Treatment of PTSD

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Treatment Options of Post- Traumatic Stress Disorder

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Abbreviations

PTSD = Post-Traumatic Stress Disorder

DSM = Diagnostic and Statistical Manual of Mental Disorders

USA = United States of America

ICD = International Classification of Diseases

SSRIs = Selective Serotonin Re-uptake Inhibitors

AEDs = Anti-Epileptics Drugs

MDMA = ±3,4-Methylenedioxymethamphetamine

MBX = Mindfulness-Based Stretching and Deep Breathing Exercise

PCL-C = PTSD Checklist-Civilian Version

EMDR = Eye Movement Desensitization and Reprocessing

CBT = Cognitive-Behavioural Therapy

IES-R = Event Scale-Revised

TFCBT = Trauma-Focused Cognitive Behavioural Therapy/Exposure Therapy

SPS = Single Prolonged Stress

HPA = Hypothalamo-Pituitary-Adrenal Axis

GR = Glucocorticoid Receptor

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1. Summary

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Post-traumatic stress disorder (PTSD) affects individuals that have experienced or witnessed a traumatic event and it affects approximately 7-8 % of the general population. Even more alarming is the PTSD prevalence in military personal throughout the world, with the PTSD prevalence in US combat veterans ranging from 6 to 31%. Severe or untreated PTSD can lead to long- term complications and consequences, including comorbid substance abuse, increased rates of depression and suicide, therefore treatment and potential prevention is key. An exploration of numerous clinical trials concerning the treatment of PTSD is necessary to conclude what the gold standard treatment should be. Considering the fatal consequences that may occur if treatment is not provided, there is great importance in reviewing multiple clinical trials and concluding what the current treatment algorithm should be. PTSD and other psychiatric disorders are not just treated via traditional pharmaceutical ways, but can also involve non- pharmacological, including but not limited to yoga and other forms of exercise. This review aims to explore the current medical treatment and non-medical treatment of PTSD and the effectiveness and safety of the drugs involved.

Key words: Post traumatic stress disorder, Treatment

2. Sažetak

Liječenje posttraumatskog stresnog poremećaja
Borislav Pekez

Posttraumatski stresni poremećaj (PTSP) se javlja u osoba koje su proživjele ili bile svjedokom traumatskog događaja, a zahvaća otprilike 7-8% osoba u općoj populaciji. Međutim, posebice zabrinjava činjenica da je prisustvo PTSP-a utvrđeno u čak 6 do 31% u Američkih ratnih veterana. Težak ili neliječeni PTSP može imati dugotrajne posljedice i komplikacije, poput zlouporabe sredstava ovisnosti, povećane stope obolijevanja od depresivnog poremećaja; stoga je liječenje PTSP-a od presudne važnosti. Neophodne su brojne kliničke studije u oboljelih od PTSP-a, kako bi se utvrdilo koji je zlatni standard liječenja ovog poremećaja. S obzirom na moguće teške posljedice u neliječenih osoba, bitan je sustavni pregled kliničkih studija da bi se sastavio algoritam liječenja. Cilj ovog preglednog rada je prikazati farmakološko i nefarmakološko liječenje PTSP-a, kao i učinkovitost i sigurnost lijekova kojima za sada raspolažemo.

Ključne riječi: Posttraumatskog stresnog poremećaja, Liječenje

3. Introduction: Post- traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a psychiatry disorder that affects individuals that have experienced or witnessed a traumatic event and it affects approximately 7-8 people out of 100 people in the general population (1). Even more alarming is the PTSD prevalence in military personal throughout the world. The combat veterans of the United States of America (USA) have the direst statistical data on PTSD prevalence, which ranges from 6 to 31% (2). Severe or untreated PTSD can lead to long- term complications and consequences, including comorbid substance abuse, increased rates of depression and suicide; therefore treatment is of utmost importance (3).

