique feature of this event was the massive and detailed media coverage, as extensive video footage of the disaster was replayed extensively in the weeks afterwards. The effects of media coverage appeared to be deleterious, as a phone survey performed the weekend after the attack found 44% of adults and 35% of children were experiencing at least one symptom of substantial stress, with higher rates associated with greater extent of television viewing of the disaster (Schuster et al., 2001). Restricting children's exposure to televised traumatic events is recommended by several professional organizations.

4.3 Gender differences in prevalence

Men experience more traumatic events over their lifetime than women, with only rape and childhood sexual abuse traumata occurring more commonly in females (Kessler et al., 1995). Despite their greater exposure to trauma, men have consistently lower rates of lifetime PTSD across studies than women. This pattern is consistent with all anxiety disorders, except OCD, which is equally common between genders. Of particular relevance to PTSD risk, women have greater risk for repeated, uncontrollable interpersonal trauma, such as childhood sexual abuse. Furthermore, traumas like these which violate the physical and emotional integrity of the victim may contribute to greater severity of subsequent symptoms (Pratchett et al., 2010). The loss of personal control over one's physical integrity as well as the extreme helplessness experienced may contribute to the high rate of PTSD following rape for both genders: 65% in men and 46% in women (Kessler, 2000). Furthermore, compared to men, women with PTSD are nearly twice as likely to have comorbidity with another anxiety disorder or depression (Breslau et al., 1997). These differences in types of trauma and rates of comorbidity may explain the higher rates of PTSD among women,

though a gender-related biological vulnerability, perhaps related to sex steroid function and stress reactivity, must also be considered (J.B. Becker et al., 2007).

Region/ Year	Disaster type	General Disaster Impact	Sample size	Time point of sampling	%PTSD Diagnosis	Other Diagnoses	Reference
Italy 2009	Earthquake	309 deaths, 1,600 injuries 65,000 displacements	512 students	10 months after disaster	37.5% PTSD, 29.9% partial P TSD		Dell'Osso et al. (2011)
China 2008	Earthquake	69,227 deaths, 374,176 injuries 4.8million displacements	2250 students 446 adults (aged 15 or older)	6 months post disaster 2.5months post disaster	15.8% PTSD 45.5% PTSD	40.5% Anxiety, Overall 48.6% of students had 1 or more diagnosis, 24.5% MDD,	Fan et al. (2011) and Kun et al. (2009)
Peru 2007	Earthquake	596 deaths,	298 adults	5 months post disaster	25.2 % PTSD		Cairo et al. (2010)
Armenia 1988	Earthquake	25.000 deaths 700,000 displacements	1785 adults	12-24 months post disaster	49.6% PTSD	82% fulfilling at least one comorbid psychiatric disorder	Armenian et al. (2000)
Turkey 1999	Earthquake	18,243 deaths, 250,000 displacements	774 adults	40 months post disaster	37.2% PTSD	67.5% comorbid PTSD/MDD, 25.2% Depression	Salcioglu et al. (2007)
USA 2005	Hurricane Katrina	1,800 deaths, 500,000 displacements	101 adults	12 months	50% above PTSD cut-off score		LaJoie et al. (2010)
Indian Ocean 2004	Earthquake Tsunami	230,210 deaths, 125,000 injuries, 1.69 million displacements	1505 vacationing Swedish adults	14 months post disaster	13-56% above PTSD cut-off score depending on trauma exposure		Wahlstroem et al. (2008)

Table 2. Recent large disasters and incidence of PTSD

4.4 PTSD among children and adolescents

The National Survey of Adolescents interviewed over 4000 American adolescents and found that 25% of the 12-17-year olds had experienced a sexual (8.1%) or physical (17.4%) assault (Kilpatrick et al., 2003). In this study, significant PTSD symptomatology was identified in 30% of girls with a sexual abuse history, and one third of the sexually assaulted girls reported substance abuse in their lifetime compared to 5% of non-sexually assaulted girls. Other studies indicate that natural disasters are equally as traumatizing for children and adolescents as they are for adults. Recent data from earthquakes in Italy and China (Dell'Osso et al., 2011; Fan et al., 2011) show PTSD rates between 15 and 37% in children, with almost half of the children displaying more than one psychiatric disorder. Although considerable research has been done on the commission of harm (such as sexual or physical abuse), the omission of care (e.g. loss of a parent, physical or emotional neglect) may also produce traumatic responses in children. The implications of childhood trauma for the person's life trajectory are profound, and are an urgent area for further research.

4.5 Civilian trauma vs. combat trauma

Although there is substantial resilience among soldiers in the face of trauma, an estimated 10-20% of currently deployed soldiers in the ongoing wars in the Middle East will develop PTSD (Hoge et al., 2004). The development of PTSD in soldiers often occurs in conjunction with depression, aggression, substance abuse and increased rates of suicide. One compelling difference between retired soldiers with PTSD and civilians with PTSD is the decreased threshold for intimate partner violence in veterans; rates of domestic violence in veterans with PTSD is 3 times higher than in veterans without PTSD or civilians (Jordan et al., 1992). Differences in civilian versus combat PTSD are also seen in responses to treatment. Many, but not all, studies of medications to treat PTSD have found poorer responses among patients with PTSD related to combat than other traumas (Benedek et al., 2009; Martenyi & Soldatenkova, 2006).

4.6 Traumatic brain injury and PTSD

Traumatic brain injuries (TBI) can be a result of concussions, originate from vehicle or fire-arm accidents, or open head injuries such as being shot during combat. Distinguishing PTSD and TBI is complicated due to the overlapping symptoms of both illnesses. Both conditions include fatigue, anxiety, insomnia, poor memory and concentration as well as irritability, anger and depression (Institute of Medicine, 2008). TBI may contribute to the development of PTSD, and they increase the morbidity of soldiers returning from deployment. In fact, rates of PTSD among US soldiers with a TBI incurred during the Iraq War, have been reported as high as 43% (Hoge et al., 2008). TBI-PTSD patients may have greater difficulty benefiting from psychotherapy interventions, due to reduced concentration and other cognitive impairments.

4.7 PTSD and medical conditions

Chronic stress has long been thought to contribute to physical disease, with particular concern about cardiovascular consequences. Persistent re-experiencing of a traumatic event as occurs in PTSD may be considered a form of chronic stress. Recent prospective cohort studies of male Vietnam veterans have identified PTSD symptom level as an independent risk factor for nonfatal and fatal cardiovascular disease (CVD), even after controlling for several other risk factors for CVD, including smoking status, family history of CVD and education level (Kubzansky et al., 2007; Boscarino, 2008). This finding was replicated in a study of PTSD patients who had been deported to Siberia during childhood. These patients also showed an increased prevalence of cardiovascular disease, as well as diabetes, and hearing difficulties compared to age-matched controls (Walczewska et al., 2011). One theorized mechanism for this association with heart disease is that high levels of catecholamines present in PTSD (see below) could lead to damage of the intimal endothelium of coronary vessels, enhancing the progression of atherosclerosis.

