

Suicidal behavior in comorbid depression and post-traumatic stress disorder

Suicidinis elgesys esant depresiniam ir potrauminio streso sutrikimams

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SUMMARY

Suicide is a major public health problem. Suicide accounts for about one million deaths resulting from about ten million suicide attempts with significant socioeconomic costs and consequences. Among suicide victims, 60% suffer from depression, about 30% have other psychiatric illnesses, including post-traumatic stress disorder (PTSD) and about 10% have no established psychiatric diagnoses. PTSD is a frequent psychiatric illness. PTSD is often comorbid with major depressive disorder (MDD) and other psychiatric conditions. I have earlier suggested that some or all individuals diagnosed with comorbid PTSD and MDD may have a separate psychobiological condition that can be termed "post-traumatic mood disorder" (PTMD). The idea was based on the fact that a considerable number of research observations found that individuals suffering from comorbid PTSD and MDD differed clinically and biologically from persons with PTSD alone or MDD alone. Patients with co-occurring PTSD and MDD are characterized by greater severity of symptoms and the higher level of impairment in social and occupational functioning compared to individuals with PTSD alone or MDD alone. Biological data supporting the concept of PTMD include the findings from neuroendocrine challenge, cerebrospinal fluid, neuroimaging, sleep and other studies. PTMD is associated with suicidal behavior. It is important to develop interventions to prevent PTMD in traumatized individuals, measures to prevent suicidal behavior in this patient population, and to study psychobiology of PTMD in order to develop treatments for PTMD. Priorities for intervening to reduce suicidal behavior in traumatized persons lie with interventions focused upon the improved identification and treatment of individuals with psychiatric disorders including PTMD.

SANTRAUKA

Savižudybės yra svarbi visuomenės sveikatos problema. Savižudybės sudaro maždaug milijoną mirčių, kylančių iš maždaug dešimt milijonų suicidinių bandymų ir palieka reikšmingas socialines ekonomines pasekmes. 60 proc. savižudybės aukų kenčia nuo depresijos, apie 30 proc. turi kitus psichikos sutrikimus, įskaitant potrauminį streso sutrikimą (angl. *post-traumatic stress disorder*, PTSD), ir apie 10 proc. neturi jokios nustatytos psichiatrinės diagnozės. PTSD yra dažnai pasitaikanti psichikos liga, dažnai kartu einanti su didžiąja depresija (angl. *major depressive disorder*, MDD) ir kitais psichikos sutrikimais. Aš anksčiau maniau, kad kai kurie ar visi asmenys, kuriems diagnozuotas potrauminis streso sutrikimas su didžiąja depresija, gali būti atskiros psichobiologinės būsenos, kurią galima pavadinti „potrauminiu nuotaikos sutrikimu“ (angl. *post-traumatic mood disorder*, PTMD). Idėja buvo pagrįsta faktu, kad didelis mokslinių stebėjimų skaičius rodo, kad asmenys, kenčiantys nuo komorbidinio PTSD ir MDD, kliniškai ir biologiškai skyrėsi nuo asmenų sergančių PTSD ar MDD. Pacientams su komorbidiniu PTSD ir MDD sutrikimu yra būdingi daug stipresni simptomai ir gilesni socialinio ir profesinio funkcionavimo pažeidimai lyginant su asmenimis, patiriančiais pavienį PTSD ar MDD. PTMD koncepciją palaikantys biologiniai duomenys apima neuroendokrininės sistemos, cerebrospinalinio skysčio, neurologinio vaizdo, miego ir kitų tyrimų rezultatus. PTMD yra susijęs su suicidiniu elgesiu. Svarbu sukurti intervencijas, trukdančias PTMD išsivystymą traumuotiems asmenims, bei priemones, padedančias išvengti suicidinio elgesio šiai pacientų grupei, ir tyrinėti PTMD psichobiologiją tam, kad patobulinti PTMD gydymą. Prioritetai skiriami intervencijoms, mažinančioms traumuotų pacientų suicidinį elgesį, kartu su priemonėmis nukreiptomis į geresnį psichikos sutrikimų, įskaitant ir PTMD diagnozavimą bei gydymą.