Symptoms of PTSD vary from individual to individual and may include nightmares, anxiety and/or flashbacks to name a few (4). PTSD is categorized in diagnostic and statistical manual of mental disorders (DSM) 5, which is trauma- and stressor- related disorders (5). A diagnostic criterion for DSM-5 is exposure to a traumatic or stressful event. The diagnostic criteria for PTSD is divided into criterion A to criterion H. Criterion A requires the patient to have one of the following in regards to the event: “direct exposure, witnessing the trauma/event, learning that a relative or close friend was exposed, or indirect exposure to aversive details of the trauma, usually in the course of professional duties” (5). Criterion B requires the patient to have one of the following in regards to persistently re-experiencing the event: “unwanted upsetting memories, nightmares, flashbacks, emotional distress after exposure to traumatic reminders, or physical reactivity after exposure to traumatic reminders” (5). Criterion C requires the patient to have one of the following in regard to avoiding trauma-related stimuli after the trauma: “trauma- related thoughts or feelings or trauma-related reminders” (5). Criterion D requires the patient to have two of the following in regards to negative thoughts or feelings that began or worsened after the trauma: “inability to recall key features of the trauma, overly negative thoughts and assumptions about oneself or the world, exaggerated blame of self or others for causing the trauma, negative affect, decreased interest in activities, feeling

isolated, or difficultly experiencing positive affect" (5). Criterion E requires the patient to have two of the following related to the trauma- related arousal and reactivity that began or worsened after the trauma: "irritability or aggression, risky or destructive behavior, hypervigilance, heightened startle reaction, difficulty concentrating, or difficulty sleeping" (5). Criterion F requires that the symptoms last for more than 1 month (5). Symptoms may occur immediately, however full diagnostic criteria is usually not fulfilled until 6 months after the trauma, which is referred to as delayed specification. Criterion G requires that the symptoms cause distress or functional impairment in the individual's social and/or occupation. Finally, criterion H states that the symptoms should not be due to medication, substance abuse or other illnesses. Also, dissociative specification means that in addition to meeting criteria for diagnosis, the patient experiences high levels of either depersonalization or derealization in reaction to trauma- related stimuli (5). Depersonalization is "experience of being an outside observer of or detached from oneself" (5), for example feeling as if this is not happening to themselves or them believing that they are dreaming. Derealization is "experience of unreality, distance or distortion" (5). Another classification is International Classification of Diseases (ICD) where PTSD is categorized under F43.1 (6).

A summary of the diagnostic criterion for PTSD is that an adult must have all the following for at least 1 month: "at least one re- experiencing symptom, at least one avoidance system, at least two arousal and reactivity symptoms and at least on cognition and mood symptom" (1).

4. Pathophysiology of PTSD

Various parts of the brain have been associated with PTSD. The amygdala is the part of the brain responsible for evaluating stress and deciding when to react. During a traumatic event, the amygdala detects danger and alerts the body by initiating the fight or flight response; it also is able to store the memory and stimuli associated with it, including sights, smells, and sounds to help detect the danger in future settings and lastly, when the danger passes, it can produce calming thoughts (7). Thus, PTSD symptoms associated with the amygdala are: anxiety, hypervigilance, avoidance of stimuli associated with the trauma, and being easily startled. (7). Thus, if the amygdala is overactive, as in the case of patients with PTSD, it's purpose becomes counterproductive because it can interfere with sleep or being able to calm down in safe situations due to hypervigilance.

The hippocampus is responsible for memory formation and during a traumatic event is stores the memory of the trauma, it is also capable of retrieving it at a later time and it can calm the amygdala alarm circuit (7). Symptoms of PTSD associated with the hippocampus are: confusion, disorientation, recurring thoughts, nightmares, flashbacks, and difficulty sleeping (7). Impaired sleep with frequent nightmares is a common and extremely frustrating symptom in patients with PTSD. Despite the hippocampus having the ability to calm the amygdala it is not able to because the new "danger" is perceived as real.

