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**Psychological Trauma, Posttraumatic stress disorder and Trauma-related depression:
A mini-review**

Wang SK *et al.* Trauma, PTSD and Trauma-related depression

Shi-Kai Wang, Min Feng, Yu Fang, Liang Lv, Gui-Lan Sun, Sheng-Liang Yang, Ping Guo, Shan-Fei Cheng, Min-Cai Qian, Huan-Xin Chen

Abstract

There are various types of traumatic stimuli, such as catastrophic events like wars, natural calamities like earthquakes, and personal trauma from physical and psychological neglect or abuse and sexual abuse. Traumatic events can be divided into type I and type II trauma, and their impacts on individuals depend not only on the severity and duration of the traumas but also on individuals' self-evaluation of the traumatic events. Individual stress reactions to trauma include posttraumatic stress disorder (PTSD), complex PTSD (CPTSD) and trauma-related depression. Trauma-related depression is a reactive depression with unclear pathology, and depression occurring due to trauma in the childhood has gained increasing attention, because it has persisted for a long time and does not respond to conventional antidepressants but shows good or partial response to psychotherapy, which is similar to the pattern observed for PTSD. Because trauma-related depression is associated with high risk of suicide and is chronic with a propensity to relapse, it is necessary to explore its pathogenesis and therapeutic strategy.

Key Words: Psychological trauma; Trauma-related depression; Reactive depression; Posttraumatic stress disorder; Antidepressant; Psychotherapy

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Core Tip: Exposure to psychological trauma may induce posttraumatic stress disorder (PTSD) and trauma-related depression. Major depression can be a progression secondary to PTSD. Both trauma-related depression and PTSD show good response to psychotherapy or prazosin, but a poor response to conventional antidepressants, suggesting that trauma-related depression should have different pathological mechanisms, like energy metabolism deficiency. It is necessary to explore the pathogenesis of and therapeutic strategy for PTSD and trauma-related depression.

INTRODUCTION

¹ Psychological trauma is a stressful event that causes distress that exceeds an individual's ability to integrate the emotions and cognitions involved in the experience^[1]. Its occurrence is unexpected and uncontrollable, often exceeding people's coping resources and making them feel powerless, helpless, and fearful. Besides natural disasters and wars, psychological trauma also ¹ encompasses various forms of physical and emotional abuse or neglect, sexual abuse, bullying, or household dysfunction experienced throughout one's entire lifespan^[2].

Psychological trauma has attracted attention when the veterans returned from the Vietnam War. Although their lives have been restored, the scenarios on the battlefield always reappear and flash up in their brain every day accompanied by fragmentary memories, sleep disorders, nightmares, unstable moods, and anhedonia^[3]. For the evaluation and intervention of the veterans' psychological crisis, posttraumatic stress

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disorder (PTSD) was first inserted in the third edition of Diagnostic and Statistical Manual of Mental Disorders in 1980^[4].

Traumatic events increase not only the risk of PTSD but also depression. Trauma-related depression, which meets the criteria of major depressive disorder, can be caused directly or indirectly by psychological trauma. Previous studies showed that 61% of patients with first-episode depression and 51% with recurrent depression reported childhood or recent trauma, including adverse childhood experiences^[5], recent life events^[6], and occupational stressors^[7]. While the pathological mechanism remains unclarified, trauma-related depression has attracted more attention because of its prolonged duration and resistance to conventional antidepressants. However, patients with trauma-related depression have a full or partial response to psychotherapy, like PTSD. Since trauma-related depression is at a high risk of suicide and is prone to relapse and be chronic, it is essential to explore the pathogenesis, therapeutic strategy, and causal relationships between psychological trauma, PTSD, and trauma-related depression. In this article, we will review the clinical characteristics of and relationship between PTSD and trauma-related depression, and their therapies.

TYPES AND CHARACTERICS OF TRAUMA

Terr^[8] divided childhood trauma into type I and type II trauma (Table 1^[8,9]) according to trauma characteristics. Type I trauma includes fully detailed memories, “omens”, and misperceptions (such as a car accident) and has characteristics including: (1) the time of trauma formation is short or at one time; (2) trauma may occur in different stages of childhood and adulthood; (3) the duration of trauma is not long, usually within three months; and (4) some heal naturally, some benefit from treatment, and some transform into type II. Type I trauma may lead to acute stress disorder (ASD), PTSD, and adjustment disorders. Among these disorders, PTSD is the most harmful. The diagnostic requirements of PTSD include re-experiencing traumatic events, avoidance, increased sensitivity or alertness, and functional impairment.