SUICIDE AS A MEDICAL AND SOCIAL PROBLEM

Suicide is a major public health problem. Suicide accounts for about one million deaths resulting from about ten million suicide attempts with significant socioeconomic costs and consequences [1]. If every suicide affects at least six family members or friends, then every year in the world there would be about 6 million new survivors. Suicide rates range from 4.0 per 100 000 in Mexico (in 2006) to 6.4 per 100 000 in the UK (in 2007) and 30.4 per 100 000 in Lithuania (in 2007) [2–4]. In the US, suicide was ranked as the 11th leading cause of death among persons ages 10 years and older, accounting for

33,289 deaths in 2006 [5]. It is the fifth leading cause of years of potential life lost before the age of 65 in the US.

Risk factors for suicidal behavior may be thought of as leading to or being associated with suicide; that is, people "possessing" the risk factor are at greater potential for suicidal behavior [6–8]. Protective factors, on the other hand, reduce the likelihood of suicide. They enhance resilience and may serve to counterbalance risk factors. Risk and protective factors may be biopsychosocial, environmental or sociocultural in nature. Although this division is somewhat arbitrary, it provides the opportunity to consider these factors from different perspectives. Understanding the interactive relationship

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between risk and protective factors in suicidal behavior and how this interaction can be modified are challenges to suicide prevention. Unfortunately, the scientific studies that demonstrate the suicide prevention effect of altering specific risk or protective factors remain limited in number. However, the impact of some risk factors can clearly be reduced by certain interventions such as providing lithium for bipolar disorder or strengthening social support in a community [6, 7].

Suicide is not simply a logical response to extreme stress and this conclusion led to the hypothesis of a stress diathesis model of suicidal behavior [6, 7]. The diathesis or predisposition to suicidal behavior is a key element that differentiates psychiatric patients who are at high risk from those at lower risk. The objective severity of the psychiatric illness or number of recent life events do not assist in identifying patients at high risk for suicide attempt. Instead it is the impact of the illness or life events on the person that varies greatly and is correlated with suicidal behavior.

Suicidal behavior has been conceptualized as a continuum of thoughts and behaviors ranging from suicidal ideation to completed suicide. Research delineated seven distinct categories of 'suicidality': (1) completed suicide, (2) suicide attempt, (3) preparatory acts toward imminent suicidal behavior, (4) suicidal ideation, (5) self-injurious behavior without intent to die, (6) non-deliberate self-harm, and (7) self-harm behavior with unknown suicidal intent [9]. Among suicide victims, 60% suffer from depression, about 30% have other psychiatric illnesses, including post-traumatic stress disorder (PTSD) and about 10% have no established psychiatric diagnoses [6, 8].

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) is a frequent psychiatric illness precipitated by exposure to a psychologically distressing event. PTSD first appeared in the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-III) in 1980 [10, 11], arising from studies of the Vietnam war, and of civilian victims of natural and man-made disasters [12, 13]. However, the study of PTSD dates back more than 100 years. Before 1980, post-traumatic syndromes were recognized by different names, including railway spine, shell shock, traumatic (war) neurosis, concentration-camp syndrome, and rape-trauma syndrome [11, 12]. The symptoms described in these syndromes overlap considerably with what we now recognize as PTSD. According to the most recent edition of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-IV-TR) [14], the essential feature of PTSD is the development of characteristic symptoms following exposure to an extreme traumatic stressor characterized by direct personal experience of an event that involves actual or threatened death or serious injury, or other threat to one's physical integrity; or witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate. The person reacts to this event with fear and helplessness, and tries to avoid being reminded of it.

PTSD holds an important place in psychiatric thinking for several reasons. First it is one of the few disorders (besides disorders induced by substances or general medical conditions) in which an etiology is specified, despite the effort

of DSM-IV to be atheoretical. As a consequence it has become a paradigm for understanding the role of the environment in psychopathology. Throughout the history of the concept of PTSD there has been a tension between an emphasis on factors relating to the host and factors relating to the nature of the trauma in the understanding of the etiology of this disorder.