Another part of the brain that can calm the amygdala when the danger is gone is the prefrontal cortex. PTSD symptoms associated with the prefrontal cortex include irritability, numbness, and avoidance. In patients with PTSD, the activity of the prefrontal cortex seems to be decreased which corresponds with the aforementioned symptoms of withdrawal and avoiding triggers of the trauma (7). As a summary, the "prefrontal cortex is unable to override the hippocampus, as it flashes a memory, so it cannot signal the amygdala that there is no real danger" (7).

Neuroimaging has shown that there are neurobiological changes in the brains of patients with PTSD, with three areas being the most affected: hippocampus, amygdala and the medial frontal cortex (8). The amygdala becomes over-reactive to stimuli associated with the trauma (sights, smells, etc) (8). Symptoms of hyper reactivity, including exaggerated startle response and flashbacks, may be related to the overactive amygdala but also the "failure of higher brain regions (hippocampus and medial frontal cortex) to dampen the exaggerated symptoms of arousal and distress" (8).

5. Comparison of Treatment Options

(A) Introduction

There are various therapies available for PTSD. These include pharmacotherapies, including anti-depressants, and also non- prescription options, including yoga. Also, there are two routes to treatment: treating the diagnosis or the specific symptoms and in the following various treatment options will be discussed and detailed. The aim of the treatment is to diminish the symptoms associated with PTSD.

(B) Pharmaceutical Treatment Options

Records of war veterans diagnosed with PTSD in 2004 were examined and it was found that 80% received psychotropic medication, and among those 89% were given antidepressants, 61% anxiolytics/sedative-hypnotics, and 34% antipsychotics (9). Patients were more likely to receive pharmacotherapy if they sought mental health services more often or had comorbid psychiatric disorders (9). Further on, depending on the co-morbidities, there are predictors to the use of medication. For example, if the co-morbidity was depressive disorders, then the patient was given antidepressants; if it was anxiety disorders, they were prescribed anxiolytic/sedative-hypnotic drugs; and if psychotic disorders, then they were prescribed antipsychotics (9). However, there was also prescriptions given unrelated to co-morbid diagnoses and that treatment was targeted at specific symptoms, including insomnia, anxiety, nightmares, rather than a diagnosis (9).

Selective serotonin re-uptake inhibitors (SSRIs) are generally used as first line treatment, however it's been found that only 60% of patients respond to it (10). PTSD is also often refractory to pharmacotherapy (10). In a double-blind, placebo- controlled study, it was found that patients with PTSD that were given SSRIs with adjunctive olanzapine has statistically significant

greater reduction in measures of posttraumatic stress, depression and especially sleep disorders, thus suggesting to add atypical antipsychotics in treating SSRI-resistant PTSD (10).

A systematic review and meta- regression analysis concluded that there was a reduction in PTSD symptoms greatest with SSRIs and tricyclic antidepressants up into 11 weeks of treatment and then after, the other medication classes were significantly greater than them (2). In combat veterans particularly, concurrent anxiety and depressive symptoms are often reported, which is further support for the use of SSRIs and tricyclic antidepressants. Evidence from the systematic review shows that the variety of pharmacotherapy may be lacking but that it does have a “positive, but modest, therapeutic effect on PTSD, anxiety, and depressive symptom severity, and it also successfully acts as a concurrent treatment for these symptoms among combat veterans” (2).

Martényi F. concluded that data supports the efficacy of SSRIs particularly in the civilian population, especially females, regardless of the trauma that they experienced (11). However, that treatment in combat- related PTSD was inconclusive or negative (11). For males that experienced combat-related trauma, improvement was found with fluoxetine, a SSRI, but that an adjuvant 5HT2 antagonist can improve the SSRI effect (11). Further on, nefaxodone, an atypical antidepressant, was better than placebo, however risperidone, an antipsychotic, added to an antidepressant “showed significant benefit compared to antidepressant monotherapy in the treatment of combat-related PTSD” (11). Despite the widespread prescription of different psychotropic agents in patients with PTSD (9), only two drugs are so far approved by regulatory agencies specifically for the treatment of PTSD: paroxetine and sertraline.

