EXPERT REVIEWS

Post-traumatic stress disorder as a comorbidity: impact on disease outcomes

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Post-traumatic stress disorder (PTSD) is associated with many psychiatric and nonpsychiatric comorbidities. Growing evidence suggests that PTSD as a comorbidity may impair drug adherence, quality of life and sleep quality, as well as increase rehospitalization rates, disease relapses, intensity of symptoms, morbidity and mortality. The aim of this article is to examine the literature regarding the effects of PTSD comorbidity on physical and mental health.

KEYWORDS: comorbidity • outcome • physical illness • post-traumatic stress disorder • psychiatric disorder

Post-traumatic stress disorder (PTSD) is characterized by the development of a set of specific symptoms following one's exposure to a traumatic event. These symptoms include persistent reliving of the trauma, constant avoidance of stimuli associated with the traumatic experience, and symptoms of increased arousal. These clinical manifestations must remain for more than a month after the traumatic event, and affect a person's social, family or occupational functioning within the society [1]. Although other authors had previously described similar reactions in war combatants and utilized other denominations, the psychiatric morbidity associated with veterans of the Vietnam War (1959–1975) brought to light the concept of PTSD, as it is known today [2]. The term PTSD was incorporated in the year 1980, in the third edition of the DSM-III and was retained with some modifications in the DSM-IV. In the year 2000, the American Psychiatric Association revised the PTSD diagnostic criteria of the fourth edition, DSM-IV-TR [1].

The traumatic event itself is not sufficient for the development of PTSD. Indeed, some individuals who have experienced stressful situations did not develop the disorder [3]. Biological and psychosocial factors are also necessary for predicting whether the individual will be affected by the disease. These factors include: personality traits, inadequate social support, presence of childhood traumatic experiences, gender, genetic vulnerability to psychiatric illness or recent stressful life changes [4]. Concerning the neurobiology of the PTSD, there are several points that need to be elucidated. It is known that an activation of the hypothalamic–pituitary–adrenal (HPA) axis and consequently the release of glucocorticoids, in particular cortisol, are triggers of a stress response. Glucocorticoids modulate physiological pathways related to stress, such as metabolic, brain and immune functions, in order to manage the stress response. A main function seems to be in the regulation and the restrain of the autonomic responses to stress, aiding on the re-establishment of the organic functions (FIGURE 1) [4–6]. In PTSD patients, a dysfunction of the HPA axis was found [6]. This may result in a reduced activity of cortisol and may also maintain an augmented stress central response and immune-inflammatory function [7,8], making the individual more susceptible to chronic diseases such as asthma, cardiovascular diseases (CVD) and arthritis (FIGURE 2) [9,10].

The prevalence of PTSD in the general population is approximately 6.8% [11]. There is a disproportional distribution between genders, with women being more likely to develop PTSD than men [3]. The comorbidity rates are high in patients with PTSD [3,12–14], with approximately two-thirds of them having at least two other disorders [3]. In the same way that PTSD may increase the number of comorbid disorders, likewise, several diseases can increase the vulnerability of people to PTSD [15]. Despite the vast literature addressing the prevalence of comorbidities in PTSD patients, few studies address the influence of PTSD on the outcome

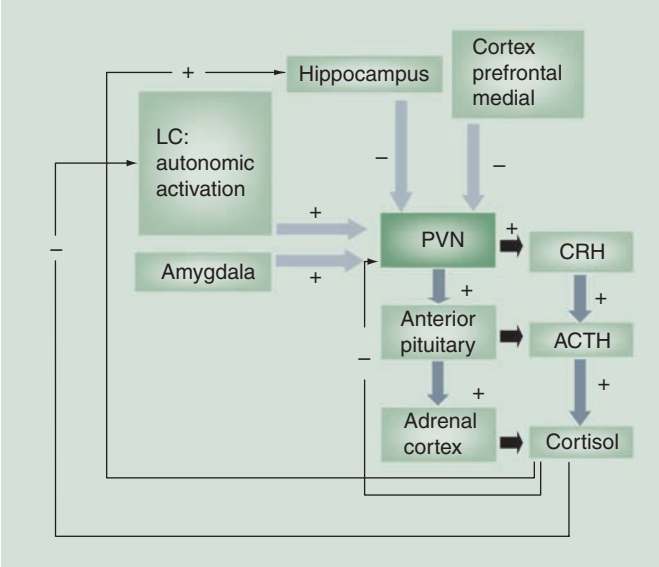

Figure 1. Hypothalamic–pituitary–adrenal axis stress response. Brain structures sensitive to danger situations connect with the hypothalamus through the PVN, which stimulates the hypothalamic–pituitary–adrenal axis stress response and consequently promotes the release of cortisol. This in turn self-regulates the axis activation by a feedback mechanism. +: Activation; –: Inhibition; ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone; LC: Locus coeruleus; PVN: Paraventricular nucleus.

of the primary disease. In addition to this, few studies describe the influence of PTSD on drug adherence, in rehospitalization, disease relapses, quality of life (QoL), intensity of symptoms, sleep quality and on morbidity and mortality. Thus, the authors aim to review literature regarding the effects on the outcomes of a primary disease when the patient suffers from PTSD's comorbidity. Knowing these factors implies understanding more about the prognosis, as well as the possible impacts and therapeutic approaches that could be carried out in order to improve the patient's life.

Method

In order to perform this comprehensive review of literature the authors searched articles regarding comorbid PTSD with psychiatric disorders and physical diseases. Among the physical diseases, the authors reviewed acute myocardial infarction (AMI), asthma, cancer, organ transplants, traumatic brain injury (TBI), chronic pain, diabetes, arthritis and hypertension. The psychiatric disorders reviewed were mood disorder (MD), anxiety disorders, schizophrenia and eating disorders. The articles reviewed until September 2011 was obtained in the Medline database. The reference lists in relevant publications were also obtained.

We searched in the Medline database for the following MeSH terms: 'post-traumatic stress disorder', 'myocardial infarction', 'asthma', 'hypertension', 'joint diseases', 'rheumatic diseases', 'neoplasms', 'organ transplantation', 'craniocerebral trauma', 'mood disorders', 'schizophrenia', 'anxiety disorder', 'obsessive compulsive disorder', 'phobia', 'panic disorder' and 'eating disorders'. Each term was initially searched separately and was subsequently combined in pairs, always using the term 'post-traumatic stress disorder' and one of the other terms.