PTSD is characterized by the presence of three distinct, but co-occurring, symptom clusters [11, 14]. Reexperiencing symptoms describe spontaneous, often insuppressible intrusions of the traumatic memory in the form of images or nightmares that are accompanied by intense physiological distress. Avoidance symptoms involve restricting thoughts and distancing oneself from reminders of the event, as well as more generalized emotional and social withdrawal. Hyperarousal symptoms reflect more overt physiological manifestations, such as insomnia, irritability, impaired concentration, hypervigilance, and increased startle responses. These symptoms must be severe enough to impair social, occupational, or interpersonal function and co-occur for at least 1 month. The impairment from PTSD is amplified by poor coping strategies, substance abuse, co-occurring mood and anxiety disorders, lack of social support, and the accelerated development of stress-related medical conditions. A large body of research indicates that there is a correlation between PTSD and suicide [11, 14]. There is evidence that traumatic events such as sexual abuse, combat trauma, rape, and domestic violence generally increase a person's suicide risk.

PTSD is a disorder of forgetting perhaps even more than of remembering [15, 16]. It is the inability to forget the trauma that leads to the pathology and suffering in PTSD. Forgetting is a critical component of recovery. Of course, if we could not forget, our brains would rapidly be cluttered with information and observations and perhaps more limited in cognitive control functions for other activities.

War, terrorism, and natural disasters like a recent earthquake in Haiti create large populations in distress [15]. Not all distress amounts to mental disorder, but fear, worry, insomnia, and changes in health-risk behaviors all contribute to the health burden of mass violence and are targets for early public health intervention. Substantial evidence supports essential principles of immediate and midterm mass trauma interventions that are now described as psychological first aid [17].

About 30 armed conflicts are occurring now around the globe involving more than 25 countries [18, 19]. For those in the United States and the United Kingdom, Iraq and Afghanistan are the present teachers of lessons long known and too often forgotten. Epidemiological surveys conducted during the current conflicts in Iraq and Afghanistan suggest that as many as 13% to 17% of service members screen positive for PTSD [20].

THE CONCEPT OF POST-TRAUMATIC MOOD DISORDER

PTSD and major depression are frequently comorbid. For example, Brown and colleagues [21] assessed lifetime anxiety and mood disorders comorbidity in a community sample of outpatients and found that PTSD was the anxiety disorder most likely to be associated with MDD, with 69% of individuals with PTSD also meeting criteria for MDD. Findings from the National Comorbidity Survey indicated that 78% of individuals meeting criteria for both disorders reported that their PTSD preceded the MDD [22].

Many research groups reported that individuals with comorbid PTSD and MDD were characterized by greater severity of symptoms and the higher level of impairment in social and occupational functioning compared to individuals with PTSD alone [23–30]. One study found that comorbidity of PTSD and MDD was associated with more severe symptoms as well as higher levels of disability on all indices (global dysfunction, distress, social impairment, and occupational disability) [30]. Another research group observed that a severity of overall symptoms was three-to fivefold greater in subjects with comorbid PTSD and MDD compared to those with PTSD alone [25]. A large-scale epidemiological survey found that the comorbid group was five times more likely to manifest functional impairment compared to those diagnosed with PTSD alone [23]. A recent study reported that patients with comorbid PTSD and MDD had higher objective MDD, impulsivity, and hostility scores and were significantly more likely to have made a suicide attempt compared to subjects with MDD alone [31]. We found that depressed subjects with comorbid PTSD tended towards earlier age of first hospitalization and a higher number of hospitalizations compared to depressed individuals without comorbid PTSD [32].

Maes et al. [33] reported that there is an association between PTSD with concurrent major MDD and lower affinity of alpha-2 adrenoreceptors, as well as higher plasma tyrosine availability to the brain, not found in patients suffering from PTSD alone. This indicates that monoaminergic mechanisms may play a role in the pathophysiology of comorbid PTSD and MDD.

Woodward et al. [34] found that patients with comorbid PTSD and MDD exhibited less slow wave sleep and less facial (mentalis) electromyographic activity, compared with PTSD patients without comorbid MDD. Patients with comorbid PTSD and MDD did not exhibit the classic rapid eye movement sleep architectural modifications associated with unipolar depression, despite the fact that several other psychophysiological indices of dysphoria were detectable in their sleep.