There has been some research on the use of anti-epileptics drugs (AEDs) as treatment to PTSD. In double-blind, placebo-controlled trials, AEDs that have been found to be effective are: lamotrigine, topiramate, and tiagabine (12). AEDs may be effective because some of them, including carbamazepine, lithium and valproate, interfere with limbic kindling. The

symptoms of PTSD may involve sympathetic nervous system hyper arousal and hyperactivity, which may include stress-induced limbic kindling (13). These symptoms include intrusive re-experiencing and increased arousal. An open clinical trial found that 10 out of 16 patients showed significant improvement while using Valproate, especially with hyper arousal/ hyper reactivity symptoms (13).

In the treatment of PTSD there will be individuals that respond to pharmacotherapy such as SSRI, AEDs, and antipsychotics, but on the other hand there are those that seem to be resistant to those types of treatments. A relatively controversial approach to treating PTSD is the rediscovered drug ±3,4-methylenedioxymethamphetamine (MDMA), better known as Ecstasy, as a therapeutic adjunct. MDMA is a synthetic drug that alters perception and mood (14). According to the National Institute on Drug Abuse MDMA increases the activity of three neurotransmitters: Dopamine, Serotonin, and Norepinephrine (14). The article states that the effects of that are “euphoria and increased energy/activity…increases heart rate and blood pressure…affects mood, appetite, sleep” (14). Other effects on health that MDMA may have are nausea, blurred vision, chills, and muscle cramping (14).

According to a 2011 randomized controlled study done by Mithoefer et al. prior to the criminalization in 1985 of the use of MDMA, it was used as a catalyst to psychotherapy (15). In their study, twenty patients who were resistant to psychopharmacology and psychotherapy were placed randomly into a control or experimental group. In the experimental group, twelve participants would go through psychotherapy with the active drug (MDMA) and the eight in the control group would be given an inactive placebo along with psychotherapy. The therapy sessions were done twice, each lasting eight hours in length. In the article it states, “Primary outcome measure was the Clinician-Administered PTSD Scale.” (15). This scale was utilized at baseline, 4 days after the experimental session, and 2 months after the second session according to the article (15). In the study the participants also went through blood pressure, neurocognitive, and temperature testing since the dangers of

MDMA are still unknown in the therapeutic setting but the effects that the drug has on the body are well established and some of which were discussed above. In the study they state, " There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases" (15). The results of the study showed that the experimental group through out all three times of assessment had significantly lower scores on the clinician-administered PTSD scale, when compared to the control group (15). The clinical response of the control group and the experimental group were (25%) and (83%) respectively (15). As their final point in the study the authors stated "MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm" (15). This study is obviously very small and needs to be repeated with more participants in order to truly make a concrete conclusion. Also, other participants that don't have treatment resistant PTSD need to be included in a future study to see how standard treatment methods such as SSRIs and antipsychotics compare in their effects on alleviating PTSD symptoms.

(C) Non- Pharmaceutical Treatment Options

A randomized control study done by van der Kolk et al. found that yoga can significantly reduce symptoms of PTSD (16). The symptoms that it specifically helps are the feelings of helplessness and fear. This is accomplished by the increase in emotional awareness and the affect tolerance that yoga provides (16). It found that these effects are even comparable to treatment of PTSD with pharmaceuticals (16). In another study, which was a long term follow up study performed by Rhodes, Spinazzola, and van der Kolk, it states that symptoms of PTSD were decreased and the potential loss of the PTSD diagnosis is linked with the greater frequency of practicing yoga (17).

