Treatment of patients with post-traumatic stress disorder

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ABBREVIATIONS

PTSD – post-traumatic stress disorder

PBD – borderline personality disorder

IBS – irritable bowel syndrome

CBT- cognitive behavioral therapy

EMDR – eye movement desensitization and reprocessing

VRE – virtual reality exposure

PET – prolong exposure therapy

WET- written exposure therapy

SSRI – selective serotonin reuptake inhibitor

SGA – second-generation antipsychotic

CGI- clinical global impressions

PANSS – positive and negative symptoms scale

HAM-A – Hamilton anxiety rating scale

HAM-D – Hamilton depression rating scale

SGB – stellate ganglion blockade

CAPS 5 – clinical administrated PTSD scale

SDS- severity of dependent scale

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Abstract

Post-traumatic stress disorder is a chronic and disabling disorder, which poses a significant public health issue for which existing therapies are only somewhat effective, and ongoing investigation and research are still being conducted to find the most appropriate treatment. The disorder affects 15- 24% of the population who were exposed to a traumatic event in their lifetime. Although 60 percent to 50 percent of men and women, respectively, experienced traumatic or life-threatening circumstances in their life, the development of the disorder is still somewhat more common among high-risk populations, such as refugees, veterans, unmarried, and those of lower socioeconomic background, younger age, and low education.

If left untreated, PTSD can have severe and fatal consequences on the individual life and can impair daily and basic functions. Today, the first-line treatment is psychotherapy. Newer approaches are being developed to target the specific damage induced by the trauma. CBT and exposure therapy are the main methods for treating patients with PTSD. However, medical therapy can target more prominent somatic symptoms like hypervigilance, sleep problems, hyperarousal, and other comorbidities such as depression, anxiety, and suicidality.

This review is aimed to display the treatment options for treating PTSD and to explore the success and effectiveness of each type of treatment, alone and combined.

Sažetak

Posttraumatski stresni poremećaj je kronični i onesposobljavajući poremećaj, te predstavlja značajan javnozdravstveni problem. Postojeća terapija je tek djelomično učinkovita, te su u tijeku brojna istraživanja pronalaženja terapije koja bi imala veću djelotvornost. Ovaj poremećaj obuhvaća 15- 24% osoba koje su tijekom života imale traumatski događaj. Iako oko 60% muškaraca i 50% žena doživi traumatsko i/ili životno ugrožavajuće iskustvo, pod povećanim rizikom oboljevanja su veterani rata, izbjeglice, osobe koje nisu u braku, mlade osobe, kao i osobe lošijeg financijskog statusa i nižeg stupnja obrazovanja.

Neliječeni simptomi PTSPa mogu imati teške posljedice, uključujući oštećenje osnovnog, svakodnevnog funkcioniranja. Prva linija liječenja PTSPa je psihoterapija. Noviji pristupi uključuju naglasak na specifične aspekte traume. Kognitivno bihevioralna terapija i terapija izloženošću se najčešće primjenjuju u liječenju PTSPa. Sa druge strane, farmakoterapija je usmjerena na ublažavanje simptoma hipervigilnosti, poremećaja spavanja, pretjerane budnosti, te komorbidnih stanja poput depresije, anksioznih poremećaja, te također suicidalnosti.

Ovaj pregledni rad ima za cilj prikazati terapijske mogućnosti u liječenju PTSPa, te prikaže njihovu učinkovitost kada se primjenjuju samostalno, ili u kombinaciji s drugim metodama.

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by behavioral and mental changes. Most patients experience chronic and disabling symptoms such as difficulties maintaining relationships with others, amnesia, dissociation, cognitive impairment, and identity disturbance. The disorder evolves after single or sometimes multiple stressful events. The stressor can vary from combat relating to natural disasters, childhood abuse, sexual abuse, motor vehicle collision, mass casualty, and more (1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5), symptoms of PTSD can be classified into four categories: avoidance symptoms, intrusion/re-experiencing symptoms, negative cognitions and mood, and symptoms of hyper-arousal(2).

The aim of the present thesis was to provide an overview of the treatment options for patients with PTSD.

Epidemiology

The epidemiology of post-trauma disorder is dependent on the epidemiology of trauma-related experience. Not all individuals who experienced trauma will develop symptoms of PTSD or any related condition, but those who have PTSD had a severe traumatic event during their life (3).