Type II is complex trauma, including denial and numbing, self-hypnosis and dissociation, and rage, which repeatedly occurs in childhood and lasts for a long time, such as physical and emotional abuse and neglect. Its characteristics include a long time to form and a broad impact on an individual's body and mind. The trauma may occur in different stages of childhood development or adult life. In general, type II trauma presents complex and diverse symptoms and will not heal naturally. 25% to 30% of type II trauma may evolve from type I trauma^[10]. Compared with type I, type II trauma has a more severe impact on individuals. It also significantly differs from type I trauma in terms of its symptoms, neuroimaging findings, treatments, and prognoses. Furthermore, it also often leads to CPTSD^[11].

The term "complex PTSD" was proposed by Herman^[11] to describe the repeated and long-term symptoms experienced by survivors of trauma, including changes in emotional regulation, consciousness, self-perception, and interpersonal relationships. This disorder can result from a single severe traumatic event or multiple chronic traumas that are difficult or impossible to escape, such as childhood abuse, domestic violence, torture, and imprisonment. The diagnosis of CPTSD in International Classification of Diseases 11th edition (ICD-11)^[9] requires not only meeting the diagnostic criteria of PTSD but also evidence of disorders in self-organization, including affective dysregulation, negative self-concept, and disorders in relationships.

There is additional type of trauma called chronic unpredictable mild stress (CUMS), which has been used to model depressive symptoms in rodents^[12]. Long-term (> 3 wk) exposure to a series of mild but unpredictable stressors can make animals depressive, which simulates a depressive state of human beings after encountering the stressors in the real world. However, there have been few clinical studies on CUMS thus far^[13].

TRAUMA AND STRESS RESPONSE

The impact of trauma depends not only on the traumatic event itself but also on the individuals' perceptions, psychological defense mechanisms, and whether the support system is timely and sufficient. Although genetic heritability is one of the risk factors for

the development of PTSD or major depressive disorder (MDD) in the population with traumas, a genetic factor ² may be less important as trauma exposure increases, that is, high levels of trauma are likely to lead to PTSD and MDD^[14].

From the perspective of psychiatric phenomenology, traumatic events may lead to a series of nonspecific mental and behavioral symptoms of post-trauma reaction. The impact of trauma on an individual's mental state is mainly determined by the trauma's intensity, duration, and age. According to the theory of the classical response to stress^[15], stress reaction can be roughly divided into alarm, resistance, and exhaustion stages^[16]. In the alarm stage of post-trauma condition, a stress reaction may manifest a "fight or flight" response by activating the sympathetic nervous system to release catecholamine. If stress reaction is insufficient, ASD will occur. After the acute stage comes the resistance stage. This stage involves adjustment to the persistent trauma or the after-effects of traumatic events via the activation of the hypothalamus-pituitary-adrenal (HPA) axis and promotion of endogenous glucocorticoids function to maintain the internal environment. If the stress reaction is insufficient, the manifestations of PTSD will appear.

If the trauma is too intense or prolonged, Individuals will encounter the exhaustion stage by excessive mobilization of the sympathetic nervous system and HPA axis, and manifests maladjustment or trauma-related depression (reactive depression). Therefore, multiple traumatic events can have cumulative detrimental effects on mental health of the victims^[17], manifesting depressive symptoms such as negative emotions, guilt, shame, self-blame, social withdrawal, or social isolation. They can also become irritable, aggressive, violent, and of self-injury or suicidal behaviors, or have persistent dissociative symptoms and acoustic and visual hallucinations similar to those that occur in psychosis^[18,19]. Individuals with post-trauma reactions are often diagnosed with depression or bipolar depression with or without psychotic symptoms or borderline personality disorder according to the ⁵ ICD-11 or the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)^[20].

PTSD AND TRAUMA-RELATED DEPRESSION

Relationship between PTSD and trauma-related depression

Studies have shown that collective trauma caused by earthquakes and plagues may lead to collective emotions accompanied by pro-social behaviors, thus reducing the adverse effects of traumatic events on individuals^[21]. However, suffering from interpersonal trauma (individualized trauma) such as abuse, neglect, or sexual violence often brings negative consequences which are easily internalized, become chronic and gradually develop into “trauma mode” as Piaget referred to^[22], which manifests as persistent depression, negative cognition, negative self-concept, and self-injury/suicide^[23].