Another treatment option that has potential is mindfulness-based stretching and deep breathing exercise (MBX). A randomised control study done by Kim et al. concluded that there is a significant reduction of PTSD-like

symptoms when utilizing MBX (18). They concluded this by not only utilizing the PTSD Checklist-Civilian version (PCL-C) but also through measuring cortisol levels. The participants in the experimental group did MBX for 8 weeks in semi- weekly session of 6 minutes and felt benefits (18). Other interventions along the lines of the aforementioned treatment is meditation. A systemic review done by Lang et al. in 2012 covered the three major types of meditation which could be used as a form of treatment for PTSD: compassion meditation, mindfulness, and mantra (19). In their paper they stated “Empirical evidence of the efficacy of meditation for PTSD is very limited but holds some promise.” They go on to say that more evaluation is warranted to analyze the mechanism that improve quality of life and reduce the PTSD symptoms (19).

Physical exercise is important for our physical and mental well-being. A randomized control trial done by Rosenbaum, Sherrington and Tiedemann discovered that not only does exercise improve sleep, reduce symptoms of depression and the waist circumference, it also reduces the symptoms of PTSD when it is paired with the usual treatment for PTSD (20). The usual treatment for this study was pharmacotherapy, psychotherapy and group therapy. The experimental group participants did 3 sessions of resistant training and for 30 minutes along with a pedometer based walking program along with the usual treatment as mentioned above (20).

Natural disasters such as earthquakes, tornadoes, and hurricanes can have devastating effects not only on the natural world around us but also on the mental health of individuals that survive these events. It is no wonder that some people got PTSD after experiencing an event like the earthquake that the people in the Sichuan Province China went through in 2008. A randomised control study was done by Chen et al. on adolescents who survived this disaster and lost parents to see if short term cognitive-behavioural therapy (CBT) was effective at treating PTSD and depression (21). Short-term cognitive behavioural therapy was compared to general supportive interventions and control group of no treatment. According to the study “CBT was effective in reducing PTSD and depressive symptoms and improved psychological resilience” (21). They go on further to say that the

only improvement that the general supportive intervention provided was psychological resilience (21).

Mother nature isn't the only force to be reckoned with when it comes to mental health. Man made conflicts, such as war, leave many people displaced from their country of origin to live a life as refugees all over the world. This again leaves many people to battle with the world around them along with the strain that it takes on their mental health, leading some to be diagnosed with PTSD. The Syrian refugees are no exception. Acarturk et al. wanted to explore if an effective treatment for PTSD was eye movement desensitization and reprocessing (EMDR) (23). According to Shapiro and the review that the author did "Eye movement desensitization and reprocessing (EMDR) therapy is an empirically validated treatment for trauma, including such negative life experiences as commonly present in medical practice" (22). Acarturk et al. set up a randomized trail where the experimental group received EMDR and the control group was put in a wait-list condition (23). The outcome of the study was measured utilizing the Event Scale-Revised (IES-R) and Beck Depression Inventory after the 4 week follow up (23). Post treatment scores showed that the EMDR group had significantly lower scores when compared to the control group. Additionally the EMDR group also had lower depression scores when compared to the control group (23).

A systemic review done in 2007 by Bisson and Andrew analyzed the literature on the topic of psychological treatments of PTSD. The authors pulled randomized control studies that contained treatment types of trauma-focused cognitive behavioural therapy/exposure therapy (TFCBT), stress therapy, and others such as supportive and hypnotherapy, to mention a few (24). After all the analysis was done they came to the conclusion that an effective psychological treatment in reducing PTSD symptoms is stress management and both individual and group TFCBT (24). According to the article the evidence suggests individual TFCBT is superior in treating PTSD symptoms when compared to stress management between 2 and 5 months following treatment. They also go on to state, "Other non-trauma focused psychological treatments did not reduce PTSD symptoms as significantly"

(24). Interestingly the authors brought up the question of if there is a harmful impact that psychological treatment may have on people diagnosed with PTSD. The evidence for this question to be answered will have to be explored in another research paper because in this systemic review the evidence was insufficient.

6. Prophylactic treatment of PTSD

Aforementioned, treatment of PTSD includes potential adjunctive therapies to current pharmacotherapy algorithms once symptoms have developed and a diagnosis is established. Prophylactic treatment would be started prior to symptoms developing. However, an early obstacle is the fact that not everyone who experiences a traumatic event will develop PTSD and of course, unnecessary treatment should be avoided (25).