The articles were selected based on the following inclusion criteria:

- Original papers and reviews of literature describing the prevalence of comorbid PTSD in patients with the selected diseases;
- Original papers and reviews of literature evaluating the influence of PTSD comorbidity on the selected disease outcomes;
- Papers written in English. In addition, we chose to include in our review studies we deemed important that appeared in the bibliography of articles already chosen.

Despite several studies showing high prevalence between PTSD and arthritis, diabetes, hypertension, chronic pain and eating disorders, the authors did not find sufficient studies about the influence of comorbid PTSD on disease outcomes, and so the authors decided to exclude them. Therefore, 133 articles were included here; among them 79 described comorbid PTSD in physical illness and 51 described comorbid PTSD in psychiatric disorders.

PTSD in physical illnesses

Much of the literature concerning PTSD deals with the influence of stress or traumatic events in childhood and/or adulthood and its connection with the appearance of physical illnesses [16–19]. Several studies aim to understand the association between PTSD and the development of physical diseases [18,20,21], as well as the association between the development of diseases acting as a cause for the development of PTSD [15,22–24].

Surveys have demonstrated that CVD, diabetes, arthritis, hypertension and asthma are the most prevalent diseases associated with PTSD [9,20,21,25]. Chronic pain syndrome also co-occurs with PTSD [26–29]. Some researches have shown that this comorbidity is associated with worse outcomes such as worsening in severity of pain [30–32], persistence of pain symptoms [33], worsening of indices of functionality [30,32], poor QoL [34] and depression [30,32]. Therefore, even comorbid chronic pain and PTSD represents a relevant topic and a more detailed analysis was beyond the scope of this review. The authors found no studies on the impact of PTSD in diabetes, arthritis or hypertension outcomes, but there were some studies on PTSD effects on AMI, asthma, cancer, organ transplants and TBI.

CVD

PTSD is an important risk factor for chronic diseases, especially CVD [35–37], and is related to biological changes, including sympathetic nervous system (SNS) activity and inflammatory pathways, affecting the cardiovascular system (Figure 2) [8]. Besides this, PTSD patients have a higher risk of using tobacco and may practice less physical activity than the general population, which can aggravate the CVD in these patients [38]. Cohen *et al.* carried out a cross-sectional study finding that PTSD predicted an increase in symptoms, loss of functionality and worse QoL in

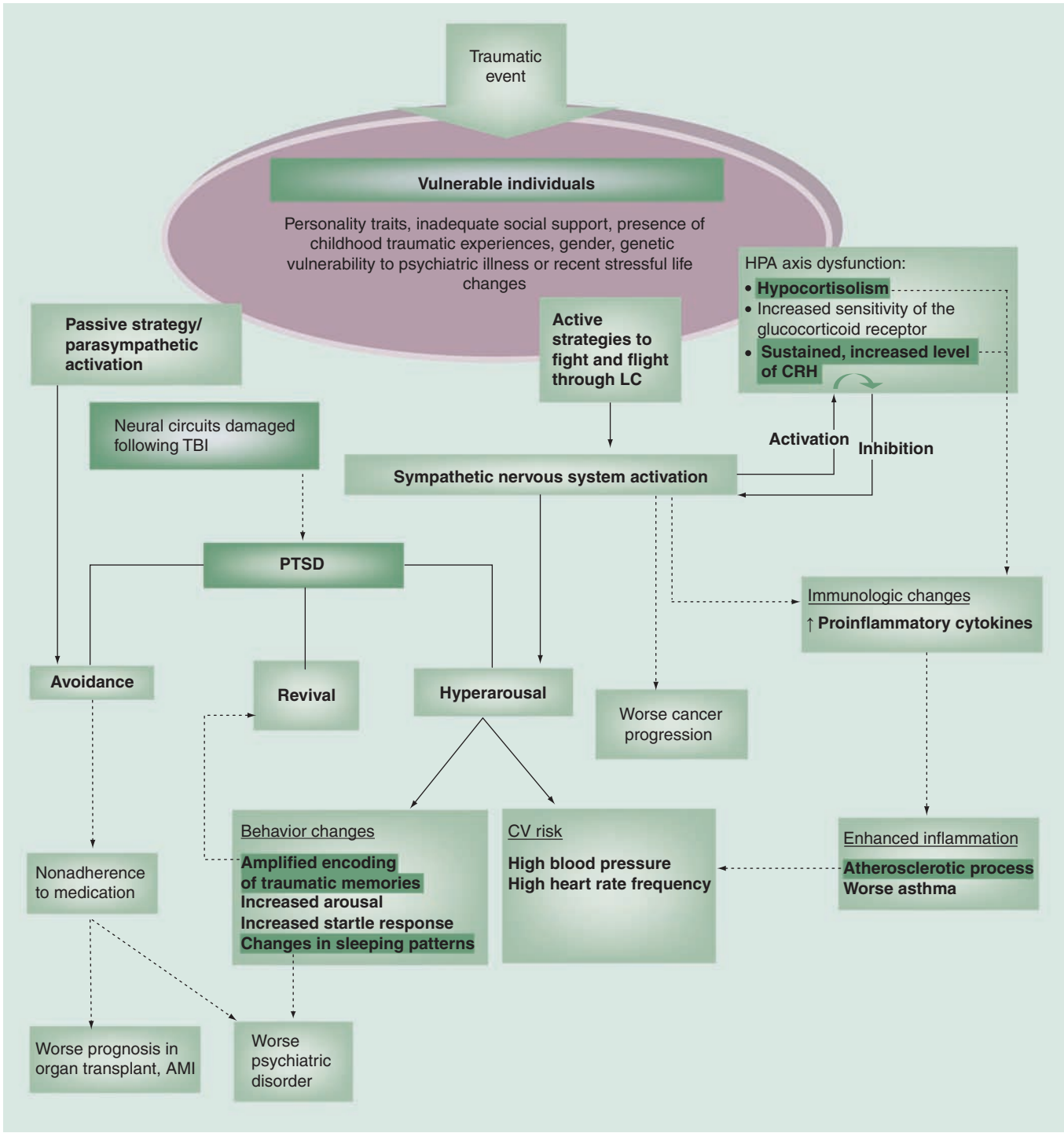

Figure 2. Possible pathways between trauma, post-traumatic stress disorder and comorbid disease. The vulnerable individual presents psychosocial and/or biological risk factors for PTSD, which lead to a dysfunction of the HPA axis. Faced with a traumatic event, the individual may have an inadequate adaptive response, favoring the development of PTSD. The neuroendocrine and immunological changes resulting from this altered response may have as a consequence both an increased risk for disease development as well as a worsening of pre-existing conditions.
AMI: Acute myocardial infarction; CRH: Corticotropin-releasing hormone; CV: Cardiovascular; HPA: Hypothalamic–pituitary–adrenal; LC: Locus coeruleus; PTSD: Post-traumatic stress disorder; TBI: Traumatic brain injury.

stable CVD patients [39]. This result did not change even after adjustment for objective measures of cardiac function (ejection fraction and inducible ischemia) and comorbid depression.