ASD usually occurs within minutes or hours after a severe traumatic event. The symptoms are transient, usually relieved within days or a week. Therefore, PTSD is the most common lasting and harmful stress response to trauma and it is dominated by negative emotions such as anxiety, fear, irritability, and depression. The onset of PTSD usually occurs one month or several years after traumatic events. PTSD and depression often occur comorbidly. As a result of a meta-analysis ($k = 57$ studies; $n = 6670$ participants), 52% of individuals with PTSD had comorbid MDD^[23]. In addition, a number of overlapping symptoms were reported. Although it is sometimes challenging to differentiate, PTSD and MDD are two significantly different diseases.

Although the depressive symptoms present in PTSD can predict the occurrence and severity of depression, some scholars, such as Freedman *et al*^[24] and Bleich *et al*^[25] argue that there is no chronological progression from PTSD to MDD. However, many studies support the continuity between PTSD and MDD^[26,27]. PTSD can lead to affective disorder^[16], significantly increasing the risk for the first-onset of major depression^[28].

The COVID-19 pandemic caused long-term psychological impacts on people, like insomnia, anxiety, depression, and burnout syndrome, which has raised public health concerns globally. Burnout is a state of physical or mental stress resulting from prolonged exposure to job stressors. Burnout prevalence differs in different specialties. Studies have shown that after a high workload or prolonged contact with patients, nearly one-third of healthcare workers met the clinical level of exhaustion and

manifested anxiety, irritation, fatigue, depression, depersonalization, and PTSD^[29,30]. A 1-year observational study showed that the prevalence of burnout and anxiety was similar at 3 mo (52% *vs* 51%) and 12 mo (23% *vs* 23%), while the prevalence of PTSD was higher than that of depression at both 3 mo (23% *vs* 11%) and 12 mo (11% *vs* 6%)^[31].

The prevalence of depression and PTSD-like symptoms in adolescents increased significantly during the pandemic period of COVID-19^[32,33]. During the COVID-19 pandemic, the comorbidity prevalence of PTSD and depression was about 50%^[34]. However, a remote telephone interview revealed that the prevalence of PTSD and depression in patients who recovered from COVID-19 was 56.9% and 29.0%, respectively^[35]. It indicates that PTSD symptoms are the main symptoms during or at the beginning of traumatic events.

In a survey of the elderly, the lifetime prevalence and 12-mo prevalence of sexual violence are 44% and 8%, respectively, while the lifetime prevalence of depression, anxiety, and PTSD are 27%, 26%, and 6%, respectively^[36]. It indicates that the long-term effects of traumatic events on individuals are mainly depressive symptoms, and the patients might be diagnosed with major depressive disorder according to DSM-5 or ICD-10. Because this type of depression is associated with psychological trauma(s), it is often resistant to the treatment and much harmful.

Treatment and potential mechanism of PTSD and trauma-related depression

Trauma-related depression is caused by intense and persistent frustration or other psychological conflict factors. It may be considered reactive depression (stress-induced depression) and different from endogenous (biogenic) depression. Reactive depression and endogenous depression were proposed by the German psychiatrist Kurt Schneider in 1920^[37] in trying to classify depression by its etiology. This classification enjoyed broad acceptance^[38] up to the introduction of DSM-IV in 1994^[39]. Since then, psychiatrists and scholars have returned to the principle of phenomenological description of mental disorders. For instance, if a patient has clinical manifestations that meet the descriptive criteria for depression, the patient will be uniformly diagnosed

with depression without emphasizing its etiological classification, which makes the diagnosis and intervention much easier. The etiology of different depression types seemed less important, particularly since the discovery of tricyclic antidepressants and the establishment of a monoamine-based hypothesis^[40].

However, since 1994 and even more since the COVID-19 pandemic, patients with reactive depression have increased markedly^[41]. The poor efficiency of conventional antidepressants in reactive depression has again drawn attention to psychological trauma and “reactive depression”, particularly depression with childhood trauma. Studies^[42,43] have confirmed that depression related to trauma (especially childhood trauma) is very complex in clinical manifestations and many other aspects, such as neurobiological factors, treatment response and prognosis.