5. Biology

Our current understanding of the biology of PTSD has derived primarily from animal models of fear learning and extinction in animals, and through cross-sectional comparison of a variety of biological markers and genes in PTSD patients versus unafflicted healthy controls. The most extensively studied biological alterations in patients with PTSD are disturbances in functioning of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), which are key drivers of the "fight or flight" response to fear. Encoding (i.e. storing into memory) of fearful events through activity in the amygdala

and hippocampus is thought to depend on the function of the HPA axis and SNS systems (Cahill et al., 1994). Pathologic fear memory formation, and the failure to learn or access safety memories (extinction), are thought to be fundamental to the development of PTSD. The two systems interact, with glucocorticoids produced through activation of the HPA axis having inhibitory effects on the SNS system (Tsigos & Chrousos, 2002).

5.1 Sympathetic nervous system

SNS activation involves increased signaling by the catecholamines norepinephrine (NE, also known as noradrenaline) and epinephrine. Activation of the adrenal medulla produces NE and epinephrine for the body periphery, whereas the locus ceruleus (LC) is the primary source of NE in the central nervous system (CNS). Inputs from the amygdala and hypothalamus, both key fear processing brain regions, drive LC activation. In turn, the LC projects to a variety of stress-responsive brain regions, including the amygdala, hippocampus, hypothalamus, thalamus, prefrontal cortex and periaqueductal gray area. The post-synaptic alpha-1, beta-1 and beta-2 receptors in the CNS mediate the NE signal, and pre-synaptic alpha-2 receptors serve as a negative feedback signal to reduce NE signaling. Greater NE activity in the CNS found in PTSD patients may serve a key role in the pathogenesis of core PTSD symptoms, particularly fear learning, hyperarousal and heightened startle response.

Greater SNS activity in PTSD patients is reflected in higher greater heart rate, blood pressure and skin conductance, than healthy controls, particularly in response to reminders of a traumatic event. Moreover, elevated heart rate and epinephrine levels immediately following trauma may predict later development of PTSD (Delahanty & Nugent, 2006). Yohimbine, an alpha-2 receptor antagonist, which acts by blocking the negative feedback effects mediated by this receptor and thus increases NE signaling, can induce flashbacks and SNS activation in PTSD patients (Southwick et al.,1999). Traumatic reminders also induce greater cerbrospinal fluid concentrations of NE in PTSD patients than controls (Geracioti et al., 2008).

Serotonin is another neurotransmitter that has been studied in PTSD, in part because medications that affect serotonin transmission have some efficacy in treating the disorder (see below). Moreover, abnormalities in serotonin signaling have been associated with greater rates of hostility, impulsivity and suicide, which are often present in PTSD (Dunlop et al., 2009). However, to date, evidence linking serotonin system dysfunction to PTSD is not compelling.

5.2 Hypothalamic-pituitary-adrenal axis

The HPA axis is a hormonal circuit that controls the stress response. Corticotropin releasing hormone (CRH, also referred to as corticotropin releasing factor), is released from the hypothalamus along with arginine vasopressin (AVP). In concert with AVP, CRH then acts on the anterior pituitary gland, where it binds to CRH receptors to trigger the release of adrenocorticotropin (ACTH) and endorphins (endogenous opioids). ACTH released from the pituitary into the systemic circulation then acts on the adrenal cortex, inducing the release of cortisol. Cortisol is the main effector hormone of the stress response. In addition it exerts negative feedback effects on the HPA circuit by binding to glucocorticoid and mineralocorticoid receptors in the hypothalamus, pituitary and hippocampus. These signaling cascades act relatively quickly, and apparently have evolved to provide the organism with a rapid, short-lived response to acutely threatening situations. However, exposure to high levels of cortisol over time leads to a loss of dendritic branching in the hippocampus, potentially reducing hippocampal volume (Sapolsky et al., 1990).

Cortisol's effect on the body's organ systems are mediated via two types of corticosteroid receptors. When cortisol concentrations are low, the type I (mineralocorticoid, or MR) is thought to mediate cortisol's effects. The type II (glucocorticoid, or GR) becomes relevant as cortisol levels increase, as happens as part of the circadian rhythm or in the face of stress. Under these conditions the MRs saturate, and cortisol signaling occurs through GRs, inducing the negative feedback signal. After binding cortisol, both MRs and GRs translocate to the nucleus, where they interact with DNA to induce changes in gene expression (Raison & Miller, 2003).

Cortisol plays a significant role in memory consolidation, and also limits memory retrieval in emotionally-charged situations (for a review see, de Quervain et al., 2009). Most individuals lose retrieval of the specific emotional memory over time, but this is not the case in patients suffering from PTSD, for whom the traumatic memory is easily and vividly accessed and thus relived unexpectedly, or reactivated due to an external event or situation that triggers the memory. Reduced cortisol concentrations immediately following trauma may allow sustained activity of the SNS and CRF systems, thus prolonging fear processing and thereby laying the groundwork for traumatic memory formation and PTSD (Pacak et al., 1995). Indeed, low cortisol concentrations measured shortly after trauma predicts development of PTSD, as do heightened levels of SNS activity after trauma (Yehuda et al., 1998). Whether these findings reflects a low basal level of cortisol or impaired HPA axis activation in the face of trauma is uncertain. Also problematic is that activity of the HPA axis post-trauma may vary considerably by the time of measurement (i.e. circadian rhythm factors) and duration in days since trauma, indicating the need for tight control over these variables in assessing hormonal states after trauma (McFarlane et al., 2010).

Studies comparing basal cortisol levels in PTSD patients versus controls have had inconsistent findings (depending on control groups and populations studied), though reduced cortisol levels in PTSD patients is suggested by several studies (Meewisse et al., 2007). Inconsistent findings have also emerged from studies of HPA axis function in PTSD patients undergoing psychological stressors, such as exposure to reminders of trauma or cognitive stress tests (Miller et al., 2007). Patients with PTSD do show greater suppression of HPA axis function when administered a low dose of dexamethasone as part of the dexamethasone suppression test than do healthy controls (deKloet et al., 2006). In addition, CSF concentrations of CRH have been found to be elevated in PTSD (Baker et al., 1999), and CRH stimulation in PTSD patients produces less ACTH response than in healthy controls, both of which suggest that CRH receptors in the pituitary are down-regulated (Yehuda, 2006). Taken together, these data suggest that the PTSD is associated with a dysregulated HPA axis, though whether this disruption reflects a risk factor for, or consequence of, PTSD is uncertain.