Cortisol response to placebo or fenfluramine was examined in depressed patients with or without comorbid PTSD and in a control group of healthy volunteers [35]. Depressed patients with comorbid PTSD had the lowest plasma cortisol; depressed patients without comorbid PTSD had the highest plasma cortisol; and healthy volunteers had intermediate levels.

We compared the effect of age on cortisol levels in depressed patients with or without comorbid PTSD and in healthy volunteers [36, 37]. We found that cortisol levels increased with age in depressed patients with PTSD alone; they did not increase in depressed patients with comorbid PTSD or in healthy volunteers. We also observed that the number of previous major depressive episodes was a predictor of the cortisol response to fenfluramine administration in depressed patients without PTSD, but not in depressed patients with comorbid PTSD.

We also reported that depressed subjects with comorbid PTSD had higher cerebrospinal fluid (CSF) homovanillic acid (HVA) levels compared with depressed subjects without comorbid PTSD or healthy volunteers [32]. Higher CSF HVA was present after adjustment for sex, lifetime aggression severity and depression scores, alcoholism, tobacco smoking, comorbid cluster B personality disorder, reported childhood abuse, and psychosis.

Davidson et al. [38] investigated the relationship between chronic PTSD and family psychiatric morbidity. A shared liability for PTSD and MDD, with familial loading for MDD predicting chronic PTSD in trauma survivors was found.

Koenen et al. [39] analyzed data from about 7,000 members of the Vietnam Era Twin Registry. They found substantial genetic overlap between PTSD and MDD and suggested that genes implicated in the etiology of MDD are strong candidates for PTSD and vice versa.

Subjects with PTSD without comorbid MDD and patients with PTSD with comorbid MDD were examined using the script-driven symptom-provocation paradigm adapted to functional magnetic resonance imaging [40]. This study found different patterns of brain activation in subjects with PTSD without comorbid MDD compared to patients with PTSD with comorbid MDD.

PTSD patients with comorbid MDD relative to both healthy controls and trauma-exposed control subject showed reduced norepinephrine transporter expression in the left thalamus [41]. PTSD patients without comorbid MDD did not show differences in norepinephrine transporter expression relative to healthy controls and trauma-exposed control subject, i.e., PTSD patients showed reduced left thalamic norepinephrine transporter expression only when having comorbid MDD.

The dexamethasone suppression-corticotrophin releasing hormone (DEX-CRH) test has shown to be a more sensitive test to assess HPA-axis dysregulation in MDD and therefore may provide a useful test tool to probe HPA-axis regulation in MDD and PTSD [42,43]. To evaluate the effect of PTSD on HPA-axis regulation, the response to a DEX-CRH test between male veterans with PTSD and male veterans, who had been exposed to similar traumatic events during their deployment, without PTSD was compared [44]. Patients and controls were matched on age, year and region of deployment. The DEX-CRH test did not reveal HPA-axis abnormalities in PTSD patients as compared to trauma controls. PTSD patients with a co-morbid MDD showed an attenuated ACTH response compared to PTSD patients without co-morbid MDD, suggesting the presence of subgroups with different HPA-axis regulation within the PTSD group. Altered sensitivity of the CRH receptors at the pituitary or differences in AVP secretion might explain these differences in response.

In summary, clinical and neurobiological evidence strongly suggests that patients suffering from comorbid PTSD and MDD differ clinically and biologically from individuals with PTSD alone or MDD alone. I have previously suggested that some or all individuals diagnosed with comorbid PTSD and MDD have a separate psychobiological condition that can be termed “post-traumatic mood disorder” (PTMD) [45,46].

THE CONCEPT OF PTMD AND SUICIDAL BEHAVIOR

War veterans

Since October 2001, approximately 1.64 million U.S. troops have been deployed for Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) in Afghanistan and Iraq [47]. The war in Iraq has presented Soldiers and Marines with a unique set of stressors that are chronic in nature, including civilian threats such as guerilla warfare tactics and terrorist

actions [20, 47, 48]. Soldiers and Marines need to maintain constant vigilance to deal with unpredictable threats like roadside bombs, and to discern safe civilians from potential enemy combatants [49]. Military personnel involved in the OEF face similar problems in Afghanistan.

