ISSN: 2690- 909X

Review Article

Advances in Neurology and Neuroscience

Pharmacological and Psychoactive Agents for Treatment Resistant Posttraumatic Stress Disorder

Hani Raoul Khouzam[1,2*]

[1]*Staff Psychiatrist, PTSD Treatment Program, VA Northern California Health Care System (VANCHCS), Mather, California*

[2]*Clinical Professor of Psychiatry and Medicine, UC Davis Health, Sacramento, California*

***Corresponding author**
Hani Raoul Khouzam, MBBCh;MPH.

Submitted: 30 March 2021; **Accepted:** 14 Apr 2021; **Published:** 27 Apr 2021

Citation: *Hani Raoul Khouzam (2021) Pharmacological and Psychoactive Agents for Treatment Resistant Posttraumatic Stress Disorder. Adv Neur Neur Sci, 4(1):83-89.*

Abstract

The Food and Drug Administration (FDA) approved two selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine for the treatment of posttraumatic stress disorder. Many patients do not respond to them and their side effects commonly occur before noticeable therapeutic effects, leading to their discontinuation. Other patients develop treatment resistance to the two approved SSRIs and are treated with other pharmacological agents. A sizable number of patients also do not respond to pharmacological agents and resort to the use of experimental psychoactive agents. This article reviews the definition of treatment resistant posttraumatic stress disorder, and summarizes the various pharmacological and psychoactive agents that have been used for treatment resistant posttraumatic stress disorder including various antidepressants, antipsychotics ,noradrenergic agents, anticonvulsants, mood stabilizers, anxiolytics, hypnotics ,antihistaminergic agents, naltrexone, buprenorphine, D-Cycloserine, neuropeptides, memantine, cannabinoids, 3,4-methylendioxymethamphetamine and ketamine.

Keywords: Posttraumatic Stress Disorder, Treatment Resistant, Psychopharmacology, Psychoactive.

Introduction

Posttraumatic stress disorder (PTSD) is a trauma- and stress-related disorder [1]. It is caused by exposure to a traumatic event that could result in serious injury or the loss of one's life. Events that can be considered traumatic could also include being witness to or coming to know of close relatives or friends being affected by trauma events as well as being repeatedly confronted with harmful effects of a traumatic event. Patients with PTSD may also develop a constellation of symptoms that mirrors major depressive disorder (MDD) including negative beliefs and expectations, negative emotional states, anhedonia, and social withdrawal [1]. In addition to these symptoms, patients may experience various traumatic reminders that may trigger prolonged and intense distress as well as physiological reactivity. Thus, external reminders and thoughts or feelings related to the trauma are often avoided. Further, negative changes in mood and cognition, and alterations in arousal could also occur [1]. PTSD has a prevalence of 8.7% in the United States, with a prevalence of 3.5% during any given 12-month period [1]. PTSD has a higher prevalence among military veterans, as well as firefighters, police officers, and emergency medical personnel. Globally, the greatest prevalence is found among survivors of rape, military combat and captivity, and politically motivated genocide [1]. PTSD is associated with poor social and family relationships, excessive educational, and occupational difficulties, lower income, and high degrees of disability, making it difficult to maintain employment and social wellness [1]. Individuals with PTSD are 80% more likely than those without PTSD to have co-occurring psychiatric disorders such as MDD, alcohol and substance use disorder, obsessive compulsive disorder, anxiety disorders panic disorder, agoraphobia, and generalized anxiety disorder [1]. Suicidality increases in the PTSD population approximately 2 to 3-fold and odds of lifetime suicide attempts increase with the presence of comorbid conditions.

There are several treatment options available for PTSD, with psychotherapy being recognized as the most effective form of treatment for PTSD [2] which include Cognitive Behavior Therapy (CBT), Cognitive Processing Therapy (CPT), Trauma-Focused Cognitive-Behavioral Therapy (TFCBT), Prolonged Exposure Therapy (PET) and Eye Movement Desensitization and Reprocessing (EMDR) [2].

From a pharmacological perspective, SSRIs including the FDA approved sertraline and paroxetine are considered first line treatment. There are many other medications that can be used for those who do not respond to sertraline and paroxetine and in those patients with co-occurring psychiatric disorders [3].