In the 80’ PTSD studies were conducted almost exclusively on Vietnam’s combat veterans, making it difficult to estimate the worldwide prevalence of PTSD. Today, studies show that about 1 out of 12 adults will be diagnosed with PTSD, which is approximately 15- 24% of the population who were exposed to a traumatic event in their life (4). In the United States, greater than two-thirds of the population have experienced a traumatic event in their lifetime. It is worth considering that different populations in different countries, who are more frequently exposed to different stressors such as terrorism, natural disasters, and war, may have a higher chance of being exposed to traumatic stress events(5).

In a specific study done in southeast Michigan, 1007 young adults were assigned to a random control trial. 39.1% reported previous exposure to one or more traumatic events. Men were more exposed to trauma than women. However, the prevalence of PTSD was 11.3% among women, compared to 6% in men (4).

Younger age, female sex, being unmarried, having less education, lower household income, and being unemployed were all linked to a higher risk of developing lifetime PTSD among trauma survivors (6).

Clinical features, symptoms, and risk factors

Post-traumatic stress disorder is a psychological and physical adjustment disorder. Symptoms can vary from emotional and psychological symptoms, manifest with marked cognitive or behavioral changes, usually in response to stimuli. Flashbacks, acute anxiety, dissociative episodes, fleeing, or violent acts are examples of these. The way patients with PTSD deal with these symptoms is mainly by avoiding the trauma. In terms of emotional numbness, it reduces the interest in any activity and may lead to detachment from society.

By definition, all patients with PTSD have the same component of the critical feature, which includes involvement in a traumatic event.

Those with PTSD have gone through a major trauma, such examples include motor vehicle accidents, military operations involving violence, house invasions/robberies, rape, and serious physical disease that threatens death.

Individuals may be the victims of these occurrences, but they may also be an observer or hear about one who has been victimized. This hypothesis is called secondary traumatic stress and it is more common among psychotherapists who treat sexually traumatized patients (7).

While some patients have a single traumatic incident as their primary trigger, many others have a history of several sequels of traumatic events.

Abuse and neglect as a youngster may have set the stage for this terrible sequel of events.

Patients may not be able to recognize a single traumatic experience if they have been exposed to intense stimuli repeatedly, such as first responders (firefighters, paramedics) or police officers.

Furthermore, in DSM 5, symptoms are subdivided into clusters according to their significant features (8):

Cluster A: intrusion symptoms – One of the characteristics of PTSD is intrusion signs, sometimes known as "re-experiencing" symptoms. Unpleasant intrusive recollections of the traumatic experience range from infrequent unwanted thoughts about the trauma to frequent nightmares and "flashbacks," among other things. Significant psychological discomfort, such as fear or panic, is often connected with intrusion symptoms. Autonomic arousal and different physiological reactions may also be present. Intrusion symptoms may happen on their own or be prompted by situations that mimic or signify a trauma or a recollection of it.

Criterion B: avoidance symptoms - Avoiding stimuli connected with the traumatic experience might result in behavioral changes that impact both personal and professional life. Patients may strive to avoid not only internal thoughts and sensations related to the trauma but also activities, persons, and situations that bring up memories of the trauma. This avoidance may hinder everyday life functioning, for example, if it causes a person to avoid driving in a car or being in a crowded environment. In addition, tragedy victims frequently avoid specific locations where the trauma occurred.

Criterion C: Negative cognitions and mood - Depression and severe mood swings may be the first signs of PTSD. Positive emotions may be difficult to experience, and patients may lose interest in activities such as work, leisure, or social contacts. They may complain about not being able to connect with people. Many patients feel a great deal of remorse about the incident and blame themselves for it. These feelings may lead to poor self-perception and, as a result, a shift in their worldview. They may come to perceive the world as a hostile, dangerous place. For PTSD to be diagnosed, these symptoms must be recognized as part of a response to a traumatic incident.

Criterion D: Arousal and reactivity changes - Patients may show signs of irritation or aggressive physical or verbal conduct at first. Other symptoms include feeling on edge, being easily startled, impaired focus, sleep difficulties, and irresponsible or self-destructive actions (e.g., substance abuse). It is critical to detect these symptoms as having begun after the traumatic incident in order to make an appropriate diagnosis.