There are a number of markers that have been proposed to distinguish patients that are at a risk of developing PTSD: lower cortisol levels, increased heart rate dynamics after traumatic event or somatic arousal (26, 27).

Another issue in prophylactic treatment is the desire to counteract the development of PTSD while not disturbing normal functioning (25).

There are various forms of prophylactic treatment. In those patients in risk populations, such as soldiers, this is termed prospective or primary prevention and treatment is given immediately after the trauma (25). If treatment is given later but before “induction or consolidation of processes leading to PTSD” then this is retrospective or secondary prevention and this broadens the amount of patients, including those in lower risks where trauma did occur, for example following a car accident (25).

In regards to primary prevention, one strategy is to enhance the patient’s stress coping and preclinical studies have demonstrated that rats exposed to single prolonged stress (SPS) showed increased inhibition of the hypothalamo-pituitary-adrenal (HPA) axis and increased expression of glucocorticoid receptor (GR) in the hippocampus (28).

In regards to secondary prevention, in another study performed on rats, it was found that microinjection of anisomycin, a protein synthesis inhibitor, prior to and after stress exposure decreased symptoms of anxiety and also avoidant behavior, reduced startle response (29). Therefore, disrupting the “process of traumatic memory consolidation may be useful” in decreasing the progression and amplitude of symptoms of PTSD (29). An obvious limitation to this is that injection of any pharmacologicals are not possible if the

traumatic event is not foreseeable. However, further studies researching this topic should be performed on humans to see the efficacy.

7. Conclusion

Everyone is an individual; everyone sees the world differently and everyone's mind works differently, thus we have people who get PTSD, while others do not, despite going through a similar traumatic event.

Current treatment algorithms, in regards to pharmacotherapy, use selective serotonin reuptake inhibitors as first line treatment, however with resistance and potential negative side effects, other drugs that are being used in conjunction with SSRIs, or instead of, include tricyclic antidepressants, anti-epileptics, antipsychotics, atypical antidepressants, and/or NMDA.

In addition, or instead of, there are many non- pharmacological treatment options of PTSD. These include yoga, meditation, MBX, cognitive behavioral therapy, and EDRM. With many of these since there are no or limited negative side effects, perhaps it is useful to try in all patients suffering with PTSD since there is a potential for positive effects. In a worst- case situation where the patient receives no benefit from any of the non-pharmacological treatments, the negative effects are minor at worst.

It is also important to monitor the development and/or progression of PTSD in individuals in high- risk groups, for example soldiers in war or abuse victims. Perhaps, examining neuroimaging of individuals in risk groups may help in noticing the developing and progression from the aforementioned neuroimaging changes that occur in individuals - in the amygdala, hippocampus and frontal cortex.

The main conclusion that can be drawn is that it is vital to personalize the treatment for each patient and also what trauma they experienced. Combining therapies is a possibility, which for some might include pharmacotherapy to stabilize the patient and then to explore possible further treatment.

With the world being in such a seemingly chaotic state currently, it is easy to assume that more and more people will be suffering and specifically suffering from PTSD due to these negative events, be they natural or man-

made. Therefore, it is upmost importance that more research and more funding is allocated for PTSD treatments.

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10. Biography

Borislav Pekez was born in Bosnia and Herzegovina and moved to Germany and then Nebraska, U.S.A. in his teen years. Upon graduating from high school, he went to University of Nebraska Lincoln and graduated with a Bachelor of Science (Psychology) and while studying was employed as a Certified Nurse's Assistant and Real Estate Agent. Afterwards, he came to the University of Zagreb: Medical Studies in English because of his passion for psychiatry and helping others. Borislav enjoys helping his fellow colleagues, including being a demonstrator for his younger colleagues in the course History Taking and Physical Examination. He is particularly interested in Psychiatry and hopes to continue pursuing this passion in his future medical career.