The heterogeneity of symptom clusters in PTSD as well as the complex co-occurrence of other psychiatric comorbidities such as mood disorders, especially MDD, anxiety disorders including panic disorder, agoraphobia, and generalized anxiety disorder, obsessive compulsive disorder and substance use disorders often lead clinicians to the use of combination of medications and especially for PTSD treatment resistant patients [4,5].

Definition of PTSD-Treatment Resistance

Although Treatment-resistant depression has been widely accepted and treated for many decades, treatment resistance in PTSD (TR-PTSD) which is a very common, serious, and a disabling condition, has been less frequently addressed and at times unrecognized as a valid clinical entity. There is also a paucity of data and little consensus on the ongoing treatment of TR-PTSD [6].

The definition of TR-PTSD may vary across studies, it has been generally described as a lack of response to all prior PTSD evidence-based psychotherapy and to confirmed medications adherence with appropriate dosage and recommended adequate treatment duration. In general TR- PTSD is frequently associated with PTSD severity , the experience of multiple traumas, the type of traumatic events , patient's gender and the co-occurrence of other comorbid psychiatric disorders such as mood disorders, especially MDD, anxiety disorders including panic disorder, agoraphobia, and generalized anxiety disorder, obsessive compulsive disorder and substance use disorders, and other vocational, situational and societal contributing factors [7] . These factors are differently manifested in the civilian, combat-veteran and refugee populations [8]. Civilian populations generally show a clinical response to antidepressant medications. Combat-veterans especially those with co-occurring psychiatric disorders have an increased severity of PTSD symptoms thus raising the likelihood of TR-PTSD [9]. In the refugee population there is often a more prolonged exposure to traumatic events resulting in extremely severe manifestation with co-occurrence of PTSD with depression, anxiety and panic comorbidity leading to TR-PTSD [10].

Pharmacotherapy for TR-PTSD

Several proposed psychotherapeutic and pharmacological approaches have been proposed for TR-PTSD. The various psychotherapeutic interventions are beyond the scope of this review which would mainly address the various pharmacological and psychoactive agents that could be considered for TR-PTSD and include antidepressants, antipsychotics, noradrenergic agents, anticonvulsants, mood stabilizers, anxiolytics, hypnotics, antihistaminergic agents, naltrexone, buprenorphine, D-Cycloserine, neuropeptides, memantine, cannabinoids, 3,4-methylendioxymethamphetamine and ketamine.

Antidepressants

The Selective Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs are the most studied medications with sertraline and paroxetine being FDA approved and considered as the first line treatment for PTSD. In TR-PTSD, clinicians have used other SSRI's such as fluoxetine, citalopram, escitalopram and fluvoxamine. Although the effects of the SSRIs on improving PTSD symptoms have been established, patients with TR-PTSD may not respond to the various SSRIs despite appropriate dosage and adequate treatment duration. This low response rate has been attributed to their adverse effects and to the presence of co-occurring depressive disorders, anxiety disorders, substance use, and the comorbidity with medical and neurological conditions such as traumatic brain injury[3,9].Other proposed causes of the development of SSRIs treatment resistance may be related to their lack of effects on other PTSD associated symptoms such as sleep .They seem neither to improve insomnia nor reduce recurrent nightmares and could contribute to existing sleep difficulties, due to their association with acute rapid eye movements (REM) sleep and sleep behavior disorder [11].

Other Antidepressants

Trazodone could be added to SSRIs, for patients who have ongoing sleep disturbances but have achieved some benefits from the SSRIs [12]. Common side effects include sedation, especially excessive morning somnolence, postural dizziness, and the rare risk of priapism in addition of monitoring for the possibility of developing serotonin syndrome when combining trazodone with an SSRI [12].

Nefazodone may benefit sleep, decrease anxiety, and improve depression [13], however it is not readily available since it has been pulled from the USA market in 2004 and carries a black box warning of hepatotoxicity.

