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NEUROLOGICAL MECHANISMS AND THERAPEUTIC STRATEGIES FOR POST-TRAUMATIC STRESS DISORDER (PTSD)

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Abstract: Objective: investigate and analyze, through scientific literature, the pathophysiological mechanisms underlying Post-Traumatic Stress Disorder(PTSD), in addition to identifying possible targets and therapeutic methods for the effective treatment of the condition **Methods:** Narrative literature review carried out from September to November 2023, through searches in the PubMed database using the search strategy((Post-Traumatic Stress Disorders) OR (PTSD)) AND ((Treatment) OR (Psychedelics) OR (Neuromodulation) OR (Virtual Reality) OR (Augmented Reality)). 2029 articles were found and, after the inclusion and exclusion criteria, 17 were selected to compose the study. **Discussion:** Different types of studies point to the influence of neuronal circuits in PTSD, demonstrating reductions in connectivity between the prefrontal cortex and subcortical structures, such as the amygdala and hippocampus. These brain changes are related to the emotional and memory symptoms that characterize or PTSD. Therefore, psychotherapies, such as cognitive behavioral therapy, functional release technique and trauma-focused behavioral therapy, associated with pharmacological treatment with serotonin reuptake inhibitors have proven to be effective in treating the disorder. Innovative neuromodulation treatments have also shown important results. **Final considerations:** It is essential to continue and develop studies and research to deepen the understanding of the mechanisms underlying PTSD and provide individualized treatment options for patients. Advancement in this field is essential to improve the quality of life of people affected by PTSD and, ultimately, to achieve more effective and complete treatments.

Keywords: Post-traumatic stress disorder, Neuromodulation, Pharmacological Therapies, Psychotherapeutic Approaches.

INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is a multifaceted and challenging psychiatric condition, manifesting in individuals who have been exposed to traumatic events. The diagnosis of PTSD requires the presence of significant impairment in the individual's occupational and social functionality, persisting for more than a month after exposure to the traumatic event (SCHRADER C.; ROSS A., 2021). Affected individuals may present with a range of disturbing symptoms, including, but not limited to, intrusive manifestations, affective and cognitive changes, depressed mood, anhedonia and suicidal ideation (MARAZZITI D. et al.,2023). The etiology of PTSD, specifically the neurobiological mechanisms that contribute to the emergence and perpetuation of symptoms, remains not fully elucidated. It is recognized that PTSD is associated with dysfunctions in several neural circuits and biological processes, encompassing several brain structures and neurotransmitter modulations (AL JOWF G. et al.,2023).

The prevalence of Post-Traumatic Stress Disorder (PTSD) varies substantially between different populations, reflecting the diversity of traumatic exposures and associated risk factors (MARAZZITI D. et al., 2023). Epidemiological studies indicate a greater susceptibility of women to PTSD, attributed in part to greater exposure to sexual violence, one of the most significant precipitants of the disorder (MERIANS AN et al., 2023). Furthermore, specific populations, such as military veterans, racial/ethnic minorities, and refugees, have high prevalences of PTSD due to the unique and disproportionate traumatic experiences to which they are subjected. Understanding the epidemiological disparities of PTSD is essential for designing appropriate prevention and intervention strategies, as well as for allocating therapeutic resources effectively.

Although the symptomatic picture is well defined, including intrusive symptoms, affective and cognitive disorders, among others, the pathophysiology of PTSD remains partially elucidated. Understanding the neural circuits and biological processes involved is fundamental for the development of effective therapeutic strategies (AL JOWF G. et al.,2023). The complexity of treating PTSD, combined with the lack of robust evidence until recently, highlights the need to investigate effective therapeutic methods. Psychotherapy, recognized as the gold standard, and pharmacotherapy, used in cases of psychotherapy failure, represent the conventional approaches. However, new neuromodulation techniques and emerging therapies, such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), have shown promise, illustrating a growing trend toward exploring innovative interventions in the treatment of PTSD (AL JOWF G. et al.,2023; MARAZZITI D. et al.,2023).

Given the complex clinical picture and varied therapeutic response associated with Post-Traumatic Stress Disorder (PTSD), this review sought to conduct a thorough and careful analysis of the pathophysiological mechanisms underlying the disorder. The aim was to identify and elucidate possible therapeutic targets that can be explored to develop more effective and innovative interventions in the treatment of PTSD. Furthermore, the aim was to synthesize recent advances in therapeutic approaches, including emerging neuromodulation techniques and other innovative treatment modalities. The objective was to provide a more in-depth understanding of the neurobiological bases of PTSD and contribute to the evolution of therapeutic strategies, aiming to improve the quality of life and prognosis of individuals

affected by this challenging psychiatric disorder.