Several individual and societal risk factors tend to influence the likelihood of acquiring post-traumatic stress disorder, influencing the progression of the disorder's presentation and severity. Pretrauma risk factors are mainly the age of the trauma, sex, race, level of education, history of trauma, single or divorced, low socioeconomic status, and more(8). Among them, being divorced or separated increases the odds of developing PTSD. The result shows that divorced/ separated/ widow tend to have higher relative odds than single/ never married or those who are legally married. Such result of this research is statistically significant (9).

Among those who were exposed to trauma, the risk to develop PTSD is higher if there was a severe and unusual traumatic event, such as a threat to one's life or body, an event resulting in severe injury, or events intended to harm the victim, events involving horrific images, witnessing or learning of violence against loved ones, trauma resulting in death, severe harm to another, or traumas resulting in a severe loss. All of these appear to increase the risk of developing PTSD (4,6,10).

Pathogenesis

The pathophysiology of PTSD development is still unclear, and new study discoveries are being published all the time. The effect of trauma on the body is various and associated with changes in multiple areas of the brain. Patients with PTSD were found to have lower volumes of the hippocampus, amygdala, and anterior cingulate cortex than matched controls, according to studies employing magnetic resonance imaging scans(11). The images, sounds, and smells connected with the event have been retained in the amygdala. Later on, the amygdala, which is a part of the limbic system and its function is associated with aggression, fear, and anxiety can detect subsequent events as danger and release signals that will trigger defensive mechanisms. The amygdala is thought to play a key part in hypervigilance, which can be beneficial in risky situations. However, for people with PTSD, which can be influenced by various triggers, the overactive amygdala can cause a serious impairment that can affect their sleep, relationship, and their ability to calm down in non-real dangerous situations (12).

The hippocampus and the adjacent perirhinal, Parahippocampal, and entorhinal cortex play an important role in short-term memory(13). In the re-experience of traumatic events, the

hippocampus plays a crucial role. When provoked by a stimulus, a painful memory may be recalled involuntarily. In patients with PTSD, the hippocampus appears to be overactive, and these memories are quite strong to handle(12).
Most patients with combat-related post-traumatic stress disorder have nightmares, flashbacks, intrusive memories, and amnesia for traumatic events from their battlefield, among other symptoms. In addition, descriptions from previous and this century's wars show that combat veterans' memories change during or after battle stress. These include forgetting one's name or identity, forgetting events that occurred shortly before the last fight, and memory gaps that may persist for many years after the conflict.

It is suggested that extreme stress causes an increase in the production of glucocorticoids. According to studies in a range of animal species, direct glucocorticoid exposure causes a loss of neurons and a decrease in dendritic branching in the hippocampus and may result in memory problems. The mechanism of glucocorticoid toxicity is thought to increase the sensitivity of neurons, leading to excitatory amino acid toxicity, which can contribute to changes in the brain's structure and function (11).

Another mechanism hypothesis is the increase in central noradrenergic activity under baseline conditions in patients with chronic PTSD. This study was done by collecting CSF samples in patients with chronic PTSD and from a control group of healthy men. The levels of norepinephrine in the CSF of males with PTSD were considerably higher than in healthy individuals. Furthermore, norepinephrine concentrationsin the CSF were substantially and positively related to the severity of PTSD symptoms (14).

Co-occurring conditions

PTSD patients have frequently at least one or more psychiatric disorders. The most common comorbidity is substance abuse. Up to 60-80% of these individuals will develop abuse or addiction to substances like alcohol, heroin, cocaine, and so on, usually to modulate and alter their feelings and sensation. Another high rate of comorbidity is major depression and/or anxiety disorders which are very common among patients suffering from PTSD (15).

Other comorbidities related to PTSD are personality disorders, mainly borderline personality disorder (BPD) and antisocial personality disorder. A study done in the USA found that BPD was diagnosed in 24% of PTSD patients(15). Those with comorbid PTSD and BPD together had more comorbidity than those who have solel one of the latter. Patients who are diagnosed with both disorders tend to have a higher risk of suicide attempts and a higher level of traumatic events in childhood than those with PTSD or BPD alone. In both conditions, trauma plays an essential role. However, exposure to a traumatic incident is not required for a diagnosis of BPD, unfavorable experiences like childhood physical and sexual abuse are common in the life history of those diagnosed with BPD, prompting some authors to believe that BPD could be considered a posttraumatic stress "syndrome" (16).