5.3 Other signaling systems

Limited data support the potential involvement of other systems in the biology of PTSD. Reduced benzodiazepine receptor expression in the frontal cortex, thalamus and hippocampus has been identified in combat-PTSD patients, suggesting diminished inhibitory capacity in PTSD, as in other anxiety disorders (Bremner et al., 2000a; Geuze et al., 2008a). Brain derived neurotrophic factor (BDNF) is a protein involved in neurogenesis and the maturation, differentiation, migration and survival of neurons, and is particularly concentrated in brain regions involved in learning and memory, including hippocampus, amygdala, cerebral cortex and cerebellum. Studies of peripheral and CSF concentrations of

BDNF have found diverging results (Rakofsky et al., n.d.). However, in a small study, lower serum BDNF concentrations in patients with chronic PTSD predicted greater responses to 12-weeks of treatment with the antidepressant escitalopram (Berger et al., 2010). Neuropeptide Y (NPY) is an anxiolytic CNS protein which may serve as a protective factor against PTSD. NPY appears to diminish sensitivity to stress, perhaps through its ability to inhibit activity in CRH and NE circuits. In a small study, soldiers exposed to combat who had not developed PTSD had greater NPY plasma concentrations than veterans with PTSD (Yehuda et al., 2006). Finally, expression of a protein important for the transport of neurotransmitters and for cell cycle progression, p11 (also known as S100-A10), may serve as a biomarker to distinguish PTSD from mood disorders. In peripheral blood mononuclear cells, p11 was downregulated in PTSD patients, whereas patients with MDD or bipolar disorder had increased levels of p11 versus controls (Ursano et al., 2010).
Pituitary adenylate cyclase-activating polypeptide (PACAP) performs a variety of functions in the body relating to stress reactivity, including regulating CRH release and SNS function. In an urban primary-care population at high risk for PTSD, peripheral blood levels of PACAP directly correlated with posttraumatic stress symptoms in women, but not in men. Moreover, the gene for the PAC1 receptor (ADCYAP1R1), which binds PACAP, has a functional single nucleotide polymorphism (SNP) in an estrogen-response binding element. A SNP in this region of the PAC1 gene in women predicted PTSD diagnosis and symptom burden in the same study (Ressler et al., 2011).

5.4 Structural and functional neuroimaging

To date, the primary brain regions implicated as being altered in PTSD include the amygdala, hippocampus, anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). The medial component of the OFC, the rostral and ventral components of the ACC, and the medial PFC are included in the brain region referred to by some authors as the ventromedial prefrontal cortex (vmPFC). Current models of the development of PTSD propose that exaggerated amygdala response to fearful stimuli lead to powerful encoding of fear memories and expression of fear reactions. The hippocampus is heavily interconnected with the amygdala, is thought to provide contextual information regarding danger, and also has crucial roles in forming explicit (i.e. conscious) memories, and in cortisol-mediated feedback after HPA-axis activation. Impaired hippocampal function in PTSD may contribute to failure to appreciate safe versus dangerous contexts following trauma. Reduced ACC and OFC function impair extinction of fear responding, and alter attention and response to fear-related stimuli (Rauch et al., 2006). Greater resting state activity of the dorsal ACC and mid-cingulate cortex may represent a risk factor for developing PTSD after trauma exposure (Shin et al., 2009).

5.4.1 Hippocampus

The hippocampus is considered particularly vulnerable to disruption in PTSD, based on the neurotoxicity hypothesis, which posits that chronic increased levels of corticosteroids resulting from stress cause atrophy and reduced dendritic branching of hippocampal neurons (Sapolsky et al., 1990). A reduced hippocampal volume may potentially limit the neuroendocrine response of the HPA axis, as shown in monkeys, who, when stressed, show increased cortisol production (Lyons et al., 2001).
Reduced hippocampal volumes are present in patients with chronic PTSD (Bremner et al., 2000b). However, it remains unclear whether smaller hippocampal volumes are present

prior to the trauma (i.e. represent a risk factor for PTSD), are a consequence of developing PTSD, or are combination of both mechanisms. (Gilbertson et al., 2002; Felmingham et al., 2009). Impairment of hippocampal function is also suggested from functional magnetic resonance imaging (fMRI) studies, in which the activity of brain regions is extrapolated from blood flow changes over time. For example, when engaged in verbal learning tasks PTSD patients demonstrate lower levels of hippocampal activation than matched non-PTSD control subjects (Bremner et al., 2003; Shin et al., 2004). Sustained treatment of PTSD for several months with the antidepressant paroxetine produced increases in hippocampal volume and cognitive function (Vermetten et al., 2003).

5.4.2 Amygdala and vmPFC

The amygdala is a crucial component of the neural circuitry controlling fear, and is the primary site involved in associating stimuli with danger. Localized lesions in the amygdala result in docile and unfearful animals (Weiskrantz, 1956). Amygdala volumes have not been shown to differ between PTSD and healthy control subjects. However, abnormalities of amygdala function in PTSD have been identified using challenge (i.e. symptom provocation) studies, in which patients are exposed to reminders of their trauma, such as words or pictures. Using these paradigms, several researchers have identified a consistent pattern of hyperactive amygdala and hypoactive vmPFC function, though some discrepant findings have been reported (reviewed in Rauch et al., 2006). Moreover, greater amygdala activity in response to subliminally presented fearful or angry faces occurs in PTSD patients, reflecting greater threat-related reactivity (Rauch et al., 2000; Armony et al., 2005).

In structural imaging studies, patients with PTSD demonstrate reduced overall prefrontal cortex volume compared to healthy controls, as well as specific reductions in anterior ACC and vmPFC volumes (Geuze et al., 2008b). Women with sexual abuse–related PTSD demonstrate hypoactivation of the OFC and medial PFC during fear extinction learning compared to healthy control women (Bremner et al., 2005). These findings are of significance because the quality of memory extinction in humans is correlated with vmPFC thickness (Milad et al., 2005), and recall of extinguished memories is associated with activation of the vmPFC in healthy controls (Milad et al., 2007).

A meta-analysis of emotion processing studies found that PTSD patients, compared to healthy control subjects, demonstrate greater activity in the amygdala, parahippocampal gyrus, insula, mid-cingulate cortex and precuneus during emotion processing tasks (Etkin & Wagner, 2007). Amygdala and insula hyperactivation also occur in other phobic disorders, such as specific and social phobias. However, reduced activation in certain brain regions versus healthy controls was found only in PTSD patients. The regions of hypoactivation in PTSD patients include the vmPFC, rostral ACC, dorsal ACC and anterior hippocampus (Etkin & Wagner 2007). Lower levels of medial prefrontal cortex activation has been associated with greater PTSD symptom severity. Hypoactivations in the ACC occur in conjunction with hyperactivation of the amygdala and insula, indicating diminished frontal control over emotion-generating limbic regions. These findings are consistent with reports of diminished ACC grey matter volume and integrity of white matter tracts connecting limbic regions with the ACC in patients with PTSD (Kasai et al., 2008; Schuff et al., 2011).

In summary, the neural network model of PTSD proposes that the illness arises from an overly powerful fear-learning process, mediated primarily by the amygdala, which occurs in conjunction with deficient control over fear and stress responses and memories due to inadequate vmPFC and hippocampal activity and/or connectivity.