METHODOLOGY

This is a narrative bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "What are the neurological mechanisms underlying Post-Traumatic Stress Disorder (PTSD) and how are current and emerging therapeutic strategies addressing these mechanisms in search of an effective treatment of the disorder?". In this sense, according to the parameters mentioned above, the population of this research refers to individuals diagnosed with Post-Traumatic Stress Disorder (PTSD), the observed variable is the Pathophysiological Mechanisms underlying PTSD and the current and emerging Therapeutic Strategies, seeking treatment effectiveness (outcome): identification of targets and therapeutic methods based on such mechanisms for effective PTSD treatment, based on scientific evidence.

The searches were carried out by searching the PubMed Central (PMC) database. The search terms were used in combination with the Boolean term "AND" and "OR" through the search strategy: ((Post-Traumatic Stress Disorders) OR (PTSD)) AND ((Treatment) OR (Psychedelics) OR (Neuromodulation) OR (Virtual Reality) OR (Augmented Reality)). From this search, 2029 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in the English language published between 2018 and 2023 and that addressed the themes proposed for this research, review and meta-analysis studies, observational studies, original studies, clinical trials and made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. A total of 17 articles were selected to compose the present study.

DISCUSSION

Post-traumatic stress disorder (PTSD) is triggered by exposure to events that cause intense stress, characterized as a psychopathology with multifaceted pathophysiology and diverse and complex clinical manifestations. Current treatment focuses on psychotherapy (gold standard) and pharmacological treatment, which despite their relative effectiveness require the introduction of new therapeutic agents for a more effective response to the disorder (MARAZZITI D. et al., 2023).

Recently, the neurobiology of PTSD has received increasing attention, with the aim of elucidating the progressive brain changes linked to this condition. Research has highlighted structural changes, especially in the regions of the frontal lobe, which are essential in managing emotions and processing traumatic memories (Al JOWF G. et al., 2023).

In subjects with PTSD, a notable reduction was observed volumetric analysis of white matter in the frontal lobe and gray matter in the dorsolateral prefrontal cortex (PFC). Volumetric decreases have also been reported in the insula, anterior temporal lobe and extrastriatal cortex, which provides insights into the impact of PTSD on brain architecture, particularly in areas involved in emotional regulation and the response to traumatic stress.

The region of the ventromedial prefrontal cortex (vm-PFC) is notable for its critical role in modulating amygdala activity, alleviating the subjective distress of PTSD patients (Al JOWF G. et al., 2023). The dynamics

between vm-PFC and amygdala are vital to understanding the neurobiological basis of the heightened emotional responses characteristic of PTSD.

Furthermore, the medial prefrontal cortex (mPFC) exerts an inhibitory function in the management of memories linked to threats, connecting to the amygdala and other subcortical structures, essential for the amplification of fear conditioning and for facilitating the extinction of fear responses. fear, and these regions are recruited in dangerous situations. The analysis of mitochondrial markers makes it possible to explore brain circuits and study the role of the hippocampus in contextualizing fear experiences. Investigations focused on different brain regions and their connections in functional circuits can include measures such as assessment of ATP production, oxidative metabolism, mtDNA, synaptic plasticity, inflammatory responses of the nervous system and biomarkers of apoptosis (KAPLAN B. et al., 2023).

The influence of neuronal circuits on PTSD is complex. Research with adults and adolescents has demonstrated reductions in functional connectivity between the ventromedial and ventrolateral PFC and subcortical structures such as the amygdala and hippocampus. These connectivity changes are intrinsically linked to the emotional and memory symptoms that characterize PTSD (Al JOWF G. et al., 2023).

When evaluating patients with Post-Traumatic Stress Disorder (PTSD), exposure psychotherapy and trauma-focused cognitive therapy are considered the reference treatments (STAPLETON P. et al., 2023). However, given the sustained prevalence of PTSD, particularly in post-pandemic contexts and current conflicts, it is imperative to develop new therapeutic strategies (MARAZZITI D. et al., 2023). This review addresses emerging therapies for PTSD, which include pharmacological options such as psychotropic drugs, in addition to psychotherapy and conventional medications such as selective serotonin reuptake inhibitors (SSRIs), for example sertraline and paroxetine (KREDIET E. et al., 2020).

Research on neuroprogression in post-traumatic stress disorder (PTSD) highlights the complexity and persistence of PTSD symptoms and their functional, immunological, and cardiovascular implications. Antonelli-Salgado T. et al. (2021) suggests the need to address neurocognitive decline and brain changes, as therapeutic targets, to develop effective interventions. Future studies focused on longitudinal mechanisms may provide valuable insights into the treatment of PTSD, potentially leading to more targeted therapeutic methods that could mitigate neuroprogression associated with PTSD and significantly improve the prognosis for affected patients.