In addition, and among others, PTSD has been found to have a high risk of irritable bowel syndrome. A comprehensive evaluation of eight studies, including over 648,000 people published in 2019, found a pooled odds ratio of 2.80 for the link between PTSD and IBS. The majority of the research was conducted on army veterans in the United States(17) the pathophysiology behind that is due to a complex interplay between the brain and gut, dysregulations in the hypothalamic-pituitary-adrenal axis, possible abnormalities in immunological function, altered levels of neuropeptide Y, and microbiota are all thought to have a role in the co-occurrence of PTSD and IBS (18).

Management

PTSD is a major health concern with only partially effective therapies currently available (19). Trauma therapy is the way to approach patients who suffer from PTSD. The therapy should be focus on psychotherapy and pharmacotherapy combined.

Psychotherapy

Individuals who have PTSD can be treated with a variety of psychotherapy approaches. Trauma-related therapies are often efficient in achieving symptom remission. However, they require a sufficient level of psychological stability to be effective. Before initiating trauma-related treatment, patients with low psychological stability may benefit from supportive, ego-strengthening, or motivational treatment beforehand (2).

Treatment for PTSD should begin as soon as possible after the diagnosis is made. The diagnosis of PTSD is made if symptoms remain for at least four weeks after the incident or more, although most individuals don't seek therapy for months, if not years. Early treatment of PTSD may, in theory, prevent chronicity, although this has yet to be proven empirically, particularly in the case of medication therapy (20).

First-line in the treatment of PTSD is psychotherapy. It is the preferred method of treatment for all PTSD patients, but should still aim at the individual needs and symptoms. Trauma-focused psychotherapy is a term that includes CBT, exposure therapy, and Eye movement desensitization and reprocessing (EMDR). Throughout treatment, trauma-focused therapies concentrate on the trauma and its impact on the individual (21).

Types of trauma-focused therapies

Cognitive-behavioral therapy (CBT)–
the essence of CBT is to divide the treatment into cognitive and behavioral parts. In cognitive therapy, the physician should recognize the patient's distorted and maladaptive beliefs and correct them. Behavioral therapy aims to reduce the symptoms and retrain daily function through thought exercises or real experiences. Moreover, CBT frequently includes relaxation exercises, coping skills training, stress management, or assertiveness training (22).

Exposure-based therapies (ET)–
exposure therapy aims to assist patients in confronting their avoided situations and disturbing memories therapeutically (23). The way it is done is by re-experiencing the trauma memories all over again. However, it is done through minor exposures that allow the memories from the trauma to be emotionally processed, so they become not as much distressing. This technique enables the individual to cope with situations that usually impair their daily life and it gives them tools to learn how to cope with their will to avoid certain situations or actions (22).

In a study that was done to compare between the treatment method of CBT and exposure therapy as treatment options for refugees who are dealing with PTSD, it was shown that ET and CBT reduced PTSD symptoms by 48 and 53 percent, depression by 54 and 57 percent and, generalized anxiety by 49 and 50 percent, respectively. At the 6-month follow-up, the results were consistent (24).

Types of methods use in exposure therapy include:

- Imaginal exposure – Imaginal exposure therapy is usually based on a patient's recollection of a traumatic event, which is re-experienced through vocal description, writing, or other means.
- In vivo exposure – Patients are exposed to a real-life, mostly safe setting that they ordinarily avoid because it reminds them of the trauma — for example, going into crowded circumstances if the trauma featured people.
- Virtual reality exposure (VRE) – Virtual reality, which is particularly adapted to reproduce events that may help envisage exposure, such as combat, catastrophic disasters, or terrible automobile accidents, is one approach for giving exposure therapy (25,26).

VRE therapy combines real-time computer graphics, body-tracking sensors, visual displays, and other sensory input devices to immerse a person in a computer-generated virtual environment that alters naturally in response to head and body motion (25).

These methods can be used in a different forms of exposure therapy. Two commonly studied therapy approaches are **Prolonged exposure therapy** (PET) and **Written exposure therapy**.

The quantity and types of components in exposure therapies vary, including the number and frequency of exposure sessions, homework assignments, and exposure methods. Following the exposure therapy session, the therapist discusses the individual's emotional response to the exposure and addresses maladaptive ideas like guilt and self-blaming (22).