Several studies have evaluated comorbid PTSD in different CVD, but the authors chose solely to review whether comorbid PTSD may influence the outcome of AMI.

AMI

There is an evidence suggesting a temporal relationship between PTSD and AMI. Falger *et al.* found that individuals with PTSD had a higher risk of experiencing an AMI in their future [40]. Kubzansky *et al.* enrolled a sample of men who served in the military without a previous diagnosis of arteriosclerotic disease [37]. After a 10-year follow-up the authors observed that PTSD subjects presented a high prevalence of coronary heart disease (CHD), and this result did not change after adjustments for confounding factors, such as depression, smoking, family history of CHD and lower levels of education, BMI, total cholesterol level, alcohol intake, blood pressure and age. Nevertheless, this adjustment did not include frequency of exercise, and this could explain the high prevalence of CHD in PTSD patients. Furthermore, Ahmadi *et al.* assessed 637 veterans without previous arteriosclerotic disease using coronary artery calcium scoring, and found that PTSD was an independent predictor of the presence and severity of atherosclerotic disease [41]. The adjustment of several confounding factors such as age, gender, diabetes mellitus, hypertension, hypercholesterolemia, family history of CHD and smoking status did not modify these results. They also reported that mortality rates were significantly higher in PTSD patients after a 42-month follow-up. Many other studies have also found an increased risk for AMI in PTSD patients [9,42].

However, most research has evaluated the prevalence of PTSD in post-AMI samples, and found frequency rates ranging from 7.7 to 32% [23,24,43–45]. Pedersen *et al.* related that people having AMI for the first time had a three-times increased risk of developing PTSD compared with those without AMI [22]. The risk decreased by more than two times, even after performing appropriate adjustments for anxiety, depression and neuroticism. Few studies address aspects regarding QoL, rehospitalization and adherence to medication. Shemesh *et al.* showed a significant relationship between nonadherence to the use of captopril and a higher frequency of adverse AMI outcomes and reported a positive association between PTSD diagnosis and worse adherence to medication [46]. In this study, adherence was assessed by counting the number of pills remaining on the card. The authors considered that, although widely accepted, this method of assessment may underestimate the number of patients who do not adhere to the medication. Shemesh *et al.* used the rates of thromboxane production by the patients' platelets as the assessment factor of nonadherence to aspirin [47]. The results of this study were similar to those of 2001, where PTSD symptoms were more prevalent in the nonadherent group. In addition, PTSD patients suffered more than twice the number of rehospitalizations because of cardiovascular problems during the study period. This study also reported that PTSD patients have an increased risk of showing depressive and anxiety symptoms, but the authors could not attribute these variables to the association with readmissions and non-treatment adherence. The authors then concluded that PTSD itself is predictive of non-treatment adherence and rehospitalizations.

Shemesh *et al.* found that cognitive–behavioral therapy (CBT) interventions in CVD patients with PTSD increased the adherence to medication, and concluded that CBT may reduce the risk of morbidity and readmissions [48]. Jones *et al.* did not find an association between PTSD and risk factors for future myocardial infarctions, such as smoking, high blood pressure and even nonadherence [45]. The authors explained these results hypothesizing that the UK primary care service, which identifies and manages risk factors, can decrease their impact on CVD, even if the patient presents PTSD as comorbidity.

Another study carried out by Doerfler *et al.* focused on PTSD as a determinant factor for increasing the number of patient rehospitalizations and showed that PTSD subjects had worse QoL and an increased number of rehospitalizations compared with subjects without PTSD [49]. Von Känel *et al.* followed a sample of CVD patients during 2.8 years, finding that the presence of PTSD increased the risk of rehospitalization by 42%, due to CVD [50]. Finally, Ahmadi *et al.* showed that PTSD is associated with the presence and severity of coronary atherosclerosis and is also a predictor of mortality, regardless of age, gender and other conventional risk factors [41].

Finally, examining all studies on AMI, we can assume that comorbid PTSD is an independent predictor for nonadherence, rehospitalization, and a worsening in both QoL and cardiovascular symptoms. Hence, we concluded that the identification of risk factors, comorbid diseases and management of these factors are important to improve AMI morbidity, as hypothesized by Jones *et al.* [45].

Asthma

Researchers have found a high association of PTSD among patients with asthma [18,21,51,52]. Goodwin *et al.* evaluated twin pairs of male Vietnam War veterans [51]. After performing the within-pair analysis, they pointed out that the link between PTSD symptoms and asthma is not explained by common familial or genetic influences. Some authors have explained the association between PTSD and asthma through changes in inflammation responsiveness [53]. Some evidence demonstrates a relationship between PTSD and an inappropriate immunological responsiveness, mediated by endothelin-1, a vasoactive proinflammatory peptide that acts as a central modulator of the stress response [21]. Besides that, the dysfunction of the HPA axis and of the altered SNS in PTSD patients seems to result in lower serum cortisol levels and higher circulating catecholamine levels [7,54]. These altered responses may aggravate the clinical course of asthma (**Figure 2**) [21].

An Australian survey of a 21-year follow-up of patients since birth assessed the relationship between PTSD and asthma attacks, the use of medications for asthma and respiratory function [55]. They found that the current or lifetime PTSD group had been more likely to use asthma-related medication during the 21 years of follow-up. However, the current PTSD association does not remain significant after controlling for potential confounder factors (sociodemographic factors, current smoking and current use of cannabis). Regarding the respiratory function, no association with PTSD was observed in the results.