Early evidence suggests that the psychological toll of these deployments—many involving prolonged exposure to combat-related stress over multiple rotations—may be disproportionately high compared with the physical injuries of combat. In the face of mounting public concern over post-deployment health care issues confronting OEF/OIF veterans, several task forces, independent review groups, and a President's Commission have been convened to examine the care of the war wounded and make recommendations. The challenge of identifying veterans or active duty military who are suffering from PTSD, MDD, and/or those at risk for suicide has been receiving high-profile attention within the military and the Department of Veterans Affairs, as well as on Capitol Hill. Concerns have been most recently centered on two combat-related injuries in particular: posttraumatic stress disorder and traumatic brain injury [50–52]. Many recent reports have referred to these as the signature wounds of the Afghanistan and Iraq conflicts. With the increasing incidence of suicide and suicide attempts among returning veterans, concern about depression is also on the rise. It has been estimated that nearly 20% of members of the military service (about 300,000 individuals) who have returned from Iraq and Afghanistan report symptoms of PTSD or MDD.

The risk of suicide attempts among the PTSD population is six times greater than in the general population [53, 54] and even higher among treatment seeking war veterans with PTSD [55]. In fact, war veterans are two times more likely to die of suicide than are nonveterans [56]. Considering these statistics, it is possible that many soldiers returning from Iraq and Afghanistan may at some time experience suicidal ideation or make a suicide attempt.

The comorbidity of one or more disorders with PTSD significantly impacts the likelihood that veterans may choose suicidal behavior as an avenue for relief [57]. Comorbidity of PTSD and mood disorders is high, compounding symptom severity and social dysfunction. Some 40% of PTSD patients acutely, and up to 95% lifetime, also meet MDD criteria [58]; and up to 34% meet criteria for dysthymic disorder [59]. Persons with PTSD and comorbid MDD are at a high risk for suicidal behavior [45, 46, 60–62]. Comorbidity of PTSD and MDD is associated with increased illness burden, poorer prognosis, and delayed response to depression treatment [45]. In one study, veterans were assessed for suicidal thinking and behaviors, and symptoms of PTSD and depression [58]. Thoughts of ending one's life and a previous suicide attempt were significantly correlated with a diagnosis of PTSD. Veterans with a diagnosis of PTSD and MDD or dysthymia were also more likely to report suicidal thinking and behaviors than veterans with only one of the diagnoses.

I have recently proposed a model of suicidal behavior in war veterans with PTMD [63]. The model consists of the following components: 1) genetic factors; 2) prenatal development; 3) biological and psychosocial influences from birth to mobilization/deployment; 4) mobilization/pre-deployment stress; 5) combat stress, traumatic brain injury,

and physical injury; 6) post-deployment stress; 7) biological and psychosocial influences after the deployment; 8) trigger (precipitant) of a suicidal act; and 9) suicidal act. The first four components determine vulnerability to combat stress. The first seven components determine predisposition to suicidal behavior, a key element that differentiates PTMD patients who are at high risk from those at lower risk. Suicidal behavior in PTMD can be attributed to the coincidence of a trigger with a predisposition for suicidal behavior.

Most likely, precipitants of suicidal acts in war veterans include interpersonal losses or conflicts, financial trouble, and job problems. Symptoms such as melancholia, insomnia, psychosis, extreme hopelessness, mixed or transitional bipolar states, alcohol and substance abuse, marked impulsivity, a poor response to medication, definite plans for committing suicide, a history of prior attempts, and a family history of suicide increase suicide risk in war veterans.

Victims of childhood abuse

In 1996 The Task Force on Adolescent Assault Victim Needs reported that the onset of PTSD in childhood or adolescence can cause life-long impairment because it can interfere with normal adolescent development and prevent children from acquiring the basic life skills needed to become independent and self-sufficient adults [64]. Indeed, there is a growing evidence of the impact of childhood trauma on the developing brain of children and adolescents [65]. Middle adolescence is an age at which major structural change occurs in the brain [66]. Trauma during this period of rapid brain development may arrest neurological development or produce a regression to an earlier stage of neural structure.

