

TARGETED DRUG DELIVERY SYSTEM IN THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER (PTSD): A REVIEW

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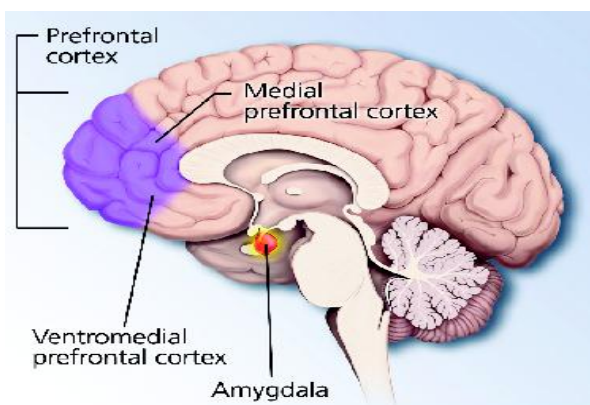
ABSTRACT

Posttraumatic stress disorder (PSTD), classified as an anxiety disorder, has become increasingly important because of wars overseas, natural disasters and domestic violence. After trauma exposes the victim to actual or threatened death or serious injury, 3 dimensions of PTSD unfold: (1) reexperiencing the event with distressing recollections, dreams, flashbacks and/or psychologic and physical distress; (2) persistent avoidance of stimuli that might invite memories or experiences of the trauma; and (3) increased arousal. Traumatic events sufficient to produce PTSD in susceptible subjects may reach a lifetime prevalence of 50% to 90%. The actual lifetime prevalence of PTSD among US citizens is approximately 8%, with the clinical course driven by pathophysiologic changes in the amygdala and hippocampus. Comorbid depression and other anxiety disorders are common. General principles of treatment include the immediate management of PTSD symptoms and signs; management of any trauma-related comorbid conditions; nonpharmacologic interventions including cognitive behavioral treatment; and psychopharmacologic agents including antidepressants (selective serotonin reuptake inhibitors most commonly), anti-anxiety medications, mood stabilizing drugs, and antipsychotics. This review of PTSD will provide the reader with a clearer understanding of this condition, an increased capacity to recognize and treat this syndrome and a greater appreciation for the role of the internist in PTSD.

KEYWORDS: Anxiety disorder: Depression: Military veterans: Posttraumatic stress disorder (PTSD): Primary care: Rape victims.

1. INTRODUCTION

Post-traumatic Stress Disorder (PTSD) is a persistent and sometimes crippling condition precipitated by psychologically overwhelming experience. It develops in a significant proportion of individuals exposed to trauma and untreated, can continue for years. Its symptoms can affect every life domain – physiological, psychological, occupational and social.



Brain Structures Involved in Dealing with Fear and Stress

Figure 1: National Institute of Mental Health: Brain Structure Involved With PTSD

Post-trauma stress reactions have been recognized throughout history. They are described in classical Greek literature and in the early literature of scientific medicine, but it was first diagnostically defined in modern times in the 1980 American Psychiatric Association Diagnostic and Statistical Manual. The surge of scientific and clinical interest in the condition over the past two decades has been largely due to awareness of problems associated with returning Vietnam combat veterans and advocacy by the feminist movement on behalf of rape victims. PTSD has not been documented in other groups including abused children, victims of crimes, accidents and natural disasters.

Not all trauma survivors develop PTSD. About 20% of crime victims, across type of crime, will meet diagnostic criteria. The rates are substantially higher for some crimes. For example, more than half of rape victims are afflicted. However, most crime victims do have some initial PTSD symptoms that subside over time.

2. History of PTSD

Cases of PTSD were first documented during the First World War when soldiers developed shell shock as a result of the harrowing conditions in the trenches. But

the condition wasn't officially recognised as a mental health condition until 1980, when it was included in the Diagnostic and Statistical Manual of Mental Disorders, developed by the American Psychiatric Association.

3. What can cause PTSD?

Types of traumatic events that can cause PTSD include:

- Combat and other military experiences.
- Sexual or physical assault.
- Learning about the violent or accidental death or injury of a loved one.
- Child sexual or physical abuse.
- Serious accidents, like a car wreck.
- Natural disasters, like a fire, tornado, hurricane, flood, or earthquake.
- Terrorist attacks.

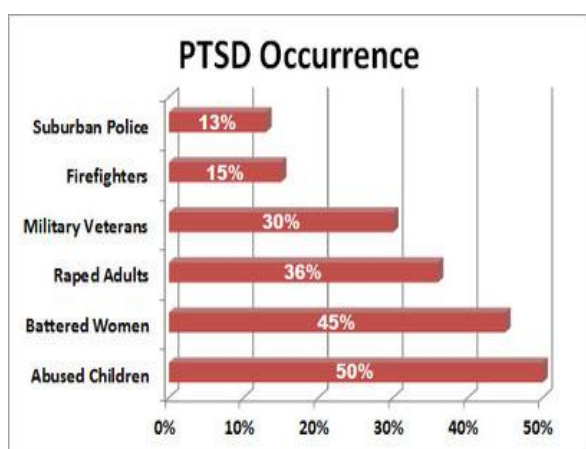


Figure 2:

4. Symptoms

Post-traumatic stress disorder symptoms may start within three months of a traumatic event but sometimes symptoms may not appear until years after the event. These symptoms cause significant problems in social or work situations and in relationships.