5.5 Startle

The startle reflex is the involuntary response to an intense unexpected stimulus, and involves flexing of the body and forward thrusting of the head. Startle is believed to indicate autonomic excitability, which can be measured by heart rate, blood pressure and skin conductance (Grossman et al., 2002). The intensity of the startle reflex can be assessed through auditory startle testing, in which the subject hears a loud unexpected noise, and the subsequent amplitude and latency of eyeblinking is measured. "Fear-potentiated startle" refers to the greater startle responding that occurs by cueing the subject that an aversive stimulus is coming so that their level of fear is heightened (Grillon, 2002). A simple 3-neuron subcortical circuit mediates the startle response but, importantly, it is modulated by inputs from the amygdala and other limbic structures (M. Davis, 1992). Startle responding patterns have been used to distinguish PTSD and non-PTSD subjects, and to differentiate between patients with PTSD versus MDD. Enhanced startle responding was found only in PTSD patients, with MDD patients not differing from controls, which suggests that startle responding may serve as a biomarker for PTSD (Jovanovic et al., 2009; Jovanovic et al., 2010a). Fear-potentiated startle assessed among healthy police academy cadets predicted development of PTSD symptom severity after one year of police work (Pole et al., 2009). This finding suggests that greater sensitivity to contextual and explicit threats and slower habituation to repeated aversive stimuli may represent risk factors for PTSD symptoms after trauma. Recent work in highly traumatized patients found greater concentrations of baseline and post-dexamethasone plasma ACTH to be correlated with greater fear-potentiated startle, thus linking abnormal HPA axis feedback with this innovative biomarker (Jovanovic et al., 2010b).

5.6 Genetics

As is the case for all psychiatric disorders, identifying specific genetic associations with PTSD is challenging due to the need for large numbers of subjects to detect small gene effects, and the variability introduced by imperfect phenotype definitions. The importance, of gene-environment interactions in PTSD is gaining increased attention, though definitive identification of PTSD risk alleles awaits further research (Mehta & Binder, 2011). The insertion-deletion functional polymorphism of the promoter region of the serotonin transporter gene (SLC6A4) in some studies modified the effects of environmental risks (e.g. trauma load or post-trauma social support) for PTSD (Koenen et al., 2009; Xie et al., 2009). Even stronger evidence is emerging for the role of FKBP5 (also known as the FK506 binding protein 51), an important intracellular regulator of the glucocortiocoid receptor complex. Functional polymorphisms of the FKBP5 gene are associated with glucocorticoid receptor resistance and consequently impaired negative HPA axis feedback after stress (Binder et al., 2008). Alleles that induce high expression of FKBP5 may serve to increase the risk of PTSD or MDD after early trauma.

6. Prevention

Some traumatic experiences cannot be avoided and are a part of our human existence (i.e., natural disasters or accidents), yet, not every individual with trauma exposure goes on to develop ASD or PTSD. Three levels of prevention to reduce the risk of mental disorders have been proposed by Mrazek & Haggerty (1994): universal, selected and indicated preventions. With regard to PTSD, universal or primary prevention encompasses general

prevention of traumatic experiences; examples include sexual assault or child maltreatment awareness programs. Individuals with identified risk factors for developing PTSD are targeted in selected prevention programs, e.g. soldiers prior to deployment or first-response disaster relief workers. These individuals have had previous exposure to potentially traumatizing situations and are offered brief psychotherapy by mental health counselors. The third and last level of prevention targets individuals who exhibit subsyndromal symptoms (e.g., irritability, dissociation, sleep disturbances) of PTSD but do not meet full criteria yet. Patients with Acute Stress Disorder or Adjustment Disorder would benefit from an indicated prevention in order to prevent chronicity and/or worsening of impairments.

6.1 Treating the acutely traumatized individual

6.1.1 Psychological first aid

In the immediate aftermath of a traumatic event, basic steps can be taken to diminish the psychological devastation felt by victims. Such "psychological first aid" has the goals of creating an environment that: 1) provides safety; 2) is calming; 3) allows connectedness to others; 4) enhances self-efficacy, and; 5) instills hope. **Table 3** provides some guidance for people assisting in the aftermath of a trauma.

DO	DON'T
Help meet basic needs (food, shelter, medical care)	React negatively to traumatized people who are upset and being difficult
Listen to people who want to talk about their trauma experience	Force people to share their experiences with you
Provide accurate information about the trauma that has occurred	Make promises that cannot be kept
Help people contact relatives and friends	Criticize existing relief activities in front of people experiencing the trauma
Provide suggestions for people to help themselves	Tell people how they should be thinking, feeling or acting after the trauma
Remind people more help is on the way (if this is indeed the case)	Give simple reassurance such as "Everything will be OK"
Establish routines, particularly for sleep/wake cycles	Limit exposure of people to information about the trauma (such as repeated news reports or video)

Table 3. Do's and don'ts of psychological first aid

The principles of psychological first aid in the prevention of PTSD and adverse psychiatric sequelae after trauma were applied in the case of 33 Chilean miners who were trapped deep in a mine after a structural collapse in August 2010. Their plight underground captured worldwide attention until they were rescued after 69 days. Their situation was certainly considered a traumatic event – a sudden experience of being trapped underground, and for the first several weeks they did not know if people on the surface knew they were alive.

By all accounts, the men coped remarkably well in their dire situation. A number of psychological first aid measures likely contributed to the good outcomes. First, by having a group of 33 trapped together, feelings of isolation were reduced, and a sense of camaraderie could be built. Importantly, a senior miner exercised judicious leadership of the men, maintaining order and social structure. He divided them into teams and assigned duties to maximize their survival and comfort. Later, rescuers provided tasks for the men to do to aid in the rescue efforts, which reduced helplessness and provided a sense of control.

When rescuers successfully established contact with the miners through a small drilled hole, it provided reassurance that help was coming, and provided a means by which the men could be informed of the rescue efforts and receive notes from loved ones. The miners maintained a 24 hour light-dark schedule using truck batteries to ensure adequate rest. Initial food and water supplies were carefully apportioned, and later supplemented by supplies from rescuers. Fortunately, none sustained significant injuries from the accident, which would have increased the psychological stress of the situation. Thus, by attending to physical needs, maintaining daily routines, establishing basis for hope and contact with loved ones, and by giving the miners a role in their own rescue, the risks for severe psychological breakdown were minimized.

Websites with information regarding trauma and PTSD that victims and families may find useful are listed in **Table 4**.