Psychological trauma that occurs early in the life cycle, tends to result in a chronic inability to modulate emotions, thus augmenting the risk of getting involved in indiscriminate relationships with others in which old traumas are, somehow, re-enacted or, in some cases, leading to the loss of social bonds [65, 67–73]. It may also lead to new trauma as a result of psychiatric pathology, maladaptive personality features, impulsive behavior, alcohol and/or drug abuse and other factors.

Children seem to be more sensitive to the effects of trauma and early life trauma exposure may induce a complex sequence of events that leads to the development of a variety of psychiatric disorders in adulthood, including depression, PTSD, and comorbid depression and PTSD [61, 74–76]. In a study of a group of severely maltreated children, the presence of PTSD was strongly correlated with the co-existence of at least one more formal psychiatric diagnosis including depression which underlies the gravity of the consequences of child maltreatment [74]. A study of large group adolescents who had attempted suicide, confirmed the existence of previous exposure to childhood abuse and neglect compared to non-suicidal controls [77]. Some studies have supported a relationship between childhood sexual abuse and depression (as well as an increase in suicidal risk) both in males and females [78–82]. Patients with histories of sexual abuse are said to represent a subgroup of depressed patients who are at high risk for psychiatric morbidity and a prolonged episode of depression [82]. The co-occurrence of a major depressive episode and PTSD, i.e., PTMD, enhances the risk for suicidal behavior in victims of childhood maltreatment [83]. We have

compared depressed subjects without a history of alcoholism in first-degree relatives and depressed individuals with a history of alcoholism in first-degree relatives, and showed that the latter group had a significantly higher prevalence of reported childhood physical and sexual abuse and PTSD, made more suicide attempts and had greater intent to die at the time of their most lethal suicide attempt, compared to the group of depressed subjects without a family history of alcoholism [84]. In a general population study in a city in Turkey, it was found that participants with a dissociative disorder had higher rates of borderline personality disorder, somatization disorder, major depression, PTSD, and history of suicide attempt than the participants without a dissociative disorder [85].

It is important to note that a very serious consequence of PTSD during adolescence is its association with the heavy use of alcohol and/or other drugs [76, 86, 87]. Adolescents are frequently exposed to socially pathological alternatives such as substance abuse, promiscuity, and criminal activity. Most do not succumb to these temptations, because they have sufficient family support and lack impulsive predispositions. But those who are vulnerable are not protected and may develop psychopathological conditions. Substance abuse has immediate consequences in the form of increased accidents, injuries, and long-term effects in terms of occupational and familial instability and early mortality. Furthermore, substance abuse, in itself, is often a risk factor for additional traumatic exposures either through accidents or interpersonal violence. The use of alcohol and/or other drugs is associated with suicidal behavior.

In summary, multiple lines of evidence suggest that a history of childhood abuse and neglect not only affects the neuropsychological development of the individual but also increases the risk of suicidal behavior in the future in a variety

of diagnostic conditions, including depression, PTSD and, probably PTMD.

CONCLUSION

Suicide prevention measures in individuals with comorbid depression and PTSD (PTMD) include:

- recognition of psychiatric problems;
- treating PTMD and other psychiatric conditions;
- preventing a relapse when the patient is in remission;
- treating suicidal ideation;
- treating medical and neurological disorders;
- social support;
- suicide prevention hotlines;
- reducing stigma for mental illness;
- reducing access to lethal means.

Treating suicidal ideation is important because suicidal ideation is one of the main predictors of suicidal acts [88–93]. Suicidal ideation in war veterans may lead to suicide or a highly lethal suicide attempt because war veterans know how to use firearms. Therefore, treating suicidal ideation is key in preventing suicide among war veterans. Both psychological and pharmacological treatments can be used to treat suicidal ideation.

Mental health pathology related to traumatic stress is a critical medical and social problem. It is important to develop interventions to prevent suicidal behavior in individuals with comorbid depression and PTSD (i.e., PTMD), and to study psychobiology of comorbid depression and PTSD (i.e., PTMD) in order to develop treatments for PTMD. Priorities for intervening to reduce suicidal behavior in traumatized individuals lie with interventions focused upon the improved recognition, treatment and management of individuals with psychiatric disorders including PTMD.

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