Childhood trauma or a recent traumatic event is an important precipitating and perpetuating factor of depression in adolescents and elderly patients^[36,43]. Severe psychological trauma can also lead to PTSD or CPTSD with comorbid depression. For example, more than 50% of PTSD patients have comorbid depression^[34]. Psychological trauma may affect the individual's response to antidepressants, clinical outcomes, and function. Regarding the treatment of PTSD, paroxetine, sertraline, fluoxetine, and venlafaxine are recommended, however, the efficiency of selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors in PTSD is comparably low (only about half as strong)^[44]. Psychotherapy is the treatment of choice for PTSD, including cognitive behavior therapy (CBT), prolonged exposure, and eye movement desensitization and reprocessing (EMDR)^[45].

The treatment of trauma-related depression, particularly in patients with childhood trauma, has been extensively studied (Table 2). Previous studies have shown that various childhood abuses is unfavorable to the treatment, and the poor response is significantly related to childhood abuse^[46-48], particularly trauma that occurred before the age of 7 years. Even after 8 wk of therapy with antidepressants, there was no remission. Moreover, there was a high risk of recurrence^[5,48]. Meanwhile, childhood trauma is also an important risk factor for suicidal ideation and the increased severity of

refractory depression^[49-51]. However, although patients with chronic depression after trauma have a comparatively good response to the psychotherapy with EMDR^[47]. Asarnow *et al*^[52] found that patients of refractory depression with a history of abuse have a significantly lower response to CBT than those without abuse. Shirk *et al*^[53] believed that trauma-focused cognitive behavioral therapy (TF-CBT) could significantly improve depressive symptoms. A meta-analysis^[54] showed that TF-CBT and EMDR are beneficial in alleviating the traumatic experience, depression, and anxiety of patients with PTSD. It was found that psychotherapy has better compliance than psychopharmacological therapy. Therefore, it is suggested that psychotherapy should be introduced in the early stage of the treatment of trauma-related depression^[55].

Taken together, for the patients with trauma-related depression, the symptomatology is more complex; the suicide rate is higher^[49]; the clinical condition is more prone to be chronic, and the response to antidepressant is poorer^[5,42,47,48]. Therefore, it is speculated that trauma-related depression may have different biological mechanisms compared to other depressed patients^[56,57]. Compared with classic depression, there are few studies on the underlying neurobiological mechanisms of trauma-related depression. It was previously thought that the occurrence of PTSD or chronic PTSD was related to noradrenergic dysfunction^[58] or cytokines^[57]. However, in recent years, we have learned by the CUMS model that energy metabolism disorder might play an important role^[59-61].

Although the etiological mechanisms underlying PTSD or trauma-related depression are not known in detail, the efficacy of certain therapies may be indicative of existing pathomechanisms^[62]. For example, in a case study, it was reported that low-dose prazosin led quickly to rapid improvement in depressive symptoms, including cognitive function in a therapy-resistant depressive patient with comorbid chronic PTSD^[63]. The patient had previously received antidepressants that work *via* serotonergic, noradrenergic, and dopaminergic mechanisms as well as several sessions of modified electroconvulsive therapy but did not benefit from these treatments, suggesting that prazosin may have acted by different pharmacological

mechanisms from monoamine hypothesis^[64]. This observation might turn out to be important in order to explore the pathogenesis of PTSD and trauma-related depression^[65].

However, there is also a meta-analysis^[50] has showed that, for adult depressive patients with childhood abuse, the effectiveness of antidepressant drugs alone, and psychotherapy alone, combined therapy is not satisfactory. In the same sense, some PTSD patients still have poor responses to psychotherapy. Therefore, we need to explore new treatment methods to improve the prognosis of PTSD patients with comorbid depression. For this purpose, it is necessary to expand our knowledge of the pathogenesis of trauma-related depression.

CONCLUSION

Exposure to psychological trauma may induce PTSD and trauma-related depression. Major depression can be a progression secondary to PTSD. Both trauma-related depression and PTSD show good response to psychotherapy or prazosin, but a poor response to conventional antidepressants, suggesting that trauma-related depression should have different pathological mechanisms, like energy metabolism deficiency. It is necessary to explore the pathogenesis of and therapeutic strategy for PTSD and trauma-related depression. Although we reviewed detailed features of trauma-related depression and PTSD, the relationship between them is ambiguous. In this article, one weakness is the limited discussion of the pathogenesis of trauma-related depression and PTSD, and the etiological roles in the pathogenesis.

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