PET - usually consists of 12 sessions that cover breathing retraining, trauma education, and processing of the traumatic information. The types of exposures depend mainly on what the patient is avoiding, the patient's willingness, and the accessibility of trauma reminders.

PET is the most researched PTSD exposure therapy protocol. It has been demonstrated to be more helpful in those subjected to many traumatic events and those who have a variety of comorbidities. A randomized study of 277 women with mostly chronic PTSD caused by various traumatic events, such as sexual assault and military warfare, compared extended exposure to

present-centered therapy, a supportive intervention. When compared to the group getting present-centered therapy, the group receiving prolonged exposure had a higher reduction in PTSD symptoms (25 versus 17 points on the Clinician-Administered PTSD Scale). It was more likely to match no longer diagnostic criteria for PTSD (41 versus 28 percent). Three months after therapy, prolonged exposure continued to demonstrate a more significant effect (27).

WET- Individuals participating in written exposure therapy write about their traumatic event in response to particular suggestions. Patients are encouraged to discuss the writing with their therapists and to pay attention to the thoughts and feelings it elicits. Imaginal exposure is used in written exposure treatment.

Eye movement desensitization and reprocessing (EMDR)-

EMDR is a type of psychotherapy that involves saccadic eye movements during exposure as well as CBT and exposure therapy components (28). It is done with the patient imagining a scene from the trauma while the therapist glides two fingers across the patient's visual area and instructs the patient to trace the digits. The pattern is continued until the patient's anxiety subsides; At this point, the patient is instructed to think of something more adaptive and calmer.

According to researchers, it was concluded that EMDR is an effective treatment for PTSD. EMDR was found to alleviate the intensity of PTSD symptoms compared to a waitlist or usual treatment in a meta-analysis that comprised six studies and 183 patients with PTSD (29).

In another study that was done in 2007, researchers were comparing EMDR, fluoxetine, and pill placebo in the treatment of PTSD, to assess the influence of the onset of the trauma (30). They compared participants with childhood- versus adult-onset trauma on treatment outcomes of EMDR. In this controlled, randomized trial, van der Kolk and colleagues found that for individuals with childhood trauma histories rather than adults who experienced recent trauma, eight sessions of EMDR treatment yielded significantly less robust responses in childhood trauma history. More accurately, 100 percent of adult-onset participants reported that they lost their PTSD diagnosis with a significant reduction in symptoms by posttreatment, compared to only 75 percent of the childhood-onset participants.

Although 89 percent of those with childhood-onset traumas had lost their PTSD diagnosis by the 6-month follow-up, just 33 percent of them were asymptomatic, compared to 75 percent of those

with adult-onset traumas. As a result, early initiation of trauma was linked to lower end-state functioning (31).

Pharmacotherapy

Psychotherapy can help the patient with daily function and enable them with proper tools in order to make them capable to live with their trauma. However, PTSD is a disorder that manifests with irritable somatic symptoms that are much harder to diminish only by psychotherapy. Hence, the combination is the goal of treatment. Intrusive thoughts, visions, phobic avoidance, pathological hyperarousal, hypervigilance, irritation and wrath, and sadness are all treated with pharmaceutical treatment. Drug therapies have been found to be most effective in reducing hyperarousal and mood symptoms like irritability, anger, and depression. For less extent pharmaceutical treatment can also reduce re-experiencing, emotional numbing, and behavioral avoidance symptoms. It is important to bear in mind that individual differences in response often outweigh treatment-specific differences (15).

First-line pharmacotherapy is SSRIs (selective serotonin reuptake inhibitors) which are a group of antidepressant drugs acting in the central nervous system and are very effective in lowering the symptoms of posttraumatic stress disorder.

A meta-analysis review was comprised of 35 randomized control trials with a duration of fewer than 14 weeks (4597 participants). In 17 trials, the medication groups had significantly lower symptom severity than the placebo groups. Similarly, summary statistics for responder status from 13 trials showed that a variety of pharmaceutical treatments were generally superior to placebo. Patients responded to medication in 59.1 percent (N = 644) and 38.5 percent (628) of cases, respectively. The evidence of treatment efficacy for SSRIs was the most persuasive of the drug classes. Medication was found to be more effective than a placebo in lowering the severity of PTSD (32).