Data derived from research on people living in New York City (NY, USA) [56], between 6 and 9 months after the 9/11 terrorist attacks, suggested that PTSD was a predictor of self-reported, moderate-to-severe asthma attacks, as well as being significantly associated with the utilization of emergency healthcare services for

asthma, and with unscheduled visits to physicians after the traumatic event. Also, the severity of asthma symptoms could be linked to the number of PTSD symptoms. Thus, the authors concluded that "PTSD and post-traumatic stress symptoms may be better indicators of risk for worsening asthma after a traumatic event."

Cancer

Despite the great number of studies on prevalence and predictors of PTSD in cancer patients [18,57–60], few studies relate PTSD and cancer outcomes. Of these, most evaluate the effects of PTSD on QoL and sleep quality.

PTSD was negatively correlated with social and cognitive functioning in QoL scores in Malaysian patients diagnosed with hematological cancer [61]. Geffen *et al.* also found that lower QoL was negatively correlated with PTSD in long-term survivors of Hodgkin's disease and non-Hodgkin's lymphoma [62]. In a sample of young adult survivors of childhood cancer, the PTSD group showed lower QoL scores in seven out of eight domains and all summary scales when compared with the non-PTSD group. Comparing the scores with those from the young adult general population, the non-PTSD group was almost identical to the general population, whereas the PTSD group scores fell below the general population mean values [63]. Women diagnosed and treated for regional breast cancer with PTSD had significantly lower functional performance status, physical health-related QoL and mental health-related QoL scores than those without PTSD [64].

Mystakidou *et al.* found that, in cancer patients, PTSD is a powerful factor to determine poor sleep quality, even more so than depression [65]. In women with breast cancer who had previously undergone autologous bone marrow transplantation, greater PTSD symptomatology was associated with poorer scores on all QoL subscales, poorer sleep quality, greater amount of sleep medication, increased sleep latency and escalated daytime disruption due to sleep difficulties [66].

There is some evidence that stress mediators, regulated by the HPA axis and the SNS, could exert some effect in cancer progression [67]. Thaker *et al.* demonstrated that chronic stress quantified by elevated organ catecholamine levels enhanced the pathogenesis of ovarian carcinoma [68]. Cortisol was also associated with enhanced cancer pathogenesis. The hormones related to SNS, such as adrenaline and noradrenaline, could act in favor of angiogenesis in human tumors. On the other hand, glucocorticoids and HPA activity can increase gene expression and replication of oncogenic viruses, such as Epstein–Barr virus (EBV), human papillomavirus (HPV), hepatitis C or B, and can also act in a synergist manner with catecholamines, facilitating cancer growth (Figure 2) [69]. Thus, if PTSD promotes a dysfunction in the HPA axis and the SNS, it could contribute to poorer outcomes in cancer patients. However, there are too many differences between chronic stress and PTSD, and even the dysfunction of the HPA axis in PTSD is not strongly defined. Finally, the clinical relevance of this data for human oncology must be confirmed.

In women with documented metastatic or recurrent breast cancer, those who reported past experience stressful or traumatic life events showed a significantly shorter disease-free interval when compared with the group who had not experienced any such events [70]. However, in this study, no statistically significant differences were found between cortisol levels and stress or trauma history. The authors argue that previous studies had shown that women with metastatic breast cancer had 'flatter' or lower cortisol levels than healthy control groups. It is also important to note that some of these patients might not have PTSD, since only stressful or traumatic life events were evaluated [70].

Organ transplants

Since organ transplants are major surgeries and life-threatening experiences, they could act as traumatic experiences and exert some effects on long-term outcomes, especially treatment adherence.

After following up to 3 years, 145 adult heart transplantation recipients selected during the first year after transplantation, Dew *et al.* found that mortality was significantly increased if patients met PTSD criteria exclusively related to transplant events [71]. The authors also found that, while other psychiatric comorbidities primarily affected the risk of acute rejection and incident cardiac allograft disease and mortality, PTSD directly affected risk of death even after intermediate morbidities were controlled. Another study evaluated PTSD as a comorbidity for heart transplantation recipients [72]. The patients were selected after the first year and before the fifth year of transplantation and evaluated during an average follow-up of 8 years. The study demonstrated a relationship between the development of intrusive post-traumatic thoughts about transplantation and adherence to medical prescriptions. Köllner *et al.* showed that, in patients who had undergone heart or lung transplants, PTSD was associated with significantly poorer QoL responses on psychological scores [73].

Regardless of the small sample size, Shemesh *et al.* showed that PTSD was associated with clinical nonadherence in pediatric liver transplant recipients, as determined by a clinician panel and blood medication levels [74]. Moreover, each noncompliant patient became compliant after the end of PTSD symptoms. Since nonadherence to medical management can be associated with graft loss and other complications, such as acute or chronic rejection [75,76], PTSD could be linked to these poorer outcomes through clinical nonadherence. Another study evaluated PTSD in liver transplant recipients and showed that six QoL domains were associated with PTSD [77]. However, the study only evaluated patients with medication concentrations in blood within the therapeutic range, and since PTSD could be associated with medication nonadherence, some patients suffering from PTSD could have been excluded.

TBI

The discussion of PTSD and mild TBI comorbidity in the literature has received more attention recently, since the military conflicts in Iraq and Afghanistan have brought out new evidence on blunt head trauma and both combat stress reactions and blast-induced PTSD [78,79]. There is a reliable body of evidence supporting a more than coincidental link between PTSD and TBI, with the suggestion that TBI is associated with more severe PTSD among Vietnam veterans; among combatants from Iraq

and Afghanistan, PTSD is more prevalent in cases of mild TBI compared both with veterans who suffered no injury or with those who suffered physical injuries not involving the head [80]. Other studies involving neuroimaging methods have suggested possible pre-existing volumetric abnormalities in some prefrontal cortical areas as risk factors for the development of PTSD following trauma exposure [81]. In cases of PTSD utilizing functional neuroimaging techniques, the overactivation of certain limbic areas, such as the amygdala and insular cortex, has raised the question of whether neural circuits damaged following TBI may mediate PTSD symptoms [82,83]. In this context, advanced MRI techniques such as diffusion tensor imaging have demonstrated white matter damage in patients with TBI in selected areas such as the frontal lobe and cingulum, providing some support for additional research in this field [84]. Unfortunately, there are no neuroimaging studies that employ control groups consisting of head trauma without PTSD, so additional studies are warranted to elucidate discrete patterns of brain lesions throughout the disorders.

