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Advances in the Treatment of PTSD: A Review of Conventional and Emerging Therapies

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Abstract. Post-Traumatic Stress Disorder (PTSD) is a mental disorder triggered by experiencing a major traumatic event, which may have long-term effects on a patient's emotions, cognition, and social functioning. In recent years, treatment methods for PTSD have continued to evolve. Traditional treatments primarily include pharmacological interventions such as selective serotonin reuptake inhibitors (SSRIs), as well as cognitive-behavioral psychotherapies like Prolonged Exposure (PE) and Eye Movement Desensitization and Reprocessing (EMDR). While these methods have shown some efficacy, they still face limitations such as limited therapeutic effects and high relapse rates. With the deepening of research, emerging methods such as ketamine and MDMA-assisted therapy have gradually gained attention and shown promising results in some clinical studies. Meanwhile, explorations at the neural mechanism level have provided new insights into the underlying principles of different treatment approaches. This paper comprehensively reviews the current mainstream treatments and research progress in PTSD, and provides an initial outlook on the future development direction of individualized and integrated treatments, aiming to provide references for subsequent research and clinical practice.

Keywords: Post-Traumatic Stress Disorder, pharmacotherapy, psychotherapy, MDMA-Assisted psychotherapy

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a chronic and debilitating psychiatric condition characterized by a constellation of clinical manifestations: persistent hyperarousal (e.g., exaggerated startle response, sleep disturbances, and hypervigilance), intrusive re-experiencing symptoms (e.g., distressing flashbacks, nightmares, and traumatic memories), and avoidance of trauma-related stimuli [1]. Affected individuals may also exhibit emotional numbing, negative alterations in cognition and mood, and significant functional impairments [2]. The lifetime prevalence of PTSD in the total NCS-R sample is 6.8% [3], with the most common triggering events being combat trauma, physical and sexual assault, natural disasters, and motor vehicle accidents [4]. Consequently, the prevalence of PTSD is higher among veterans and first responders, classifying it as one of the most prevalent and debilitating mental disorders on a global scale. Furthermore, the prevalence of PTSD is influenced by factors such as gender, educational attainment, personal economic status, and sociocultural factors [5]. For instance, women demonstrate a 2- to 3-fold increased propensity to

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develop PTSD in comparison to men. The traumatic events experienced by men and women often differ; women are more likely to experience sexual assault and childhood sexual abuse, both of which are among the highest risk factors for developing PTSD [5].

At the neurobiological level, PTSD has been associated with dysregulation of key brain circuits involved in threat detection and emotional regulation, particularly the amygdala, hippocampus, and prefrontal cortex [6]. Neurochemical changes, including alterations in serotonergic and glutamatergic signaling, further contribute to persistent fear responses and cognitive distortions, which are characteristic of the disorder. These biological disruptions exhibit significant inter-individual variability, resulting in heterogeneity in symptom presentation and treatment response [6].

At present, there are a number of treatment options for PTSD, encompassing a variety of psychological and pharmacological therapies. First-line pharmacological therapies include SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and others. Trauma-focused psychotherapies encompass behavioral therapies such as exposure therapy, cognitive therapy, and EMDR. However, pharmacological therapies vary in efficacy and can have side effects. Similarly, psychotherapy is often limited by emotional avoidance and high dropout rates. Therefore, effectively treating PTSD remains challenging, and novel PTSD therapies are being developed and tested.

The latest International Society for Traumatic Stress Studies (ISTSS) treatment guidelines recommend 26 treatments [5]. New methods such as ketamine infusion, MDMA-assisted psychotherapy, and virtual reality exposure therapy have shown promising results. This review aims to appropriately summarize current PTSD treatment methods, introduce several important emerging therapies, and predict future research and clinical application directions.

2. Pharmacotherapy

2.1. Conventional pharmacotherapy

At present, the first-line therapeutic agents most frequently employed in the treatment of PTSD are SSRIs. The FDA has approved only two SSRIs—sertraline and paroxetine—for PTSD treatment [7]. Serotonin (5-HT) is a key neurotransmitter that regulates mood, emotion, and stress response. Normally, it helps maintain emotional balance and promotes stress adaptation. In PTSD patients, serotonin function is impaired, with studies showing reduced activity in brain areas like the amygdala and prefrontal cortex, which may contribute to heightened fear, anxiety, and difficulty processing traumatic memories. These medications work by blocking presynaptic serotonin transporters, thereby increasing extracellular serotonin levels in the synaptic cleft, which enhances serotonergic neurotransmission and produces therapeutic effects [7].

The utilization of SSRIs has been linked to a variety of deleterious effects, with gastrointestinal disturbances and central nervous system effects (including insomnia, fatigue, and sexual dysfunction) frequently documented [7]. Paroxetine is more likely to induce anticholinergic effects, such as xerostomia and sedation, while sertraline has been found to be more frequently associated with adverse effects, including nausea, diarrhea, and sexual dysfunction [8].