ORGANIZATION	INTERNET ADDRESS
American Psychological Association	http://www.apa.org/topics/ptsd/index.aspx
Anxiety Disorders Association of America	http://www.adaa.org/understanding-anxiety/posttraumatic-stress-disorder-ptsd
United States Department of Veterans Affairs/ The National Center for PTSD	http://www.ptsd.va.gov/
PTSD-help network (veteran-to-veteran network)	http://www.ptsdhelp.net/
Deployment Health Clinical Center	http://www.pdhealth.mil/clinicians/ptsd.asp
The PTSD Alliance	http://www.ptsdalliance.org/
National Institute of Mental Health	http://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml
Victim Assistance Online	http://www.vaonline.org/trauma.html
The European Society for Traumatic Stress Studies	https://www.estss.org/learn-about-trauma/
The National Crime Victims Research and Treatment Center	http://colleges.musc.edu/ncvc/
National Child Traumatic Stress Network	http://www.nctsn.org/

Table 4. Internet resources for PTSD

6.1.2 Psychological debriefing

Psychological Debriefing refers to psychological interventions initiated within days after a traumatic event that aim to prevent maladaptive responses to trauma. Psychoeducation about expected reactions to trauma exposure is a component of all debriefing techniques. Perhaps the most widely used form of acute post-trauma intervention is Critical Incident Stress Debriefing (CISD). Originally developed for occupations frequently exposed to potentially traumatizing situations, such as emergency medical personnel, firefighters or police officers, CISD has been increasingly applied to the direct victims of trauma (Mitchell & Everly, 2001). CISD typically is performed in the course of a single, several-hour group session and involves several phases. Besides psychoeducation, other key components of CISD are the elicitation of thoughts and feelings experienced during the trauma, recounting

the worst part of the incident, and identification of stress reactions and how to manage them. Although CISD has been employed in a wide range of group-trauma situations, there is now substantial doubt about the intervention's effectiveness. Meta-analyses of clinical trials have not shown CISD to prevent the development of PTSD (van Emmerik et al., 2002); in fact some studies suggest CISD may produce an increase in psychopathology over untreated controls. (Bledsoe, 2003; Mayou et al., 2000). Adverse outcomes may be due in part to the group setting in which everybody is invited to share their experiences, irrespective of the extent of their traumatization, which may add to the sense of carnage and danger. Additionally, sharing personal reactions to a traumatic situation with strangers may heighten anxiety in vulnerable individuals.

6.1.3 Early pharmacological interventions

Given that resilience is the typical response to trauma, the use of *a priori* medication approaches as a selected preventive treatment immediately after trauma may reflect a therapeutic over-reach, particularly given our limited understanding of the biology of PTSD (Sones et al., 2011). Nevertheless, the inroads made in understanding PTSD pathophysiology have led to the exploration of several pharmacological approaches to prevent PTSD development, with particular focus on the noradrenergic and HPA axis systems. To inhibit the effects of greater SNS activation and NE signaling among people who will eventually develop PTSD after a trauma, the beta-adrenergic receptor antagonist ("beta-blocker") propranolol has been studied as a prospective treatment for emergency room trauma and surgical trauma patients. Despite early data suggesting benefit in reducing traumatic memory consolidation (Brunet et al., 2008), subsequent studies have not found propranolol effective at preventing PTSD in these settings (Hoge et al., 2011; M.B. Stein et al., 2007). Clonidine, an alpha-2 receptor antagonist that acts to reduce norepinephrine release, has also been proposed as a preventative treatment for PTSD, though there are no controlled studies of this intervention. Finally, based on the finding of low cortisol concentrations post-trauma in patients who later develop PTSD, administration of hydrocortisone (a glucocorticoid) soon after trauma was found to prevent the development of PTSD in small studies, a finding worthy of further pursuit (De Quervain & Margraf, 2008).

Two recent naturalistic studies of physically injured patients suggest that administration of an opiate medication, morphine, immediately after trauma may lessen later PTSD severity (Bryant et al., 2009; Holbrook et al., 2010). Opioids reduce norepinephrine transmission, though wheher any preventive effects derive from that mechanism, which would imply benefit in non-injured patients, or simply through the benefits of pain control are unknown.

7. Treatment

7.1 Treatment of acute stress disorder

Cognitive behavioural therapy (CBT) approaches incorporating a combination of prolonged exposure and cognitive restructuring have been the most extensively studied treatments for ASD. Several studies have demonstrated that a short course (approximately 5 sessions) of CBT is effective in preventing the progression of ASD to PTSD, and that the gains can be maintained for years following treatment (Bryant et al., 2003). There is growing evidence that the prolonged exposure component, rather than cognitive restructuring, is the more potent part of the therapy (Bryant et al., 2008), which is consistent with the growing focus on prolonged exposure for the treatment of PTSD. An Israeli study that compared cognitive

therapy, prolonged exposure therapy, escitalopram 10-20 mg/d or placebo found substantial superiority in preventing PTSD for both psychotherapies over the antidepressant, which did not separate from either placebo or an untreated control group (Shalev, 2007).

7.2 Treatment of PTSD

All the leading guidelines and evidence-based reviews of treatments for PTSD recommend some form of psychotherapy as the preferred first line treatment for PTSD. However, controversy arises regarding the stage at which pharmacotherapy should be considered. The Institute of Medicine (2008) report goes so far as to assert there is insufficient evidence for the efficacy of pharmacotherapy, though it should be noted that this report did not definitively conclude that medications were ineffective for PTSD. Some national guidelines recommend SSRI medication or psychotherapy as first line treatments (Baldwin et al., 2005; Swinson et al., 2006; Ursano et al., 2004; Benedek et al., 2009) whereas others recommend relegating medications to second line treatments to be used only if psychotherapy fails or is unavailable (Forbes et al., 2007; National Collaborating Centre for Mental Health, 2005). Actual treatment choices in clinical practice are influenced by other factors, including treatment availability, patient preference, and the presence of significant comorbid disorders, such as depression, bipolar disorder, or other anxiety disorders (Rakofsky & Dunlop, 2011).

7.2.1 Psychotherapies

CBT refers to a variety of psychological interventions that address the dysfunctional thoughts and maladaptive behaviors that serve to maintain a state of mental illness. For PTSD, the behavioral intervention of exposure is a key component of CBT treatment, and includes the confrontation of the traumatic memory in a safe, therapeutic setting. Once the trauma memory is activated, the patient processes the information and the emotion repeatedly ("habituation"), ultimately forming new, non-fear inducing memories of the traumatic event ("extinction"). CBT also commonly includes cognitive restructuring of maladaptive beliefs, such as guilt and overly pessimistic views about the world and self, by identifying and replacing excessively negative perceptions and interpretations with more realistic appraisals (Bryant et al, 2008).

7.2.1.1 Prolonged exposure

A specific form of CBT often used for PTSD, called Prolonged Exposure, is delivered over the course of 9-12 ninety minute sessions (Foa et al., 1999). Initial sessions involve education about common reactions to trauma and breathing control for relaxation. Subsequently, prolonged and repeated recounting of the memory is performed (called "imaginal exposure"), during which the patient is encouraged to include as much sensory and emotional detail of their traumatic experience as possible. Between sessions, patients are assigned homework, which includes listening once or twice daily to an audiotape of their imaginal exposure created in session with the therapist. Later in therapy in vivo exposure is introduced, in which patients confront places and objects in the real world they have avoided due to their association with the traumatic event, but when in fact they are objectively safe. Throughout the treatment, the therapist discusses with the patient their thoughts and feelings related to the exposure experiences. All these components are intended to directly challenge the fear associated with the trauma.