Different possible mechanisms can lead to the association between PTSD and TBI. For instance, combatants are exposed to both psychologically traumatic events that may cause PTSD and shock waves with the potential to cause blast-related TBI. Therefore, independent causal mechanisms to both disorders cannot be excluded, which represents a confounding factor. Among the possible causal mechanisms involving PTSD and TBI, the authors have mentioned neuropsychological dysfunction following TBI as a predisposing factor for PTSD. However, further complicating issues are the possible mechanisms involved in PTSD symptoms development and its relationship with TBI predisposition. Some authors have argued the neuropsychological performance as a major risk factor for PTSD before traumatic experience [85–87]. In this context, impairments on executive functions, particularly response inhibition, attention regulation and decision-making, are detected as pre-existing vulnerabilities to PTSD. The authors speculate that these neurocognitive deficits may predispose individuals not only to PTSD, but also to TBI, especially in those exposed to battle fields. In addition, a recent suggestion in the literature about pituitary abnormalities after blast-related TBI raises an important issue, as many symptoms between hypopituitarism and PTSD are overlapping. Hypopituitarism can be successfully reversed or improved with appropriate hormone replacement therapy, and routine endocrine evaluation may be desirable in this population [88].

With these issues in mind, there is a significant concern that the two conditions may exacerbate each other, leading to challenging clinical presentations and important implications in terms of outcome. In fact, PTSD may be a major predictor of postconcussive symptoms and is associated with the development of physical disorders over time, such as CVD [89,90]. In addition, neuropsychological functions may be an important issue, as some authors have suggested that mild TBI may reduce neuropsychological performance and compromise adaptive behaviors such as problem-solving and emotional regulation, leaving an individual more susceptible to PTSD and possibly limiting responsiveness to PTSD therapies, such as cognitive–behavioral interventions [91,92]. Neuropsychological tests demonstrate similar deficits in attention, working memory, executive functioning and episodic memory [93] in both disorders and neuropsychological dysfunction may increase as PTSD symptoms become more chronic [94], which can represent a problem in terms of differential diagnosis and treatment of these disorders in clinical contexts.

PTSD in psychiatric disorders

PTSD frequently overlaps other psychiatric diagnoses [3,95]. Data from the National Comorbidity Survey showed that 88.3% of men and 79.0% of women with PTSD also met criteria for at least one additional psychiatric diagnosis [3]. There are some causal hypotheses addressing this, to explain the high frequency of psychiatric comorbidities in PTSD. In the development of PTSD, mental disorders may be a risk factor for traumatic event exposure, or they may increase susceptibility to traumatic event effects, as well as to ordinary stressful life events. Moreover, they can also be a consequence of trauma exposure and PTSD. Despite these issues concerning causality, it is widely known that the presence of two or more psychiatric diagnoses may negatively influence their course of illness [96,97], so this may be true for PTSD comorbidity. It is possible that the presence of comorbid PTSD affects clinical measures such as chronicity and severity of illness, treatment response rates, suicide risk, functional and social disability, QoL and sleep changes.

MD

MD is commonly comorbid with PTSD [98] and the prevalence of PTSD in MD is higher than those observed in the general population [99]. The frequency rates of this comorbidity range from 20.6 to 94.1% for major depressive disorder (MDD) [3,96,100–106]. Otto *et al.* reviewed eight studies on the prevalence of association PTSD and bipolar disorder (BD), and found a high prevalence, with rates between 7 and 40%, with weighted mean for these studies (n = 1214) being 16% [107].

There is an increasing amount of research concerning the PTSD–MDD comorbidity, regarding possible predictors, treatment and outcomes, but only a few studies were found on PTSD–BD [96,97]. Traumatic experiences and PTSD symptoms may have a wide impact on the development and course of BD [98,108–110]. For example, it is possible that PTSD symptoms in bipolar patients can induce mood instability, since this comorbidity seems to be associated with a high frequency of rapid cycling among bipolar patients [108], which, in turn, can be associated with a lower likelihood of recovery [108,109]. Another reported effect was a greater occurrence of substance use disorder [109].

PTSD tends to have a chronic course and studies that aim to examine whether the MDD comorbidity may predict this outcome are discordant in their results. For McFarlane *et al.* [105], comorbid depression seems to be associated with chronicity of PTSD, but for Shalev *et al.* [100] it does not. Individuals with comorbid PTSD and major depression reported more symptoms [100]. Investigators have reported that co-occurrence of PTSD–MDD is associated with an increased severity of PTSD [104,111,112] or of MDD [101,112,113]. Maguire *et al.* investigated effects of trauma in bipolar patients and observed that although comorbid PTSD was associated with

more severe BD presentations, it was unrelated to the number or duration of admissions of bipolar patients [110].

The presence of suicidal ideation or suicidal behavior and psychotic symptoms are other disease severity indicators that are commonly assessed in clinical studies. Since both PTSD and MDD episodes are individually associated with a risk of suicidal behavior [108,114,115], it is reasonable to assume that patients with PTSD and MDD may have even higher risk. Oquendo *et al.*, who investigated this matter, have demonstrated that more patients with PTSD–MDD attempt suicide than those with only MDD and that suicidal ideation was severest in the depressed patients who had current PTSD [116]. Prigerson and Slimack found an increased risk of suicidality in young females with elevated symptoms of depression and/or PTSD [117]. Campbell *et al.* examined a clinical sample consisting of 677 military veterans, dividing them into two groups for comparison according to the presence of probable PTSD [113]. They related that depressed patients screened for PTSD, after adjustment, showed more reports of suicidal ideation than those with MDD only. Unlike these results, another study did not observe these differences on suicidal ideation between these two groups [100].

Simon *et al.* [109] noted a significant higher frequency of history of suicide attempts among bipolar patients with current and lifetime PTSD compared with those without anxiety disorders, and Dilsaver *et al.* [99] found that the presence of PTSD was associated with an increased risk of suicide attempts in bipolar juvenile patients. In order to evaluate the presence of psychotic symptoms in patients diagnosed with depression and PTSD, Zimmerman and Mattia reported that PTSD is four times more frequent in depressive patients with psychotic symptoms [118]. Psychotic MDD patients with PTSD seem to show even greater severity and impairment than those without the comorbidity or nonpsychotic MDD with PTSD [119].