Mirtazapine could be also added to an SSRI as an alternative to trazodone for ongoing sleep difficulties. It could contribute to a general reduction of PTSD symptoms especially those that are related to the associated sleep disturbances [14]. In addition, mirtazapine's sedative effects may help lessen the hyperarousal which prevents patients with PTSD from falling asleep, and can also lead to increasing the stages of slow-wave, restorative sleep. The most reported adverse effects are transient somnolence, increased appetite, and weight gain.

Doxepin which belongs to the class of tricyclic antidepressants (TCAs), has been reintroduced as a hypnotic agent and can be used at low doses as an adjunctive agent for sleep difficulties [15]. It is important to address its adverse effects of cardiac conduction, potent anticholinergic and anti-adrenergic adverse effects and its lethality in cases of intentional or accidental overdose.

Although other TCAs such as imipramine, nortriptyline and amitriptyline could be used as adjunctive agents to improve symptoms of depression, anxiety, and sleep difficulties in TR-PTSD. These are rarely prescribed by clinicians due to their multiple adverse effects especially their cardiac, anticholinergic and anti-adrenergic adverse effects and lethality in cases of intentional or accidental overdose.

Bupropion could also be used and would add dopamine and noradrenergic action to the SSRIs serotonergic effects, and although

not evidenced base it may also help reduce SSRI-induced sexual side effects [16]. Due to its potential adverse effects of hyperactivation, decreased appetite and inducing seizures, it should not be recommended for TR- PTSD if agitation, anorexia, and history of seizures are present. Bupropion could also be beneficial in smoking cessation in patients with TR-PTSD and comorbid tobacco use disorder [17].

Mono Amino Oxidase Inhibitors (MAOIs)

The MAOIs such as phenelzine have shown promises in improving depression and anxiety in TR-PTSD, however their interaction with many medications and the need for dietary restriction with tyramine-containing foods and drinks have limited their clinical usefulness [18].

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

The SNRIs are combined serotonin and norepinephrine reuptake inhibitors and include venlafaxine, and duloxetine. Both venlafaxine and duloxetine have been used in the treatment of TR-PTSD [18,19]. The SNRIs evidence-based potential as second line treatment option for core PTSD symptoms still need to be confirmed. Nausea, insomnia, anxiety, restlessness, headache, drowsiness, dry mouth, loss of appetite, and decreased libido could emerge with the SNRIs, and increased blood pressure could occur with venlafaxine thus warranting periodic blood pressure monitoring, especially in patients with hypertension and those at risk of developing hypertension.

Novel Antidepressants

Desvenlafaxine, levomilnacipran, vortioxetine and vilazodone are FDA approved for the treatment of MDD and have been used as adjunctive treatment for patients with co-occurring depression and PTSD. There is paucity of data currently about their utility in improving TR-PTSD.

Antipsychotics

Although the first generation or typical antipsychotic fluphenazine could be used for reducing avoidance, re-experiencing, and hyperarousal symptoms in TR-PTSD, it is seldom used due to its associated extrapyramidal adverse effects and the risk of developing tardive dyskinesia. The second generation(SGAs) or atypical antipsychotics have been used in TR-PTSD especially in severe cases that have not responded to the standard treatment with SSRIs or other antidepressants[13,20] .The SGAs such as risperidone, quetiapine, olanzapine, and aripiprazole could be used as adjunctive agents for the treatment of re- experiencing phenomena or flashbacks, recurrent intrusive thoughts, sounds, and images of traumatic events, and "paranoid" ideas, such as the fear of being attacked when exposed in public places, agitation, anger, hypervigilance, exaggerated startle, chronic sleep difficulties, and persistent depression. The metabolic syndrome, which is manifested by elevated diastolic blood pressure, increased waist circumference, and increased low high-density lipoprotein cholesterol, could develop among PTSD patients treated with the SGAs [3]. This syndrome could also be related to lifestyle factors of improper diet, lack of regular physical activities and/or long-term overactivation of stress response pathways. Based on the currently available literature, it appears that olanzapine and risperidone are the most used SGAs for TR- PTSD [3,21], however more research with larger sample sizes and more double blind randomized controlled trials are needed to substantiate the effectiveness and safety of these agents in individuals with TR-PTSD.