Prolonged exposure is the only treatment with sufficient scientific support to be recommended by the Institute of Medicine (2008) for the treatment of PTSD. Unlike other

psychotherapies that have demonstrated benefit only in relation to a no-treatment wait-list control condition (which fail to control for the non-specific effects of therapy), prolonged exposure has demonstrated benefit in reducing PTSD symptoms beyond other non-trauma-related treatment, such as present-centered therapy (Schnurr et al., 2007) and narrative therapy (Bichescu et al., 2007). Exposure therapy has demonstrated maintenance of treatment gains for up to 5 years post-treatment (for further review, see Ponniah & Hollon, 2009). The primary drawback from prolonged exposure treatment is patient drop-out, presumably due to distress induced by the procedure. Moreover, it may be difficult to get patients with high levels of avoidance to agree to this form of treatment. Unfortunately, prolonged exposure therapy is not yet routinely used in clinical practice, due to inadequate training of therapists, as well as excessive concerns about re-traumatization or decompensation of the patient.

7.2.1.2 Eye movement desensitization and reprocessing (EMDR)

EMDR uses two simultaneous attention tasks to enable the patient to process the traumatic event. The patient is asked to focus on the negative, fear-inducing emotions and thoughts (a form of exposure) while simultaneously engaging in a repetitive task, such as hand tapping, eye-movements, tactile stimulation or sounds. These are done together until the initially felt distress wanes and can be replaced by positive or neutral trauma-related thoughts (Shapiro, 1989). Benefits of EMDR have been demonstrated in various patient populations, such as rape victims (Rothbaum, 1997), combat veterans (Carlson et al., 1998) or interpersonal violence victims (van der Kolk et al., 2007). The concept of EMDR is not without criticism, especially the eye-movement component (Institute of Medicine, 2008). Critics note that treatment success may be obtained solely through the cognitive and emotional processing of the traumatic memory as well as the learning of coping skills, rather than from the eye-movement technique itself.

7.2.1.3 Cognitive processing therapy (CPT)

CPT is a form of CBT often used in the treatment of PTSD (Resick & Schnicke, 1993). CPT conceptualizes PTSD as a *disorder of non-recovery* in which maladaptive beliefs surrounding the traumatic event cause strong negative emotions that prevent the natural cognitive processing of the situation. The goal is for the patient to understand the pattern of trauma memory avoidance and associated belief systems. Problematic belief systems, such as survivor guilt, are identified as 'stuck points' that interfere with resolving the traumatic event. Traditionally, patients are asked to write a detailed emotional account of their traumatic experiences and read them out loud to the therapist, thus breaking the pattern of avoidance. Utilizing Socratic dialogue (i.e., asking questions to enable the patient's own insights instead of providing advice), as well as teaching the patient cognitive skills to identify and modify affected belief systems (such as safety, trust and control) are effective ways to teach the patients to cope with the traumatic event. CPT has demonstrated superiority over wait-list control groups for veterans with PTSD (Monson et al., 2006), and has been found to be equally effective as prolonged exposure among female rape victims (Resick et al., 2002).

7.2.1.4 Stress inoculation training

SIT, also referred to as Stress-Management training, is not trauma-specific and includes relaxation techniques as well as stress-inoculation training. The patient learns skills such as

abdominal breathing, progressive muscle relaxation, positive statements, distraction, and assertiveness. The primary focus of SIT is to help the patient increase confidence in his or her ability to cope with the fear and anxiety that arise from reminders of their trauma. SIT is sometimes used as an active control comparison condition in psychotherapy studies of anxiety disorders, but it has also been found to be as effective as PE in some studies (Foa, et al., 1999).

7.2.2 Pharmacotherapies

7.2.2.1 Monotherapy

Selective serotonin reuptake inhibitors (SSRIs) are the preferred initial medication treatment for PTSD. Two SSRIs, paroxetine and sertraline, have received regulatory approval for the treatment of PTSD in the United States and Europe. A recent Cochrane Collaboration meta-analysis found that among medication treatments for PTSD, SSRIs had the most convincing effect, and that the included trials were of relatively high quality (D.J. Stein et al., 2006). Several other agents also have data suggesting efficacy, including venlafaxine, mirtazapine, some tricyclic antidepressants (TCAs, amitriptyline, imipramine) and the monoamine oxidase inhibitor (MAOI) phenelzine. Mirtazapine positively affects sleep, and is recommended as a second line agent by many guidelines. The clinical trials supporting the use of TCAs and MAOIs for PTSD had methodological limitations, but these medications can be effective for some patients. An exception is the reversible MAOI brofaromine, which showed no benefit in two large placebo-controlled trials (Baker et al., 1995). TCAs and MAOIs are usually prescribed only after failure with SSRIs, SNRIs or mirtazapine, due to their potential for serious cardiovascular events and drug interactions.

An additional agent used for the treatment of PTSD is nefazodone. This 5HT2a receptor antagonist and weak serotonin reuptake inhibitor has support of efficacy from a placebo-controlled trial, and has been widely employed in the treatment of combat veterans (L.L. Davis et al., 2004). Use in recent years has declined due to its association with a low-risk of hepatotoxicity (the estimated rates of liver failure are 1 case per 30,000 – 250,000 patient-years of exposure), relegating its use to patients unresponsive to other treatments.

Dose ranges for medications used to treat PTSD are similar to those required to treat MDD, and should be up-titrated at 4 week intervals until remission is obtained or intolerance occurs. Response to medication may take 1-3 months. More sustained treatment can provide further gains and reduced likelihood of relapse (Davidson et al., 2002). Should the first SSRI treatment prove ineffective or intolerable, a second SSRI or venlafaxine should be tried (Davidson et al., 2006).

7.2.2.2 Augmentation

Pharmacological treatment decisions become more challenging when medication provides a clear benefit, but the patient continues to have some significant ongoing symptoms. In these cases, it is probably better to add a second medication ("augmentation") rather than switch to another monotherapy. There is some evidence that the atypical antipsychotics olanzapine and risperidone can augment SSRI response in patients with PTSD (M.B. Stein et al., 2003; Bartozkis et al., 2005). Open-label data suggest that quetiapine may also have value in the treatment of PTSD, particularly for sleep-related symptoms (Robert et al., 2005). However, the side effect risks with these medications, including significant risk for weight gain and metabolic disturbances, argue that they should be reserved for the most treatment-resistant cases. The choice of augmenting medication may be guided in part by the types of persisting symptoms.

Prazosin, at a dose of 2-15 mg/day, has demonstrated specific effects on sleep quality and nightmares in patients who were also receiving other medications for PTSD (Raskind et al., 2003; Raskind et al., 2007; Taylor et al., 2008). Other adrenergic agents sometimes used adjunctively in combat veterans are guanfacine and clonidine. In contrast to prazosin, which is an alpha-1 receptor antagonist, these alpha-2 receptor agonists, which act to reduce noradrenergic signaling via inhibitory feedback, did not prove superior to placebo (Neylan et al., 2006). The efficacy of beta-blockers in chronic PTSD have not been studied in controlled trials.