Treatment of PTSD and comorbid conditions is still a challenge. Evidence to support the efficacy of any specific pharmacotherapy is insufficient [120]. While it is known that a particular group of drugs is prescribed to patients who have a presence of comorbidity with other mental disorders, it is still observed that the prescription of medicine is more targeted at controlling the symptoms rather than treating a specific disorder [121]. The presence of anxiety or depressive disorders as a comorbidity do not seem to influence the response to treatment of patients with PTSD. Brady and Clary carried out a trial to evaluate the efficacy and tolerability of sertraline in a subgroup of PTSD patients suffering from anxiety or depression in comorbidity and reported that patients treated with sertraline improved PTSD symptoms compared with placebo, even those who had depressive or anxious comorbidity [104]. Sleep disturbances may occur as symptoms of several mental disorders causing significant distress. This is especially true in the case of MDD, where insomnia and hypersomnia are included in MDD diagnostic criteria. Sleep-related complaints and nightmares are also common in PTSD patients [107,122] and, although not necessary for the diagnosis of PTSD, are included in DSM criteria. It was reported that patients with comorbid PTSD–MDD show more insomnia than those without the comorbidity [100]. Woodward *et al.* evaluated 27 Vietnam combat-related PTSD inpatients, and noted that comorbid PTSD–MDD showed less slow-wave sleep and less facial electromyographic activity [123]. Dow *et al.* evaluated the sleep and dreams of Vietnam veterans suffering from only PTSD or MDD and PTSD–MDD, and showed that sleep latency was prolonged in the MDD patients compared with the other two groups [124]. However, it is important to highlight that these sleep changes may also be attributed to the use of antidepressant medicaments by the MDD–PTSD groups.

BD patients with PTSD frequently have sleep impairment as a consequence of chronic over-arousal [125]. It is assumed that impaired sleep has a direct impact on the course of BD and is associated with risk for new episodes [107]. After that, symptoms of PTSD such as hyperarousal, impaired sleep and nightmares, may aggravate the course of BD due to the risk of triggering new mood episodes.

It is widely accepted that the impairment in social and occupational functioning indicate poor clinical outcome of a mental disorder. Some evidence supported that comorbid PTSD–MDD is associated with greater overall impairment in psychosocial and occupational functioning and increased distress compared with subjects having only PTSD [111,126]. Blanchard *et al.* assessed victims of motor-vehicle accidents with and without diagnosis of PTSD as well as those with subsyndromal PTSD [127]. The authors noted that those who developed PTSD comorbid with MDD (regardless of the number of depressive symptoms) had a greater intensity of distress and greater impairment in social functioning as well as less possibility of spontaneous remission of symptoms in the short term than did those with PTSD only. Comorbidity of lifetime bipolar patients with current PTSD was more significantly associated with impairment and poor social functioning than BD patients without anxiety comorbidity [109,128].

Mittal *et al.* assessed the impact of PTSD comorbidity in MDD regarding the perceived QoL in 324 patients enrolled in the collaborative care depression study of the Department of Veterans Affairs and reported that MDD–PTSD comorbidity is associated with worse scores on the assessment of QoL compared with patients without comorbid PTSD [129]. In addition, patients with comorbid depression and PTSD seem to feel less satisfaction with their physical health [130]. It is relevant to emphasize that in patients with MDD and no comorbid conditions low scores in QoL are expected. Besides that, the decrease in the intensity of symptoms following the antidepressant treatment improves these scores. But, even so, the perception of QoL remains lower than that observed in the general population [131]. Two studies have evaluated QoL in bipolar patients with comorbid PTSD and both showed that comorbidity with current PTSD was associated with consistent and significant QoL score impairment compared with BD alone [108,109].

Anxiety disorders

Anxiety disorders tend to display higher rates of comorbidity to other anxiety disorders. Koenen *et al.* followed cohorts from birth until 32 years of age, looking for the presence of trauma or PTSD, and observed that all patients who had been diagnosed with PTSD had also been previously diagnosed with another mental disorder [14]. Patients at age 26 years who were diagnosed with current or lifetime PTSD, experienced, respectively, 67.5 and 67.8% other anxiety disorders. In general, studies show that generalized anxiety

disorder and phobia are the most prevalent anxiety comorbidities in PTSD [3,13,132]. This fact indicates the current need to investigate further into these comorbid anxieties and what influence PTSD might have on their outcome. The overlap of both PTSD and anxiety symptoms can determine an overdiagnosis of these comorbidities. For instance, Huppert *et al.* reviewed several epidemiological studies and noted that most of them did not corroborate with the observation of some case reports, wherein PTSD and obsessive–compulsive disorder (OCD) were strongly associated [133]. The authors concluded that both PTSD and OCD symptoms were overlapping, and because of this it is possible that there may be an equivocal association among these anxiety disorders.

Few studies in literature focus on specific anxiety disorders in comorbidity with PTSD. For example, the authors could not find any study addressing PTSD and its relationship with generalized anxiety disorder outcome. Concerning phobia, Crowson *et al.* showed that veterans with PTSD and other anxiety disorders had a greater difficulty in interpersonal interactions, suggesting that this may influence their social and functional skills [134].

On the other hand, OCD symptoms may act as a protection to keep individuals from thinking about trauma that would be very uncomfortable [135]. Gershuny *et al.*, studied 15 patients with refractory OCD and found that eight also met the diagnostic criteria for PTSD [135]. Additionally, patients were treated with a program of exposure and response prevention, specific to OCD symptoms.

They observed that patients with OCD and PTSD did not show improvement in OCD or depressive symptoms compared with those that only had OCD. In some cases, the symptoms of OCD and depression increased even further, so they concluded that behavioral treatment of OCD could be adverse for patients with comorbid PTSD. As a result, it was suggested that when the patient had concomitant PTSD and OCD, OCD treatment should be combined with a systematic treatment for the PTSD symptoms. Shavitt *et al.* evaluated a sample of 219 nonrefractory OCD patients, but did not find an association between PTSD and a negative response to the treatment of OCD with cognitive–behavioral therapy or selective serotonin reuptake inhibitor [136]. The authors observed that, despite PTSD's influence on the severity of OCD symptoms, this did not necessarily influence the treatment outcome.

Finally, with respect to panic disorder, Cougle *et al.*, analyzing the National Comorbidity Survey Replication sample, found that panic attacks were common in individuals with PTSD, and that these individuals were more likely to be, in the last year, diagnosed with substance dependence or abuse, MDD, other anxiety disorders and increased complaints of pain without a medical explanation [137]. Comorbidity with panic attacks was also associated with a lower number of hours worked in the previous week and previous year. Likewise, it was associated with greater functional impairment and disability, even when adjusted for confounding variables.