Noradrenergic Agents

Also known as sympatholytic agents, adrenergic modulators, or adrenergic-inhibiting agents could modulate and decrease symptoms of hyperarousal, anxiety, decrease nightmares and improve TR-PTSD. This class of medications includes prazosin, clonidine, and propranolol. Prazosin can be useful in reducing combat trauma related nightmares, and possibly normalizing dreams leading to improved sleep quality and increasing sleep duration [22]. Clonidine reduces nightmares, anxiety, hypervigilance, startle reactions, and outbursts of rage among some severely traumatized TR-PTSD individuals [23]. Propranolol could also decrease. anxiety and hyperarousal [23]. Orthostatic hypotension, dizziness, drowsiness, fatigue, lightheadedness, and syncope are potential adverse effects of the noradrenergic agents.

Anticonvulsants

Kindling, is a phenomenon in which repeated sub-threshold stimulation of the central nervous system (CNS), predispose the neurons to become over sensitive to various stimuli which has been shown to occur in the amygdala and the limbic regions of the CNS, that are linked to fear and stress and seem to be hyperactivated in some patients with PTSD [24]. The anti-kindling effects of the anticonvulsants have been proposed as a possible treatment for TR- PTSD. Among the many available anticonvulsants, carbamazepine, valproic acid (valproate and divalproex), topiramate, lamotrigine, and gabapentin have been used in TR-PTSD. Potentially life-threatening reactions to carbamazepine may include aplastic anemia, toxic hepatitis, pancreatitis and skin reactions, specifically Stevens-Johnson syndrome and toxic epidermal necrolysis. Divalproex can cause acute hepatitis with liver failure, acute pancreatitis, polycystic ovarian syndrome and may cause birth defects during pregnancy. It is very important to drink an adequate amount of fluid daily to avoid the possible side effect of developing of kidney stones with topiramate. Although most patients who develop a rash while receiving lamotrigine have mild to moderate symptoms, some individuals may develop the serious skin reaction of Stevens-Johnson syndrome, which would require immediate emergency hospitalization. Gabapentin could cause depression, hostility, severe dizziness, confusion, or coordination problems in addition to the development of rash, hives, itching, and swelling.

Mood Stabilizers

The benefits of using the mood stabilizers in the treatment of TR-PTSD is based on their effectiveness in stabilizing co-occurring bipolar disorder. These agents have also been used as adjunctive therapy in non-bipolar TR-PTSD patients based on their effects on stabilizing the associated PTSD symptoms of irritability, anger, aggression, impulsivity, and rage [25]. Mood stabilizers include three main categories, some SGAs, the anticonvulsants and lithium. The SGAs have been described in a previous section. Among the anticonvulsants only carbamazepine, valproic acid (valproate and divalproex) and lamotrigine have been approved as mood stabilizers and their beneficial and adverse effects have been summarized in the previous section. In regard to lithium, it may be helpful in stabilizing co-occurring bipolar disorder in TR-PTSD, and in reducing anger and irritability in non-bipolar TR-PTSD patients [26]. Giddiness, blurred vision, tinnitus, severe shakiness, and sei-

zures are some of the serious effects of lithium, it should also be avoided in patients with thyroid or kidney problems and those who are maintained on a low-sodium diet. Adequate hydration is necessary to prevent lithium toxicity.

Anxiolytics

Benzodiazepines

The anxiolytic class of benzodiazepines exert their effects by sedation, inducing sleep, decreasing anxiety, causing muscle relaxation, as well as adjunctive antiepileptics. They are contraindicated as a treatment option for PTSD due to their effects on the worsening of cognitive dysfunctions, decreasing concentration, causing memory difficulties, and precipitating behavioral disinhibition. They could lead to the development of addiction and withdrawal symptoms when abruptly discontinued. They are also lethal in accidental or intentional overdose especially if combined with alcohol, opioids, or other sedative hypnotics. There is currently no evidence to support the use of benzodiazepines due to their lack of efficacy and effectiveness in TR-PTSD [27].

Buspirone

The non-benzodiazepine anxiolytic buspirone could be used as an adjunctive in treating persistent anxiety in TR-PTSD. It has the advantage of a relatively benign side-effect profile and the lack of addictive potential. It could decrease intrusive thoughts and nightmares in some patients [28]. It can also act as an augmenting agent in potentiating antidepressant medications effects in the management of treatment resistant depression. As such it may also benefit patients with co-occurring treatment resistant depression and TR-PTSD [29].