Another medication with positive sleep effects is mirtazapine, which is recommended as a second line agent by many guidelines. The anti-epileptic agent and GABA modulator valproic acid was not found to be effective as a monotherapy in an 8-week placebo-controlled trial in veterans with PTSD (L.L. Davis et al., 2008). Nevertheless, valproic acid is sometimes used as an adjunctive agent, particularly among combat veterans with prominent hyperarousal symptoms (Fesler, 1991; Clark et al., 1999).

Other anti-epileptic agents have been studied for use in chronic PTSD. The most promising is topiramate, an agent thought to act by blocking voltage-gated sodium channels, which significantly reduced re-experiencing symptoms and improved remission rates in a 12-week placebo-controlled study (Tucker et al., 2007). A very small randomized trial suggested efficacy for lamotrigine, another voltage-gated sodium channel antagonist (Hertzberg et al., 1999). In contrast, tiagabine, a GABA reuptake inhibitor, proved ineffective compared to placebo in a large 12-week trial (Davidson et al., 2007). In addition, small open label studies suggest potential benefits for phenytoin, levetiracetam, and carbamazepine (reviewed in Berger et al., 2009).

Benzodiazepines are commonly used to treat anxiety, but there is little support for their use in PTSD. A specific concern about benzodiazepines is their impairing effect on learning. Recovery from PTSD is thought to require new learning about the meaning of stimuli and contexts associated with the trauma, and benzodiazepines may diminish that ability. It is important to note that very little research on the use of benzodiazepines to treat PTSD has been performed, so a definitive statement about inefficacy cannot be made (Braun et al., 1990). Nevertheless, they should not be considered as monotherapy agents for patients with PTSD, and generally should not be used to treat anxiety in the acute aftermath of a traumatic event (Gelpin et al., 1996; Mellman et al., 2002).

A consistent finding across nearly all medication trials for PTSD is that patients with civilian trauma demonstrate more benefit from active medication than patients with combat-related trauma. It is important to note that no guidelines recommend the use of bupropion as a standard agent for the treatment of PTSD, and a large placebo-controlled trial showed no benefit for this medication in treating PTSD (M.E. Becker et al., 2007). Unfortunately, no large trials have compared different pharmacotherapies, so support for the relative efficacy of one class of medications over another does not exist, and there are no predictors for which medication is best suited for a particular individual. Rather, issues of cost, availability, potential side effects and other comorbid illnesses often guide treatment selection.

Other problems that complicate treatment choices for PTSD are the relative paucity of studies of long-term outcomes, and minimal study among patients with prominent comorbid conditions (e.g. substance abuse), or treated in primary care settings. Thus, the generalizability of findings from clinical trials remains uncertain. In general, comorbid substance abuse should be treated before or simultaneously with treatment for PTSD. Also,

in patients with comorbid bipolar disorder, optimization of mood stabilization treatment should usually be the initial focus of treatment (Rakofsky & Dunlop, 2011).

DRUG	MECHANISM	CLINCIALTRIALS.GOV IDENTIFIER(S)
Aprepitant	Antagonist of neurokinin type 1 receptors, thereby blocking effect of Substance P. May reduce alcohol cravings in PTSD patients with alcohol dependence	NCT00896038
Carvedilol	Beta receptor blocker; blocks the effect of norepinephrine at these receptors. Being studied in low dose form.	NCT01221792
D-Cycloserine	Glutamate receptor modulator. May improve extinction learning in PE	NCT00356278; NCT00875342
Ganaxolone	Synthetic neurosteroid; modulates GABA-A receptors.	NCT01339689
GSK561679	CRH type 1 receptor antagonist.	NCT01018992
Hydrocortisone	Synthetic glucocorticoid; acts like cortisol. Being studied as monotherapy and adjunctively to improve extinction learning in PE.	NCT00706173; NCT01090518; NCT00751855
Ketamine	NMDA glutamate receptor antagonist	NCT00749203
Methylene Blue	Metabolic enhancer; increases brain utilization of oxygen. May improve extinction learning in PE	NCT01188694
Nepicastat	Inhibits enzyme dopamine beta hydroxylase, thereby reduces norepinephrine production	NCT00659230

(GABA: Gamma-aminobutyric acid; NMDA: N-methyl D-aspartic acid; PE: prolonged exposure therapy)

Table 5. Exploratory pharmacologic interventions for PTSD

7.2.3 Sleep therapies

Sleep disturbances in PTSD are extremely common and often become a focus of treatment. Specific sleep problems in PTSD include insomnia and recurrent nightmares. It is unclear whether nightmares occur during rapid-eye-movement (REM) sleep or non-REM sleep, or both. Nightmares can contribute to sleep-related anxiety, such as fear of going to sleep, fear of going back to sleep after awakening, and fear of the dark. Sleep-related anxieties may be particularly evident among PTSD patients whose trauma is associated with nighttime or beds, such as rape victims. Often, to combat insomnia and nightmares, patients will use alcohol to induce sleep and suppress dreams. Although alcohol may provide these short-term benefits, there are long-term consequences from sustained alcohol use including sleep fragmentation, rebound REM sleep from alcohol withdrawal, and risk of abuse and dependence (Lamarche & De Koninck, 2007).

Despite the high frequency of subjective complaints about sleep disruption, objective assessments of sleep in patients with PTSD have been very inconsistent, with no clear abnormalities identified. One large community-based polysomnography study found only that PTSD patients had more frequent brief arousals after REM sleep than control patients; (Breslau et al., 2004). This study suggests that some PTSD sleep complaints may be stem from greater subjective perceptions of brief awakenings, though whether this effect represents a vulnerability for PTSD or a consequence of the illness is unknown. In general, patients with PTSD should be screened for the presence of any other sleep disorders that may aggravate insomnia, such as obstructive sleep apnea and restless legs syndrome;

treatment of these comorbid conditions may improve PTSD treatment outcome (Lamarche & DeKoninck, 2007).

Sleep problems that persist despite psychological or pharmacological interventions for PTSD can be addressed through insomnia-specific treatments. CBT packages developed specifically to treat insomnia, which include strategies like sleep restriction, stimulus control, education, and alteration of beliefs about insomnia, have been successfully applied in patients with PTSD (Ulmer et al., 2011). To target nightmares specifically, imagery rehearsal therapy (IRT) has demonstrated benefit among civilian PTSD patients. In IRT, patients write down the recurring dream(s), then re-write it into a non-threatening form, and finally use imagery to rehearse the revised dream as practice during the day (Krakow et al., 2001).