Compared to SSRIs, there are fewer trials evaluating the efficacy of serotonin-norepinephrine reuptake inhibitors for PTSD.
In a 6-month, double-blind, placebo-controlled trial on PTSD patients with venlafaxine extended-release, it was shown that the venlafaxine ER group improved significantly more than

the placebo group in cluster scores for re-experiencing and avoidance/numbing, but not for symptoms of hyperarousal (33).

Second-generation antipsychotics - randomized clinical trials show that second-generation antipsychotics can be effective in treating PTSD as monotherapy or in combination with SSRIs. However, the side effect of this group of drugs outweighs the benefit of the treatment. Some of the side effects are metabolic syndrome, parkinsonism-like symptoms, hyperprolactinemia, and QT interval prolongation (15).

Monotherapy with quetiapine and other SGAs was reported to improve PTSD symptoms in military and non-military patients in clinical trials when compared to placebo (34). In a randomized clinical trial of eighty individuals, who are military veterans with chronic PTSD, patients were randomly allocated to either quetiapine or placebo medication. The Clinician-Administered PTSD Scale (CAPS) was the primary outcome measure. Quetiapine was started at a daily dose of 25 mg and raised to a maximum of 800 mg after a 1-week placebo run-in; the average amount was 258 mg (range, 50-800 mg). The quetiapine group showed considerably higher reductions in CAPS total, and in reduction of re-experiencing, and hyperarousal ratings than the placebo group. The Davidson Trauma Scale, CGI severity and improvement ratings, PANSS positive symptom and general psychopathology subscales, HAM-A, and HAM-D all showed greater improvements with quetiapine than with placebo. Adverse effects were minimal and predictable based on previous quetiapine trials in this and other patient populations (34).

Alpha-adrenergic receptor blockers - For certain PTSD patients, prazosin appears to reduce overall PTSD symptoms, nightmares, and sleep disturbance. Prazosin is by some experts recommended as a monotherapy or as a supplement to SSRI or SNRI therapy.

In a randomized controlled clinical trial, subjects were randomly randomized to therapy with prazosin or placebo in a trial including 67 active-duty United States Army veterans with PTSD returning from combat deployments in Iraq or Afghanistan. In terms of reducing nightmares, improving overall sleep quality, and improving overall clinical symptoms, prazosin outperformed placebo. Because of the early benefit seen with prazosin, the trial was called off early (35).

In a meta-analysis of six randomized clinical trials of six randomized controlled studies of prazosin for sleep problems in PTSD patients (sample n=240), prazosin was found to be statistically significantly more effective than placebo in improving sleep quality, as well as reducing overall PTSD symptoms and sleep disturbances in particular (36). Prazosin is usually started at 1 mg before night and escalated to 3 to 15 mg as tolerated. Patients who are hypotensive or who are at risk for orthostatic hypotension (if they are on other drugs that can induce this) should be handled with caution. Prazosin should not be stopped suddenly because it can cause rebound hypertension; patients should be warned about this (15).

Benzodiazepines (BZDs)- Benzodiazepines are often used to treat posttraumatic stress disorder, however, no systematic review or meta-analysis has looked into this treatment. The use of benzodiazepines as a treatment option for patients with PTSD is quite common, however, it is still controversial. Among the population of PTSD patients, it is estimated that 30% to 74% are prescribed benzodiazepines (37). In a systemic review and metanalysis, There were a total of 5236 individuals participated in eighteen clinical trials and observational studies. Qualitative and quantitative syntheses, as well as meta-analysis, were used to evaluate the outcomes. The results show that BZDs are ineffective for treating and preventing PTSD, and the hazards of using them outweigh any potential short-term benefits. BZDs have been linked to particular difficulties in people with PTSD, including worse overall severity, a considerably higher chance of developing PTSD with usage after recent trauma, poor psychotherapy outcomes, aggression, sadness, and substance use. In addition, they may cause sedation, tolerance, dependence, and withdrawal symptoms, as well as paradoxical aggressive reactions. Therefore, BZDs should be considered relatively contraindicated for patients with PTSD or recent trauma, according to the findings of this systematic review. Evidence-based PTSD treatments should be preferred over BZDs (37).

In a randomized, Placebo-Controlled Trial of mirtazapine for veterans who suffered from PTSD, mirtazapine monotherapy was not shown to be an effective treatment option. Between April 2006 and November 2010, researchers at the Tuscaloosa and Birmingham Veterans Affairs Medical Centers in Alabama conducted a multi-site, randomized, double-blind, placebo-controlled experiment. For an eight-week double-blind period followed by an 8-week open-label phase of mirtazapine treatment, US military veterans who fulfilled DSM-IV criteria for PTSD, were randomly allocated to placebo (n = 39) or mirtazapine (n = 39) titrated up to 45 mg/d.