Hypnotics

The Z-drugs

Sleep complaints are common and have a direct impact on PTSD treatment outcomes, many clinicians have been using benzodiazepine and non-benzodiazepine hypnotics like zolpidem, zaleplon, and eszopiclone as agents to help initiate and maintain sleep. This class of hypnotics also sometimes referred to as "the Z drugs" have been associated with residual morning drowsiness, memory lapses, erratic actions, such as sleep-driving, making phone calls, preparing and eating food while asleep. These side effects occur at a higher incidence when these medications are taken above the recommended dose, or when combined with alcohol or other sedative hypnotics. Anaphylactic reactions and facial angioedema could also occur. The use of benzodiazepine [29] or the Z drugs are not recommended for the treatment of sleep difficulties in TR- PTSD [30].

Ramelteon / Melatonin.

Although ramelteon and melatonin are considered a safer alternative to the benzodiazepines and the Z drugs due to their benign side effects profile, their use has not been confirmed as effective agents for the management of sleep difficulties in TR-PTSD. Patients with PTSD and co-occurring sleep disorders need to be evaluated to determine the cause of their sleep disorders. If sleep difficulties persist and is confirmed as a feature of TR- PTSD, then further evaluation of their overall pharmacological treatment would need to be pursued and undertaken to explore non-pharmacological and behavioral management of their sleep patterns [31].

Antihistaminergic Agents

The antihistaminergic agents such as diphenhydramine, hydroxyzine, or cyproheptadine have been temporarily used to induce drowsiness and sleep in nightshift workers, during periods of time zone adjustment and for jet lags. they may have some utilities in managing daytime anxiety and sleep difficulties in TR-PTSD [32]. The side effects of these agents include drowsiness, day time sleepiness, and anticholinergic effects, such as dry mouth, blurred vision, constipation, urinary retention, exacerbation of asthma and breathing difficulties, cognitive impairment, dizziness and additive CNS depressant effects when they are combined with other sedating pharmacological agents [3]. Clinicians prescribing these agents need to be vigilant in monitoring their broad side effects profile which could adversely impact the daily functioning of individuals with TR-PTSD.

Naltrexone

Individuals with comorbid substance use and TR-PTSD especially those who use alcohol and or opioids could benefit from naltrexone in decreasing their craving for these substances and ultimately leading to improvement in TR-PTSD. However, the safety and efficacy of naltrexone in the treatment of TR -PTSD have not been tested in controlled clinical trials [33].

Buprenorphine

Certain patients with TR-PTSD and opioids use disorder who report improvement in their PTSD symptoms when they received buprenorphine as a component of their opiates use disorder treatment have led certain clinicians to consider buprenorphine as an adjunctive agent in TR-PTSD even in the absence of an opioids use disorder [34]. It has been suggested that buprenorphine effects on the CNS opioid receptors would improve dysphoric mood, anxiety and stress responses resulting in improved TR-PTSD. Prospective studies are needed to determine whether these effects are reproducible.

D-Cycloserine

A partial N-Methyl-d-aspartic acid or N-Methyl-d-aspartate (NMDA) agonist has shown to be effective in facilitating the exposure/extinction therapy and to improve the efficacy of treating anxiety disorders, however it has not shown effectiveness as an adjunctive treatment in PTSD or TR-PTSD [35].

Neuropeptides

The neuropeptides such as oxytocin, neuropeptides Y and S may play a relevant role in the pathophysiology of PTSD. Their suboptimal concentrations in various brain regions, particularly in the amygdala, hippocampus, prefrontal cortex, hypothalamus, and brain stem, may play a role in the clinical manifestations of PTSD. Ongoing clinical experiments aimed at validating a role CNS neuropeptide in PTSD pathology are important. These studies will provide the rationale for moving forward with human studies on the effects of neuropeptide treatments in PTSD and TR-PTSD [36].