Current literature highlights that Cognitive Behavioral Therapy (CBT) is recognized as a safe and effective approach for the treatment of Post-Traumatic Stress Disorder (PTSD), both in its acute and chronic forms, covering all age groups (KAPLAN G. et al., 2023). The American Psychological Association (APA, 2017) recommends trauma-focused psychotherapy as the preferred treatment. Latimer et al. (2021) emphasize that, according to the existing database, Trauma-Focused Behavioral Therapy (TF-CBT) is the most research-based modality for treating PTSD. It is also observed that psychological therapies, both with a direct focus on trauma and those without this specificity, are expanding and demonstrating effectiveness for cases of PTSD.

Additionally, the Functional Release Technique (EFT) has been proposed as an innovative modality, in which patients are instructed to manually stimulate acupoints,

replacing the use of traditional acupuncture needles (KAPLAN G. et al., 2023).

Tan et al. (2023) state that mind-body movement therapies (MBE), which combine physical exercises with meditation practices, body postures and diaphragmatic breathing techniques, present themselves as effective non-pharmacological treatments for PTSD. Examples include tai chi, a low-impact martial art with slow movements, and yoga. Additionally, mind-body exercise (MBE) interventions that integrate physical and mental health, such as yoga and tai chi, teach PTSD patients to control their breathing and movements (TAN L. et al., 2023).

Treating Post-Traumatic Stress Disorder (PTSD) with Emotional Freedom Techniques (EFT) has shown promising results, with studies indicating significant and large effects compared to waitlist controls or usual care. Research suggests that EFT, which incorporates cognitive and somatic elements and utilizes Cognitive Behavioral Therapy and Prolonged Exposure techniques, may offer similar benefits to other evidence-based therapies for PTSD. Additionally, positive physiological changes have been observed following EFT sessions, including changes in EEG that may correlate with improvements in PTSD. Additional research with controlled and randomized clinical trials is needed to confirm these findings and establish clinical guidelines for the use of EFT in the treatment of PTSD (STAPLETON P. et al.,2023).

In the pharmacological field, although SSRIs are widely used in the treatment of PTSD, they do not promote full recovery from the disorder, highlighting the need for new drugs and therapies.

To date, the most promising research has focused on substances such as ketamine, 3,4-methylenedioxymethamphetamine (MDMA), classic psychedelics (LSD) and cannabinoids, although there are discrepancies between studies on the effectiveness of these agents (SACHDEVA B. et al., 2023; KREDIET E. et al., 2020; LATIMER D. et al., 2021).

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is implicated in the pathophysiology of PTSD, where excessive NMDA activation may be related to the reactivation of traumatic memories (SACHDEVA B. et al., 2023). Ketamine must be administered in a hospital environment, without integration with psychotherapy during administration, preferably intravenously at a dose of 0.5 mg/kg. Ketamine side effects include tachycardia, anxiety and myocardial depression, due to its sympathomimetic effects (KREDIET E. et al., 2020).

On the other hand, therapy with MDMA (Methylenedioxymethamphetamine), which inhibits the norepinephrine, dopamine and serotonin transporter, has demonstrated efficacy in the treatment of PTSD, associated with the dysregulation of serotonin and noradrenergic activity in the disorder (LATIMER D. et al., 2021, MITCHELL, JM et al., 2023). MDMA is generally administered orally, in doses ranging from 75 to 125 mg, and is ideally used in conjunction with therapeutic sessions. Side effects are similar to those of ketamine, but include additional risks of neurotoxicity and potential for abuse, necessitating strict medical supervision (KREDIET E. et al., 2020).

Classic psychedelics, such as LSD, which have an agonist action at the 5-HT2A receptor and can reduce amygdala reactivity, have been investigated, although there are few clinical trials aimed at

to PTSD. LSD is used within therapy, but, unlike MDMA, the first few hours of its administration require little or no interaction with the therapist. Side effects include nausea, physical discomfort and anxiety (KREDIET E. et al., 2020).

Regarding the use of cannabinoids,

Tetrahydrocannabinol (THC) and Cannabidiol (CBD) have been the most studied, acting on the endocannabinoid system, which is related to emotional memories and chronic stress, and can also reduce the reactivity of the amygdala. Cannabinoids have been researched to alleviate acute symptoms of PTSD and can be used in conjunction with therapies. Administration methods include oral and inhalation, and common side effects are dry mouth and dizziness (KREDIET E. et al., 2020).