Seventy-eight subjects were randomly assigned, with 61 finishing the 8-week controlled phase and 48 finishing the open-label phase. During the controlled phase, there were no significant differences between groups on the primary outcome of a structured interview to assess PTSD symptoms. Mirtazapine monotherapy was not shown to be effective in the treatment of PTSD in this trial (38).
Antidepressant medications other than SSRI\SNRI have inadequate evidence of their benefit and outcome in PTSD.

Beta-adrenergic receptor blockers - Although early reports suggested that beta-adrenergic blockers like propranolol could be used to prevent or treat PTSD in the early stages, subsequent studies have refuted this assertion, and more research is needed (39). on the other hand, according to a 2018 randomized clinical study, trauma memory reactivation followed by propranolol medication reduced PTSD symptoms more than placebo-pretreated trauma memory reactivation. In a study involving 60 people with long-term PTSD in a 6-week, double-blind, placebo-controlled, randomized clinical trial. Once a week for 6 weeks, propranolol or placebo was given 90 minutes before a brief memory reactivation session. Patients who received propranolol had a considerably lower rate of PTSD symptoms (as indicated by the Clinician-Administered PTSD Scale) than those who received a placebo (40,41).

Treatments under investigation (experimental treatment)

Ketamine - N-methyl-D-aspartic acid antagonist is an anesthetic drug. It causes dissociative anesthesia, a trance-like condition that relieves pain while also delivering sleepiness and forgetfulness. In a randomized, double-blind, crossover trial that was done on Forty-one patients with chronic PTSD, it was shown that early administration can aid with PTSD symptoms. In the study, researchers compared ketamine with an active placebo control, midazolam, by administration of intravenous infusion of ketamine hydrochloride (0.5 mg/kg) and midazolam (0.045 mg/kg) (41).
Moreover, in a study that was done to investigate PTSD prevalence among veterans burned victims who were treated in a military therapeutical center.
Six hundred three burned casualties were in the center, of which 241 were determined as PTSD positive or negative according to the PTSD Checklist-Military (PCL-M). Of those, 147 men were

needed to be operated on. 119 patients received preoperative ketamine as an anesthetic and the rest 28 did not. The prevalence of PTSD was 27 percent (32 of 119) vs 46 percent (13 of 28), respectively (42).

Cannabis and synthetic cannabinoids - Treatment outcome studies on PTSD using whole-plant marijuana and related cannabinoids are sparse and lack methodological rigor, making a conclusion regarding their potential therapeutic effects unfeasible. In a study of ten individuals with difficult-to-treat PTSD, the synthetic cannabinoid nabilone was found to be beneficial in certain cases. In this study, ten Canadian male military veterans who suffer from chronic PTSD and continued to have trauma-related nightmares despite normal treatment underwent double-blind treatment with 0.5mg nabilone capsule or placebo, then titrated to the effective dose (nightmare suppression) or a maximum of 3.0mg. Subjects were monitored for 7 weeks before being titrated with the other study drug and monitored for another 7 weeks after a 2-week washout period. The results show that in the nabilone capsule group five out of ten (50%) were much improved versus one out of nine (11%) in the placebo group (43).

Nevertheless, marijuana use has been associated with negative mental consequences, including depression, anxiety, psychosis, and drug abuse, all of which are typically comorbid with PTSD. The evidence supporting marijuana's negative effects on the development of psychosis and drug abuse is stronger than that for sadness and anxiety. In naturalistic investigations, marijuana use is linked to poor treatment results and maladaptive coping methods, both of which may contribute to the persistence of PTSD symptoms (44).

3,4 methylenedioxymethamphetamine (MDMA) - MDMA, the recreational drug which is also known as ecstasy, may be beneficial in the treatment of severe PTSD. MDMA is a synthetic drug that induces the release of serotonin via binding to presynaptic serotonin transporters 12. It is known that MDMA effect individual awareness and perception of reality and in addition can alter mood and cognition. In animal models, MDMA has been found to improve fear memory extinction, alter fear memory reconsolidation and improve social behavior.
In a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial, patients with severe and chronic PTSD symptoms, as well as those with other comorbidities including

depression, dissociation, childhood trauma, and history of alcohol and substance abuse problems, were assigned.