Schizophrenia

A large number of studies have shown that the prevalence of PTSD in patients with schizophrenia is high [138,139]; however, some of these authors reported that this comorbidity is not properly recognized and diagnosed, thus not receiving a proper treatment [138,139]. Comorbid PTSD in schizophrenia has caused negative impacts on clinical outcomes of affected patients. Studies have shown a reduction in QoL of this population [140–142], increased use of health services, increased need for hospitalization [140] and also the predisposition for suicidal behavior or suicide attempts. Calhoun *et al.* found in a cohort of 165 men suffering primary schizophrenia or schizoaffective disorder that 41% of them met criteria for PTSD [140]. Comorbid PTSD was significantly associated with decreased QoL and increased use of medical services, including increased psychiatric-linked hospitalization and increased outpatient physical health visits, even after conforming results for other demographic and clinical variables among this sample of primary patients who suffered from schizophrenia.

Fan *et al.*, examining a sample of individuals with schizophrenia who had been exposed to trauma, found that 17% of them met criteria for PTSD [141]. The PTSD group obtained significantly worse cognitive performance when compared with non-PTSD patients, especially in the areas of attention, working memory and executive function. There was also a worsening in QoL, obtained by a patient's self-assessment questionnaire.

Calhoun *et al.* found a PTSD prevalence of 47% in a sample of veterans suffering from schizophrenia, although only 14% of those screened positive for PTSD had a diagnosis of PTSD in their medical record [139]. Their results suggest that PTSD is highly prevalent and misdiagnosed among individuals with schizophrenia. In those screening positive for PTSD, an association with more severe symptoms of PTSD and combat exposure was found.

Strauss *et al.* showed that comorbid PTSD was present in almost half of a sample of male veterans with schizophrenia or schizoaffective disorder [143]. These, in turn, reported higher rates of suicidal thoughts and suicidal behavior when compared with those without PTSD as a comorbid disorder. Of the patients suffering from PTSD and schizoaffective disorder, approximately 50% had suicidal ideation and 10% reported suicidal behavior in the last 6 months. It was observed that comorbid PTSD was independently associated with increased risk of suicidal thoughts. In addition to suicidal behavior, high rates of substance abuse were also found, with 42.4% for current use of alcohol and 30.3% for a current drug abuse. Since patients with these disorders have high rates of victimization, PTSD remains often unrecognized and therefore untreated.

Expert commentary

PTSD is a mental disorder that requires an exposure to a traumatic event for diagnosis. In this respect, it resembles other clinical diseases where it is possible to infer an etiological agent, but also follows the model of complex disease seen in psychiatric disorders, whose pathophysiological hypotheses involve multiple interactions between the environment and genetics as risk factors. Therefore, PTSD seems to be an interesting topic for neuroscience research, as a consistent model of mental illness development, where an interaction with the environment is clearly identified, through psychosocial stressors and their physiological changes in individuals vulnerable to trauma exposure.

PTSD is classified according to the current nosological systems, the DSM-IV and ICD-10, as an anxiety disorder, although this

classification is controversial. Some scholars postulate that the reactions triggered by a traumatic event are not exclusively anxious [97,144]. In fact, PTSD is a heterogeneous condition, with a wide range of clinical presentations including affective, mood and psychotic symptoms, impairment in impulse control, changes in circadian rhythms, in HPA axis and in neuroendrocrine paths, as well as cognitive impairment.

This review aimed to systematize the existing information on the impact of PTSD in the clinical prognosis of clinical diseases and mental disorders when it occurs in comorbidity. However, we highlight that the majority of these studies investigating PTSD comorbidity have only measured the frequency in which they occur or have indicated associated factors, since most of them used descriptive, cross-sectional or retrospective evaluation designs, without controlled samples. For this reason, their biases interfere in a proper analysis of risk factors, and prevent the establishment of risk and causal relationships.

Studies with clinical samples indicate that high frequency of comorbid PTSD and other psychiatric and clinical conditions are in agreement with epidemiological studies enrolling a sample from a population-based study [3,145]. The nature of PTSD comorbidity may have some implications such as the causal relationships between these disorders and the validity of comorbidity diagnosis in the case of MDs [146], as well as possible changes in clinical presentation of these diseases, the possible consequences of overlapping disorders in the clinical course of the disease and the effectiveness of the therapy used.

In regards to the PTSD comorbidity phenomenon and its causal relationships, different authors have assumed some hypothetical interactions of causality between PTSD and other medical conditions. PTSD can occur in consequence of certain clinical conditions, which itself may play a role in traumatic events, such as the experience of suffering an AMI, an asthma attack or being diagnosed with cancer, as well as having a terrifying psychotic experience by a schizophrenic patient. Some of them postulate that PTSD also develops as a consequence of the increased risk of exposure to traumatic events that may be observed in certain psychiatric disorders. For example, bipolar patients in manic episodes commonly expose themselves to potentially dangerous situations. Some mental disorders, such as anxiety or major depression, can also increase the 'host' vulnerability to develop PTSD by damaging the building of resilience factors or the development of coping strategies. Otherwise, the traumatic event and PTSD symptoms may be a triggering factor for several clinical conditions such as coronary events or MDs [147]. These questions cannot be answered yet and future longitudinal studies are needed to provide knowledge on this topic.

PTSD is a chronic and often disabling condition, and its presence may negatively influence the outcome of their comorbid diseases. However, only few studies evaluated the impact of PTSD specifically on the clinical outcome of the reviewed diseases. Besides this, for most of the research, the outcome factors analyzed have been limited to the impairment in QoL and to functionality. Notwithstanding, some of them have pointed to the positive association among PTSD and nonadherence to therapeutics, more rehospitalizations, disease relapses, worsening in sleep quality and increasing of illness severity. Indeed, the PTSD symptoms in either full or partial presentation could lead to a worse clinical course of diseases [148]. For instance, avoidant behavior of PTSD patients could decrease treatment adherence, contribute to isolation and reduce treatment-seeking behavior. Likewise, changes in sleep patterns may destabilize the mood of bipolar patients, favoring relapses. Moreover, the occurrence of substance-use disorder, and higher frequency of suicide attempts also seem to be associated with comorbid PTSD, and these factors may be implicated on the great morbidity and mortality of the main diseases reported in some studies. Thus, we emphasize the need to increase vigilance by clinical staff in identifying symptoms and comorbid diagnosis of PTSD. The identification of risk factors would allow preventative action. Therefore, awareness of the PTSD comorbidity may minimize possible effects of this comorbidity, which remained hidden, and could negatively affect the prognosis of clinical and psychiatric conditions.