Memantine

Memantine was shown to improve cognitive symptoms, PTSD symptoms, and mood in veterans with PTSD. Randomized double-blind studies are needed to validate these preliminary observations and their clinical implications in the overall treatment of

PTSD and TR-PTSD [37].

Psychoactive Agents

Multiple alternatives have been evaluated and studied for their uses in treating TR- PTSD in patients who have not responded to various pharmacological agents or who refuse to take pharmaceutical industry "big pharma!" products. Among these are cannabinoids, methylenedioxymethamphetamine and ketamine.

Cannabinoids

There has been a recent surge of interest regarding the use of cannabinoids in the treatment of PTSD.

Cannabinoids have been advertised and promoted by several organizations including some Veterans support groups as safe natural products that may help reduce PTSD symptoms cluster of depression, anxiety hypervigilance, increased arousal, sleep disturbances, and nightmares. Although cannabinoids may decrease sleep disturbances and nightmares in some patients they have not been consistent in improving global clinical outcome in TR-PTSD indicating that future well-controlled, randomized, double-blind clinical trials are highly warranted and urgently needed especially in the context of the legalization of marijuana use in many States of the union despite being illegal according to the penal Federal laws. Decline in neurocognitive functioning and the precipitation of psychosis are potential risks of regular marijuana users regardless of their age and overall health status. Nabilone which is a synthetic cannabinoid that activates the Cannabinoid receptors type 1 (CB1) cell receptors which are abundantly expressed in the CNS .When given to participants in a study, nabilone resulted in a decrease in PTSD related symptoms of recurrent nightmares, flashbacks, and improved sleep time[38].It is not advisable from a clinical perspective to use cannabinoids or any of their synthetic products as recommended treatment of TR-PTSD until the evidence in regard to their clinical effectiveness, and evidence-based guidelines are clearly identified and synthesized .

3,4-Methylendioxymethamphetamine (MDMA)

Clinical trials have shown MDMA to improve mood, well-being, relaxation, and to enhance emotional sensitivity, responsiveness, openness, and feeling of closeness to other, in addition to fear reduction while maintaining a state of alertness. Preliminary results regarding MDMA-assisted psychotherapy for TR-PTSD may be promising however it warrants further well-controlled, randomized, double-blind clinical trials [39], especially in the context of MDMA safety as described in the scientific literature and as perceived by the general public. The adverse effects of MDMA may include nausea, vomiting, jaw clenching, muscle aches, feelings of numbness, headache, dizziness, fatigue, sweating and decreased appetite. Detrimental effects on neurocognition could occur precipitating deficits in cognition and retrospective memory, disturbed sleep, depression, confusion and psychosis.

Ketamine

Ketamine is an N-methyl-d-aspartate receptor antagonist and other psychedelic agents such as psilocybin and Lysergic acid diethylamide (LSD), also known colloquially as acid ,have been used in experimental trials to treat depression, social anxiety disorder, obsessive-compulsive disorder, and PTSD. Ketamine is FDA approved for treatment resistant MDD, but not for TR-PTSD. Its therapeutic effects remain controversial regarding its potential in precipitating anxiety, but the perceived benefit of a rapid reduction of PTSD symptoms makes it worthy for studies in TR-PTSD.[40]. The immediate effects of ketamine in leading to a near complete resolution of MDD symptoms is also speculated to occur in TR-PTSD. Randomized placebo control trials to confirm Ketamine effectiveness in the treatment of PTSD and TR-PTSD especially in the context of its 1–2 weeks transient lasting effects.

Summary

The conventional first line treatment of PTSD include psychotherapy, pharmacotherapy, or their combination. Despite these available treatments, many individuals continue to exhibit ongoing PTSD symptoms and discontinue treatment due to the lack of effectiveness and the slow onset of action of the two FDA approved SSRIs medications, sertraline and paroxetine in addition to the burden of their side effects. Patients who consistently over an extended period of treatment continue to exhibit a lack of clinically observable improvement may be categorized as TR-PTSD .The use of other SSRIs,various other antidepressants, SNRIs, novel antidepressants , antipsychotics ,noradrenergic agents, anticonvulsants, mood stabilizers, anxiolytics, hypnotics, antihistaminergic agents, naltrexone, buprenorphine, D-Cycloserine, neuropeptides, memantine, cannabinoids, 3,4-methylendioxymethamphetamine and ketamine despite their proposed benefits for the treatment of TR-PTSD they continue to show inconsistency in replicating their benefits. Well-designed randomized double-blind, placebo-controlled research clinical trials are needed to confirm these alternatives as evidence-based PTSD treatment modality. Until then, clinicians are behooved to exert prudence and wise clinical judgement prior to recommending any of these agents as proven treatment modalities for TR-PTSD.