Despite being regarded as primary pharmacological interventions, the efficacy of SSRIs in the treatment of PTSD remains restricted. As indicated by clinical trials, the response rate to SSRIs is approximately 60% of patients, with only 20% to 30% achieving complete symptom remission [7]. Among these, sertraline demonstrated an efficacy rate of 53% compared to placebo in alleviating PTSD symptoms, while paroxetine achieved an efficacy rate of approximately 62% compared to placebo [8]. Consequently, combination therapy or the administration of medications with different mechanisms of action is necessary. SNRIs such as venlafaxine are also effective and are often used

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as an alternative or adjunct to SSRIs when the latter are ineffective. These medications have been demonstrated to inhibit the reuptake of both serotonin and norepinephrine, thereby offering efficacy in the treatment of core PTSD symptoms, including hyperarousal and mood symptoms [8]. Other traditional treatment medications include tricyclic antidepressants (TCAs) such as amitriptyline and imipramine, agents with anticonvulsant and mood-stabilizing properties such as carbamazepine, which can stabilize mood and reduce impulsivity and were initially used to treat epilepsy, benzodiazepines (BDZs), and monoamine oxidase inhibitors (MAOIs) [4]. Furthermore, research suggests that certain atypical antipsychotics may be utilized as adjunctive therapy and for the management of symptoms in PTSD, including risperidone, which has been observed to reduce hypervigilance and aggressive behavior, although it has also been associated with side effects such as weight gain and elevated prolactin levels. Quetiapine, on the other hand, is helpful in addressing symptoms like insomnia, nightmares, and irritability [8].

2.2. Emerging therapies

2.2.1. Ketamine

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promising therapeutic potential in the treatment of chronic PTSD and comorbid depression [9]. By enhancing neuroplasticity and increasing prefrontal cortex (PFC) activity, ketamine facilitates neural processes essential for fear extinction – a key mechanism impaired in PTSD [9]. Mechanistic studies indicate that ketamine may exert its effects by modulating PFC-amygdala circuitry, which is critically involved in emotional regulation and traumatic memory processing [9]. This neural network overlaps with the primary targets of exposure-based psychotherapies, suggesting a potential neurobiological synergy [9]. Such convergence has led to ongoing clinical investigations into combined treatment approaches that could transform PTSD management.

Ketamine was originally developed as a rapid-acting antidepressant and has been found to be effective in treating severe depression. A study demonstrated that the depressive symptoms of seven patients diagnosed with severe depression exhibited a marked improvement within 72 hours of ketamine infusion (Hamilton Depression Rating Scale score decreased by 14 ± SD 10 points) [10]. In recent years, there has been mounting evidence to suggest that in the majority of civilian populations, symptoms of PTSD improve significantly within 24 hours of a single ketamine infusion [11]. A case report described a veteran with severe treatment-resistant PTSD who experienced symptom improvement after receiving a single subanesthetic dose of ketamine [12]. Nevertheless, it is important to note that ketamine can also induce certain adverse effects. The studies have indicated that ketamine use may result in the induction of transient dissociative states. Further research is required to ascertain its safety [13]. Furthermore, research conducted on animals and on a small number of human subjects suggests that while ketamine can alleviate symptoms, the effects are short-lived, with effects lasting only 1–2 weeks [13].

2.2.2. MDMA-assisted psychotherapy

MDMA (3,4-methylenedioxymethamphetamine), a ring-substituted amphetamine derivative classified as an entactogen, exerts multifaceted neurobiological effects relevant to trauma processing [14]. lt elevates oxytocin levels, enhancing trust, emotional openness, and interpersonal connectedness, while concurrently reducing amygdala activation, thereby dampening fear responses [15]. Furthermore, MDMA modulates synaptic plasticity and promotes hippocampal neurogenesis,

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facilitating the reprocessing, reconsolidation, and emotional decoupling of threat-related memories [15].

Standardized MDMA-assisted psychotherapy protocols have been developed, typically comprising up to 3 MDMA sessions integrated within a broader course of 12 non-drug psychotherapy sessions. These sessions are conducted using a non-directive, patient-centered approach, emphasizing empathetic presence, active listening, and minimal therapist intervention to support self-directed processing [15]. Compared to conventional pharmacotherapies such as SSRIs, MDMA-assisted psychotherapy has demonstrated superior efficacy and tolerability in early-phase trials. For instance, Phase 2 studies (N=103) and Phase 3 trials (N=134) have shown significant and sustained symptom reduction, with fewer adverse effects among patients [16]. However, these findings are derived from relatively small cohorts and large-scale multicenter trials remain necessary to confirm the long-term efficacy and safety. There is also a risk of abuse. If MDMA becomes more accessible for therapeutic purposes, it may increase the risk of its circulation in illegal markets, leading to abuse and posing a threat to public health and social security. Regulatory approval of MDMA as a legal therapeutic agent will depend on the outcomes of these ongoing investigations.

3. Psychotherapy

3.1. Conventional pharmacotherapy

3.1.1. Prolonged Exposure(PE)

Global mental health organizations and government agencies consistently recognize exposure therapies—particularly PE, the most extensively researched and validated form—as an evidence-based treatment for PTSD across trauma types. As a core component of cognitive-behavioral therapy (CBT), these exposure-based interventions demonstrate robust efficacy in clinical guidelines worldwide [17]. PE and other exposure-based therapies work by systematically activating and extinguishing fear responses through controlled exposure to trauma-related cues. This process helps patients form new, neutral associations with traumatic stimuli, facilitating fear extinction and reducing PTSD symptoms. The mechanism involves both fear extinction and emotional learning [18].