In this study, the participants (n = 90) were randomized 1:1 to undergo manualized treatment with MDMA or a placebo group, after other psychiatric medications were washed out. In addition to receiving the medication, the therapy was combined with three introductory and nine integrative therapy sessions. The Clinician-Administered PTSD Scale for DSM-5 and the Sheehan Disability Scale was used to assess PTSD symptoms and functional impairment at baseline.

MDMA was observed to cause a significant and robust reduction in CAPS-5 score and a significant reduction in SDS total score. In the MDMA group, the mean change in CAPS-5 scores after treatment was significantly reduced in comparison to the placebo group. It was also shown that MDMA did not cause any risk for abuse, suicidality, or QT prolongation. These findings suggest that, when compared to manualized therapy with an inert placebo, MDMA-assisted therapy is highly effective in people with severe and disabling PTSD and that it is both safe and well-tolerated, even in those with comorbidities. The severity of childhood trauma or the type of PTSD (dissociative versus non-dissociative) had no influence on this outcome. It was concluded that MDMA-assisted therapy is a potentially transformative treatment that requires immediate clinical testing and more investigation (19).

Procedure for PTSD treatment

stellate ganglion blockade - Two stellate ganglion blockade treatments, given two weeks apart, were beneficial in decreasing the Clinician-Administered PTSD Scale for eight weeks in a sham-controlled randomized clinical trial. The method involves an injection in and around the stellate ganglion, in the lower part of the neck, with a local anesthetic to momentarily block its function. 113 participants were eligible and randomized (74 to SGB and 39 to sham therapy), with 108 (95.6 percent) completing the research. The SGB and sham therapy groups had similar baseline characteristics. The adjusted mean total symptom severity score changed for those getting SGB treatments was 12.6 points in an intent-to-treat analysis, compared to 6.1 points for those receiving sham therapy. the result showed that over the course of 8 weeks, two SGB treatments, given two weeks apart, were successful in lowering CAPS-5 overall symptom severity scores.

The study's findings are limited in their generalizability due to the mild-moderate baseline level of PTSD symptom severity and short follow-up time, but the study suggests that SGB merits additional testing as a PTSD treatment adjunct (45).

According to comparative clinical trials, monotherapy with SSRIs or trauma-focused therapy with exposure are basically comparable in terms of effectiveness for PTSD, with psychotherapy having a slight edge, and the decision between the two should be based on patient predilection (46). Participants in a 24-week randomized experiment involving 207 PTSD patients were randomly allocated to receive sertraline plus boosted medication management, either prolonged exposure therapy plus placebo, or prolonged exposure therapy plus sertraline. PTSD symptoms were reduced in all groups, even though the amount of the reduction did not differ (47).

Summary

Post-traumatic stress disorder is a major matter in the psychiatric field. The exact mechanism of developing the disorder is still not known however it is necessarily dependent on the individual personality and past experiences in life. People who were dealing with multiple small events of trauma can experience symptoms similar to those who experience one major traumatic event. Furthermore, there are people who can experience the same or similar traumatic event and will result in a different outcome.

The goal in treating patients with PTSD is to start with the therapy as soon as possible. As I acknowledged in my thesis the best treatment is dependent on the patient's will. Therefore, adherence to treatment is of highest value.

Treatment options are abundant and need to be tailored to the patient's PTSD type, with favor for psychotherapy alone at the onset of treatment and the addition of pharmacotherapy later on in treatment course. First-line pharmaceutical options are SSRIs with only two drugs being officially labels for PTSD treatment: paroxetine and sertraline. Both proved to show a reduction in symptoms and their benefit outweighs their harm.

Today, with the increased prevalence of PTSD in certain populations across the globe, other clinical approaches should be investigated and explored by experts.

Biography

Mayan Menashes was born on April 21, 1994. Mayan was born in Haifa, Israel. Mayan served in the Israeli defense forces (IDF) as a medic in the intelligence unit, between the years 2012-2014. During the years 2016-2022 Mayan studies general medicine in school of medicine University of Zagreb, Croatia. On the 6th year of the studies Mayan spent two months in the university of psychiatry hospital, Vrapce, in Zagreb, and one month in gynecology and obstetrics department in Merkur clinical hospital.

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