Acknowledgments

Sincere appreciation to Drs, Tanya Aaen, David Gellerman, Scott Summers and Mr., David W. Ferguson for their support and thankfulness to my wife Lynn and children, Andrew, Adam, Andrea and her husband Nic and daughter Abigail, my sisters Hoda and Héla, and my brother Hadi for their encouragement.

Conflicts of Interests

No conflicts of interests. The materials described in this article are those of the authors and do not reflect the views of the Department of Veterans Affairs or the VA Northern California Health Care System or UC Davis Health, Sacramento, California.

References

1. American Psychiatric Association. (2013) Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Association.
2. Sciarrino NA, Warnecke AJ, Teng EJ: (2020) A systematic review of intensive empirically supported treatments for post-traumatic stress disorder. Journal of Traumatic Stress 33: 443-454.
3. Khouzam HR (2013) Pharmacotherapy for Posttraumatic Stress Disorder. Journal of Clinical Outcomes Management 20: 21-33.
4. Difede J, Olden M, Cukor J. (2014) Evidence-based treatment of post-traumatic stress disorder. Annu Rev Med.65: 319-332.

5. Office of Quality and Performance and the Veterans Affairs and Department of Defense Development Work Group. Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version 3.0. Washington, DC: Veterans Health Administration and Department of Defense; 2017.
6. Sutherland ME (2019) Identifying treatment-resistant PTSD. Nat Hum Behav 3 :549.
7. Fonzo GA, Federchenco V, Lara A. (2020) Predicting and Managing Treatment Non-Response in Posttraumatic Stress Disorder. Curr Treat Options Psychiatry. 7: 70-87.
8. Mittal D, Drummond KL, Blevins D, Curran G, Corrigan P, et al. (2013) Stigma associated with PTSD: perceptions of treatment seeking combat veterans. Psychiatr Rehabil J 36: 86-92.
9. Asnis GM, Kohn SR, Henderson M, Brown NL (2004) SSRIs versus non-SSRIs in post-traumatic stress disorder: an update with recommendations. Drugs. 64: 383-404.
10. Sonne C, Carlsson J, Bech P, Elklit A, Mortensen EL (2016) Treatment of trauma-affected refugees with venlafaxine versus sertraline combined with psychotherapy - a randomised study. BMC Psychiatry.16: 383.
11. Brownlow JA, Harb GC, Ross RJ (2015) Treatment of Sleep Disturbances in Post-Traumatic Stress Disorder: A Review of the Literature. Curr Psychiatry Rep. 17: 41.
12. Khouzam HR. (2017) A review of trazodone use in psychiatric and medical conditions. Postgrad Med. 129:140-148.
13. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, et al. (2010) Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 6: 389-401.
14. Schneier FR, Campeas R, Carcamo J, Glass A, Lewis-Fernandez R, et al. (2015) Combined mirtazapine and SSRI treatment of PTSD: a placebo-controlled trial. Depress Anxiety. 32: 570-579.
15. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. (2017) Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 13: 307-349.
16. Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, et al. (2016) Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. Depress Anxiety. 33: 792-806.
17. Hertzberg JS, Carpenter VL, Kirby AC, Calhoun PS, Moore SD, et al. (2013) Mobile contingency management as an adjunctive smoking cessation treatment for smokers with posttraumatic stress disorder. Nicotine Tob Res. 15: 1934-1938.
18. Aurora RN, Zak RS, Auerbach SH, Casey KR, Chowdhuri S, et al. (2010) Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 6: 389-401.
19. Walderhaug E, Kasserman S, Aikins D, Vojvoda D, Nishimura C, et al. (2010) Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. Pharmacopsychiatry. 43: 45-49.