Within the studies analyzed, there is agreement on certain results, such as the effects of MDMA, where Krediet E. et al. (2020) describe an improvement in PTSD symptoms in 105 patients, while Latimer D. et al. (2021) report improvements in CAPS (Clinician-Administered PTSD Scale) and IES-R (Impact of Event Scale-Revised) in a smaller group of patients, highlighting the therapeutic potential of MDMA. However, there is disagreement regarding the use of atypical antipsychotics; Latimer D. et al. (2021) indicate that quetiapine may be beneficial, while Zhang Z. et al. (2023) highlight the lack of consensus on its effectiveness based on a previous meta-analysis.

Among the emerging approaches, exposure therapy through virtual reality stands out, which creates immersive and interactive environments allowing the patient to confront their source of anxiety and promote habituation through controlled exposure (WIEBE A. et al., 2022). This modality offers the advantage of simulating scenarios that would be unfeasible in practice (WIEBE A. et al., 2022).

Research by Van Loenen I. et al. (2022) indicate that virtual reality-assisted cognitive behavioral therapy (CBT) may be as effective as traditional CBT in treating severe anxiety, although these findings were limited by small sample size and reporting quality. In contrast, studies by Wiebe A. et al. (2022) point to the effectiveness of virtual reality therapy, but without a significant cost-benefit advantage over conventional exposure therapy. The efficiency of this therapy when administered via low-cost smartphones is also questioned, which could make it more accessible. Accessibility is crucial, as more economical treatments offer significant administration advantages compared to more costly methods, such as deep brain stimulation (D'URSO G. et al., 2018).

Transcranial direct current stimulation (tDCS) has been investigated as a promising method in the treatment of neuropsychiatric disorders, including post-traumatic stress disorder (PTSD). The research reviewed in the article indicates that tDCS, when applied to the dorsolateral prefrontal cortex, can reduce PTSD symptoms, although the small number of patients treated in this research limits the ability to draw definitive conclusions about effectiveness. However, the combination of tDCS with cognitive training is considered an area of interest for future investigation, suggesting a multimodal therapeutic approach. The evidence of clinical efficacy of tDCS, together with the possibility of widespread and home use of the therapy, highlights its potential as an accessible and customizable treatment for PTSD (D'URSO G. et al., 2018).

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising therapy, although current evidence is still preliminary. Studies indicate that rTMS, particularly when applied in combination with psychotherapy or exposure techniques, may offer therapeutic benefits for patients with PTSD. However, confirming the effectiveness of this approach requires randomized controlled clinical trials with sufficient sample sizes. Furthermore, a deeper understanding of the mechanisms of action of rTMS and the

neuropathology of PTSD could facilitate the optimization of treatment parameters. The potential of rTMS as a non-invasive, focused method for PTSD is remarkable, promoting continued research to establish robust clinical guidelines and personalized treatments (KOZEL FA, 2018).

FINAL CONSIDERATIONS

This study provided a comprehensive overview of Post-Traumatic Stress Disorder (PTSD) and existing and emerging therapeutic strategies for its treatment. PTSD is a debilitating condition that affects a significant portion of the population, especially in post-pandemic and war contexts. Although exposure psychotherapy and Trauma-Focused Cognitive Behavioral Therapy are gold standard treatments, the need for additional approaches is evident given the clinical complexity of the disorder. Conventional therapies, including Selective Serotonin Reuptake Inhibitors (SSRIs), are widely used, but recently, new pharmacological options and non-pharmacological therapies have been explored. Among the drugs being studied are ketamine, MDMA, classic psychedelics like LSD and cannabinoids, all of which demonstrate potential in treating PTSD. However, it is essential to emphasize the need for medical supervision due to the possible side effects of these substances. In addition to pharmacological therapies, non-pharmacological approaches, virtual reality exposure therapy, and deep brain stimulation are emerging as viable options. These therapeutic modalities show efficacy in preliminary studies, but issues such as accessibility and cost remain challenges. Advances in the neurobiological research of PTSD reveal progressive brain changes, particularly in the frontal lobe, amygdala and hippocampus regions, which are fundamental in emotional regulation and the processing of traumatic memories. Functional connectivity between these regions is also crucial for understanding PTSD symptoms. In summary, PTSD requires a multidisciplinary approach to its treatment. Current and emerging therapies bring hope, but challenges persist. Continuing research to deepen the understanding of PTSD, develop more effective and accessible therapies, and offer individualized treatments is essential to improving the lives of those affected by the disorder and achieving a more complete and efficient therapeutic approach.

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