Psychosocial interventions seem to be effective in order to improve PTSD symptoms, and CBT has been considered a choice treatment for PTSD [149]. For instance, a CBT two-phase treatment developed by Cloitre *et al.* targeting adults diagnosed with PTSD related with childhood abuse seems to be effective to relieve PTSD symptoms, increase affective regulation and improve functionality [150]. They noted that better results and less drop-outs occurred when a strong therapeutic alliance between therapist and client was established.

The psychoeducational approaches that consist of offering to the patients and their relatives information about their disease, and treatment and prognosis through bibliographic material and active group intervention, must be vigorously employed. This is necessary to give them a better understanding of PTSD, improve the medication compliance of these patients, facilitate coping strategies and decrease the morbidity related with exposure to stressful situations. A recent meta-analysis performed by Donker *et al.* has confirmed effectiveness in reducing anxiety and depressive symptoms in depressed and anxious patients, and has also emphasized the low cost and easy implementation in a primary care setting [151].

Finally, those suffering from PTSD and comorbid conditions form a patient group with clinical features of a more severe disease course, associated with a worse clinical course, but surprisingly there is little evidence reporting on therapeutics for the PTSD in comorbidity. It is known that in comorbidity approaches, we must be careful with the risks of polypharmacy and drug interactions, as well as the effect of psychotropic drugs used on the comorbid disease. Clinical trials involving pharmacological interventions and factors related to interaction, safety, clinical effectiveness as well as psychotherapy, are therefore required to offer these patients a more effective and safer treatment. There is no consensus yet on the therapeutic approach of PTSD in comorbidity with other mental disorders and studies point to a tendency to treat these patients with specific target symptoms such as anxiety, psychosis, changes in mood and sleep [120]. We need investigations that focus on the therapeutic approach when it occurs in PTSD comorbidity.

Five-year view

The study of PTSD has received increased attention in the last two decades, but even with advances in knowledge, PTSD is still

a frequent, chronic and disabling condition. PTSD co-occurring with other diseases seems to worsen their clinical course, but unfortunately, there are few studies focusing on this issue. In the next few years, more research is needed in order to evaluate the effects of PTSD on disease outcome.

The effectiveness of early intervention after exposure to traumatic events, to prevent chronicity of PTSD symptoms, has interested some researchers as an attractive investigation issue. It is necessary to delineate research protocols in order to reach these goals. The information obtained from these surveys will help in developing public health programs aiming to promote preventive healthcare and, consequently, improve the patient's life.

PTSD patients seem to present inflated physiological response, resulting in several biological changes. There is also growing evidence about the neuroendocrine effect of PTSD on others disease's physiopathology, which could bring interesting findings in the coming years.

While much of the evidence from military literature highlights new knowledge about neuropsychiatry of TBI, current conceptual models of PTSD will probably be revisited in terms of etiology and neurobiology as well; the more recent neuroimaging techniques will represent promising tools in this setting.

It is important to address more about the outcome in hypertension, diabetes and arthropathies, as well as evaluate the impact of PTSD on treatment adherence, since this is an essential aspect for good long-term prognosis of several diseases. Regarding organ transplantation, most studies that analyzed this relationship concerned liver or heart recipients. We hope to see future studies evaluate other organ transplantations, such as the kidney.

Finally, more studies are needed to demonstrate the relationship of PTSD with BD, schizophrenia, eating disorders and anxiety disorders. Most studies on PTSD and mental disorders show methodological limitations that hinder generalization-making, such as convenience samples and small sample sizes, besides retrospective analysis. Further research is expected over the next few years using longitudinal studies as well as clinical trials to better delineate the relationship between PTSD and mental disorder, and to answer the questions that are still being elucidated.

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Key issues

- Post-traumatic stress disorder (PTSD) can co-occur frequently with other physical and psychiatric diseases and this fact may modify the outcome of the primary disease.
- Individuals with PTSD seem to be at more risk for experiencing an acute myocardial infarction (AMI) and, conversely, patients have a high probability for developing PTSD after their first AMI attack.
- Comorbid PTSD–AMI was also associated with decreased adherence, readmission by cardiovascular diseases and worse quality of life (QoL). PTSD can be a predictor of mortality regardless of age, gender and other conventional risk factors in AMI patients.
- There is a strong association between PTSD and asthma, not explained by common familial or genetic influences. PTSD is a predictor of moderate-to-severe asthma attacks, as well as being significantly associated with the utilization of emergency healthcare services for asthma attacks.
- Regarding patients diagnosed with cancer, comorbid PTSD was associated with worsening in QoL, poor sleep quality and increased sleep disturbances.
- PTSD was associated with significantly poorer QoL and nonadherence to medical prescription in transplant patients. Mortality rate was significantly increased in transplanted patients with PTSD.
- PTSD is more prevalent in cases of mild traumatic brain injury compared with both veterans who suffered no injury and those who suffered physical injuries not involving the head. Traumatic brain injury is associated with more severe PTSD and may be a major predictor of postconcussive symptoms.
- The prevalence of PTSD in mood disorders is higher than those observed in the general population. Patients with comorbid major depressive disorder and PTSD attempt suicide more than those with only major depressive disorder, and suicidal ideation was most severe in depressed patients who had current PTSD.
- PTSD symptoms in bipolar patients can induce mood instability, since this comorbidity seems to be associated with high frequency of rapid cycling and more occurrence of substance use disorder.
- Generalized anxiety disorder and phobia are the most prevalent anxiety comorbidities in PTSD. Patients with comorbid panic disorder and PTSD might be more likely to be associated with a lower number of hours worked in the previous week and previous year and to be associated with greater functional impairment and disability.
- The comorbid PTSD in schizophrenia has caused negative impact on clinical outcomes; some studies have shown a reduction of QoL in this population, worse cognitive performance, high rates of substance abuse, an increased use of health services and the need for hospitalization, and also the predisposition for suicidal behavior or suicide attempts.

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