20. Compean E, Hamner M. (2019) Posttraumatic stress disorder with secondary psychotic features (PTSD-SP): Diagnostic and treatment challenges. Prog Neuropsychopharmacol Biol Psychiatry. 88: 265-275.
21. Pae CU, Lim HK, Peindl K, Ajwani N, Serretti A, et al. (2008) The atypical antipsychotics olanzapine and risperidone in the treatment of posttraumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Int Clin Psychopharmacol. 23: 1-8.
22. Green B (2014) Prazosin in the treatment of PTSD. J Psychiatr Pract. 20: 253-259.
23. Davidson JR (2006) Pharmacologic treatment of acute and chronic stress following trauma: 2006. J Clin Psychiatry. 67: 34-39.
24. Berlin HA (2007) Antiepileptic drugs for the treatment of post-traumatic stress disorder. Curr Psychiatry Rep. 9: 291-300.
25. Ehret M (2019) Treatment of posttraumatic stress disorder: Focus on pharmacotherapy. Ment Health Clin. 9: 373-382.
26. Forster PL, Schoenfeld FB, Marmar CR, Lang AJ (1995) Lithium for irritability in post-traumatic stress disorder. J Trauma Stress. 8: 143-149.
27. Guina J, Rossetter SR, DeRHODES BJ, Nahhas RW, Welton RS (2015) Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. J Psychiatr Pract. 21: 281-303.
28. Duffy JD, Malloy PF (1994) Efficacy of buspirone in the treatment of posttraumatic stress disorder: an open trial. Ann Clin Psychiatry. 6: 33-37.
29. Hamner M, Ulmer H, Horne D. (1997) Buspirone potentiation of antidepressants in the treatment of PTSD. Depress Anxiety. 5:137-139.
30. El-Solh AA, Riaz U, Roberts J (2018) Sleep Disorders in Patients with Posttraumatic Stress Disorder. Chest.154:427-439.
31. Micic G, Lovato N, Gradisar M, Burgess HJ, Ferguson SA, Kennaway DJ, Lack L. Nocturnal Melatonin Profiles in Patients with Delayed Sleep-Wake Phase Disorder and Control Sleepers. J Biol Rhythms. 2015;30(5):437-448.
32. Ahmadpanah M, Sabzeiee P, Hosseini SM, Torabian S, Haghighi M, et al. (2014) Comparing the effect of prazosin and hydroxyzine on sleep quality in patients suffering from posttraumatic stress disorder. Neuropsychobiology. 69: 235-242.
33. Sofuoglu M, Rosenheck R, Petrakis I (2014) Pharmacological treatment of comorbid PTSD and substance use disorder: recent progress. Addict Behav. 39: 428-433.
34. Lake EP, Mitchell BG, Shorter DI, Kosten T, Domingo CB, et al. (2019) Buprenorphine for the treatment of posttraumatic stress disorder. Am J Addict. 28: 86-91.
35. McGuire JF, Wu MS, Piacentini J, McCracken JT, Storch EA. (2017) A Meta-Analysis of D-Cycloserine in Exposure-Based Treatment: Moderators of Treatment Efficacy, Response, and Diagnostic Remission. J Clin Psychiatry. 78: 196-206.
36. Schmeltzer SN, Herman JP, Sah R (2016) Neuropeptide Y (NPY) and posttraumatic stress disorder (PTSD): A translational update. Exp Neurol. 284:196-210.
37. Battista MA, Hierholzer R, Khouzam HR, Barlow A, O'Toole S. (2007) Pilot trial of memantine in the treatment of posttraumatic stress disorder. Psychiatry. 70: 167-174.
38. Cowling T, MacDougall D. Nabilone for the Treatment of Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Feb 20.

PMID: 31553551.

39. Morgan L (2020) MDMA-assisted psychotherapy for people diagnosed with treatment-resistant PTSD: what it is and what it isn't. Ann Gen Psychiatry. 19:33.

40. Liriano F, Hatten C, Schwartz TL (2019) Ketamine as treatment for post-traumatic stress disorder: a review. Drugs Context. 8: 212305.

Copyright: *©2021 Hani Raoul Khouzam. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.*