PE typically consists of between 8-15 weekly 90 min individual therapy sessions and includes both imaginal and in vivo exposure. In imaginal exposure, the patient is guided in repeatedly recounting memories of the trauma in a safe environment. In vivo exposure involves gradual, systematic confrontation with fear-inducing stimuli, which may include simulated scenarios in the clinic or real-world situations [17].

Although PE is an effective PTSD treatment, its imaginal exposure component—requiring patients to repeatedly recount traumatic memories—presents a challenge for some patients. This approach directly contradicts a core diagnostic feature of PTSD: trauma-related avoidance. Consequently, many patients exhibit treatment reluctance, premature dropout, or impaired emotional engagement, which leads to diminished therapeutic outcomes [17].

3.1.2. Eye Movement Desensitization and Reprocessing (EMDR)

EMDR is a psychotherapeutic method that was originally developed to treat PTSD. The EMDR treatment protocol comprises eight phases. In the fourth phase, the desensitization phase, patients are asked to focus on painful memories while receiving bilateral stimulation, moving their eyes from

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one side to the other. This process serves to mitigate the discomfort and strain associated with the target memory. In the fifth phase, the installation phase, positive thoughts, feelings, and beliefs are instilled and associated with the traumatic memory to alter the patient's emotional intensity [19]. EMDR has been demonstrated to effectively reduce patients' negative emotions and beliefs by promoting the processing and integration of traumatic memories, thereby alleviating psychological stress and anxiety [19].

The treatment method was first described by Francine Shapiro in the late 1980s. The research demonstrated that a single EMDR session successfully desensitized 22 participants' traumatic memories and significantly altered their cognitive assessments of related situations, with effects that persisted over an extended period [20]. Following extensive research, the American Psychological Association has formally acknowledged EMDR as a reliable and efficacious treatment for PTSD [21]. Similarly, the ISTSS has also recognized EMDR as a valid treatment for PTSD [21]. The integration of EMDR with other therapeutic approaches has also become an increasingly prominent topic, including its combination with CST, trauma-informed care methods, exposure therapy, and others, thereby highlighting the flexible and personalized nature of EMDR therapy.

3.2. Virtual Reality Exposure Therapy (VRET)

VRET represents a promising PTSD treatment modality that utilizes immersive 3D environments to simulate trauma-related scenarios. By incorporating multisensory stimulation (visual, auditory, tactile), VRET enables patients to confront trauma reminders within a safe, controlled setting. This approach effectively activates the fear network while facilitating fear extinction through systematic exposure [18].

Research evidence indicates that VRET demonstrates superior patient engagement and reduced avoidance behaviors compared to traditional exposure therapy [18]. The customizable nature of virtual environments enables the simulation of high-risk trauma scenarios while maintaining rigorous safety controls. To date, specialized VR environments have been developed for diverse trauma types, including Vietnam War combat, 9/11 attacks, motor vehicle collisions, etc. [18].

Despite its therapeutic potential, VRET presents several implementation challenges. Although technological advancements have reduced costs and improved usability, the required equipment remains substantially more expensive than traditional behavioral therapy tools. Regarding tolerability, while most patients adapt well to VRET with minimal adverse effects, a subset of users may experience dizziness, motion sickness, or physical reactions to the VR headset [18].

4. Conclusion

This review set out to look at recent developments in the treatment of PTSD, with attention to both established and emerging approaches. The findings show that SSRIs, SNRIs, and trauma-focused psychotherapies are still the most commonly used methods, but newer treatments such as ketamine infusion, MDMA-assisted psychotherapy, and VRET have produced encouraging early results. Taken together, these findings suggest that PTSD treatment is gradually moving beyond traditional options toward more varied and innovative approaches.

The contribution of this review is that it brings together and organizes current knowledge in a way that can help readers, especially those just entering the field, quickly understand the treatment landscape. The review also provides a useful reference for clinicians and researchers who want to think about more integrative and patient-centered strategies.

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However, the review has limitations. The literature is relatively narrow, and many cited studies are small or in early trial phases. Differences between study populations, such as veterans versus civilians, were not explored in detail, and methodological variability across studies was insufficiently addressed. These issues may limit generalizability. Also cultural and socioeconomic aspects of PTSD treatment were not discussed in depth, though these likely influence access and outcomes.

Future research should broaden references, especially by including large-scale, multi-center randomized controlled trials and studies with longer follow-ups to assess long-term efficacy and safety. Additionally, cross-cultural research should be strengthened, and interdisciplinary findings from neuroscience, psychiatry, and digital health should be integrated to establish a more comprehensive framework for PTSD treatment.

Overall, this review provides a clear overview of strengths and limitations of current approaches. By identifying what is known and where evidence is lacking, it offers a useful starting point for future studies and supports the shift toward more personalized, evidence-based care for PTSD.

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