In addition to the use of prazosin for nightmares, and mirtazapine for insomnia, additional medications are often used for sleep complaints in PTSD patients. Trazodone (dosed at 50-200 mg at bedtime) and the non-benzodiazepine sedatives, such as zolpidem, are among the most commonly employed, although there are no placebo-controlled studies of these medications for PTSD-specific insomnia. Low dose quetiapine (25-200 mg at bedtime) is also used for severe sleep complaints, but this medication requires ongoing monitoring for metabolic and movement disorder risks.

8. Future of PTSD

Our understanding of PTSD continues to evolve. Significant advances in the coming years are likely in the areas of the characterization of the illness, approaches to treatment, and our understanding of decision-making in PTSD patients.

8.1 Diagnostic criteria

A new edition of the DSM, DSM-V, is expected to be published in the near future (http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=165). Major proposed revisions to the DSM-IV criteria for PTSD include:

1. Dropping the A2 criterion, due to a lack of evidence that experiencing a sense of horror, terror or helplessness at the time of the trauma has any diagnostic utility.
2. A revised definition of "trauma" that better specifies what experiences are considered to cross the "traumatic threshold."
3. Separating the current "C"-criteria into two categories: one specifically for avoidance of reminders of the trauma, and the second focusing on overall negative emotional experiences, chosen from factor analyses of symptoms.
4. Eliminating the distinction between Acute and Chronic PTSD due to lack of evidence supporting this distinction.

8.2 New treatments

A key component of prolonged exposure therapy is the reactivation of the traumatic memory as intensely and thoroughly as possible. To enhance this process, computers can be used to augment the sensory experiences associated with the memory. Virtual reality is a computer-based form of prolonged exposure therapy in which the patient actively participates in a three-dimensional virtual world by means of head-mounted displays. The virtual reality device incorporates display screens for eyes, as well as earphones and head-tracking devices. If desired, vibration platforms and olfactory stimuli can be integrated, creating a maximally real sensory experience. Immersion in this virtual world enhances the

emotional engagement with the traumatic memory, as well as controlling all stimuli relevant to the individual trauma (Rothbaum et al., 2010). In this therapeutic model, patients are gradually exposed to their traumatic event and the therapist adjusts the multimodal stimuli to elicit the appropriate anxiety response. Pilot studies suggest benefit of the use of virtual reality in exposure therapies, and large trials of this treatment modality are underway.

New medications currently in clinical trials for PTSD are listed in Table 5 Most new treatment approaches to PTSD look to build on our increasingly sophisticated understanding of memory formation and extinction (e.g. Ressler et al., 2004). Several medications are being explored as means to augment the extinction learning that occurs in prolonged exposure therapy. The most advanced of these medications is D-Cycloserine (DCS), a drug previously used to treat tuberculosis, which acts as a partial NMDA (N-methyl-D-aspartate)-glutamatergic receptor agonist and thereby enhances synaptic formation during learning. Indeed, DCS has been found to enhance memory in humans (Tsai et al., 1999). Multiple trials have also demonstrated benefit of DCS over placebo in enhancing exposure-based treatments for phobic disorders (for review, see M. Davis et al., 2006). In these studies, DCS is dosed approximately one hour prior to each exposure therapy session (usually about 5 total sessions); the medication is not taken on a daily basis between therapy visits. Current studies combining DCS with exposure therapy, including virtual reality prolonged exposure for war veterans with PTSD, will soon determine whether the benefits of DCS enhancement of psychotherapy observed in other anxiety disorders can be extended to PTSD.

Memory erasure represents the ultimate manipulation of memory processes. Although in its infancy, this approach proposes to eliminate the powerful emotions developed in connection to the memory a traumatic event, rather than simply reduce their impact, as occurs through extinction learning in current PE treatment. Recent work in mice identified that fear reactions associated with a newly-learned memory can be erased through subsequent behavioral experience by removing certain calcium-permeable alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors from the synapses in the lateral amygdala during a short time window after fear learning has occurred (Clem & Huganir, 2010). Manipulating this process in humans may allow for complete erasure of a traumatic memory, though the ethical implications of memory erasure shall need consideration as this research goes forward.

More traditional medication-based symptom-suppression approaches are also being explored. Theories postulating dysfunction in the HPA axis in PTSD (and MDD) have spawned a significant effort to discover agents that can modify this system (Holsboer & Ising 2008). Several CRH type 1 receptor antagonists have been developed, but none have yet proven superior to placebo in the treatment of MDD. Whether these agents may be of benefit in PTSD will be determined from an ongoing trial.

8.3 Decision making

Imaging research to date has focused primarily on the fear, anxiety and impaired cognition of patients with PTSD. However, a diagnostic criterion present in most patients with PTSD is a markedly diminished interest or participation in activities. This hedonic item reflects a change in risk-reward experience in PTSD. As discussed by Stein & Paulus (2009), this change represents a manifestation of a new homeostatic steady state between approach and avoidance. Emerging work employing neuroeconomic approaches to analyze decision-making in patients with many psychiatric disorders, including PTSD, may greatly inform

the underlying biological disruptions in these conditions, and identify targeted approaches for psychotherapeutic and pharmacologic treatments (Elman et al., 2009).

9. Conclusion

PTSD is now firmly established as a characteristic psychological reaction to a sudden, unexpected terrible event. Although much more work is required to further delineate the biology of this disorder, the ability to model fear responding in animals gives hope that this disorder will be one of the more tractable psychiatric illnesses in the years ahead. If applied with rigor and concerned caring, cognitive behavioral forms of psychotherapy can be tremendously helpful to many patients with PTSD. Much remains to be done to improve pharmacotherapy approaches for PTSD, for which new neurobiological discoveries are necessary to guide innovation. Perhaps most promising is the potential to combine psychotherapy with medication, such as with D-cycloserine, to enhance outcomes combined with prolonged exposure therapy. Though the illness of PTSD is daunting for patients and clinicians alike, there is a justifiable basis for optimism about future treatment of this condition.

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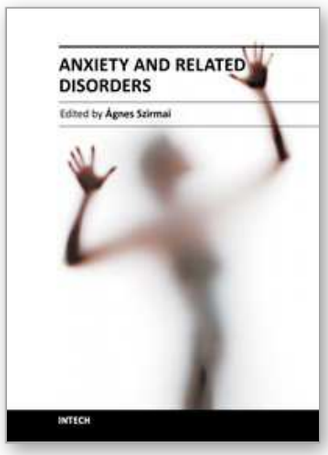
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Anxiety disorders are one of the most common psychiatric disorders worldwide and many aspects of anxiety can be observed. Anxious patients often consult primary care physicians for their treatment, but in most cases they do not accept the diagnosis of anxiety disorder. Anxiety is a symptom that could be seen in many organic disorders and can accompany almost any psychiatric disorder. Anxiety disorders are frequent and are associated with significant distress and dysfunction. Stigmatization is an important factor in insufficient diagnosis. The problems of anxiety cover all fields of life. This book intends to describe the epidemiological aspects and the main co-morbidities and consecutive diseases of the anxiety disorders.

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