Post-traumatic stress disorder (PTSD) symptoms are generally grouped into four types

- Intrusive memories
- Avoidance
- Negative changes in thinking and mood
- Changes in emotional reaction

4.1. Intrusive memories

Symptoms of Intrusive memories may include:

- Recurrent, unwanted distressing memories of the traumatic event.
- Reliving the traumatic event as if it were happening again (flashbacks).
- Upsetting dreams about the traumatic event.

- Severe emotional distress or physical reactions to something that reminds you of the event.

4.2. Avoidance

Symptoms of Avoidance may include:

- Trying to avoid thinking or talking about the traumatic event
- Avoiding places, activities or people that remind you of the traumatic event.

4.3. Negative changes in thinking and mood

Symptoms of Negative changes in thinking and mood may include:

- Negative feelings about yourself or other people.
- Inability to experience positive emotions.
- Feeling emotionally numb.
- Lack of interest in activities you once enjoyed.
- Hopelessness about the future.
- Memory problems including not remembering important aspects of the traumatic event.
- Difficulty maintaining close relationships.

4.4. Changes in emotional reaction

Symptoms of Changes in emotional reaction (also called arousal symptoms) may include:

- Irritability, angry outbursts or aggressive behaviour.
- Always being on guard for danger.
- Overwhelming guilt or shame.
- Self destructive behaviour such as drinking too much or driving too fast.
- Trouble concentrating.
- Trouble sleeping.
- Being easily startled or frightened.

5. Risk Factors for Development of PTSD

There is a large body of literature on the risk factors for PTSD and several published reviews of risk factors for PTSD. Two key meta-analyses of PTSD risk factors have been conducted by Brewin *et al.*^[20] and Ozer *et al.*^[21] Figure 3 shows a summary of the empirically validated risk factors for PTSD that have been demonstrated across various samples.

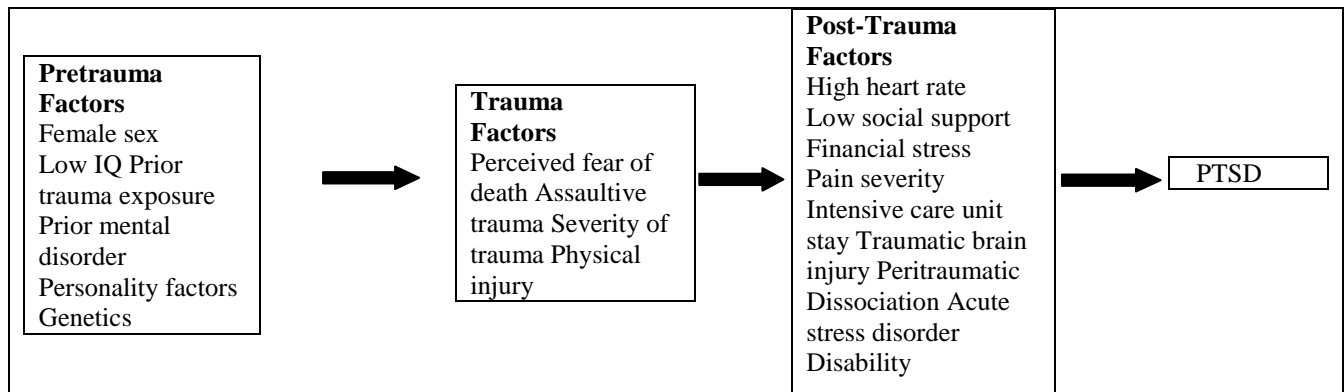


Figure 3: Empirically-derived risk factors for development of posttraumatic stress disorder (PTSD)

Several pretrauma risk factors for PTSD have been identified in different populations. Females are at higher risk for PTSD than males. For most traumatic events, women showed greater risk for developing PTSD than men. Age, race, socioeconomic and marital status have not been strongly associated with risk for PTSD. Cognitive vulnerabilities (for example, low IQ or previous history of head injury) are associated with increased vulnerability for PTSD. Exposure to life stressors (for example, childhood maltreatment or other adult life stressors) prior to the index trauma (trauma considered by the person as the inciting stressful event) has been associated with an increased risk for PTSD. A pretrauma history of mental disorders, especially mood and anxiety disorders and conduct disorder, is associated with PTSD.^[22-24] Personality factors, such as neuroticism^[25] and avoidance coping^[26-27], have been shown to be associated with increased risk for PTSD, while extraversion has been shown to be protective. There has been an expanding body of literature on the genetic risk factors associated with the development of PTSD. Many genetic markers are currently under investigation, including the serotonin transporter gene^[28], as well as genes associated with the hypothalamic pituitary adrenal axis.^[29] Regarding trauma-related risk factors, many studies have examined the type and severity of trauma as a risk factor for development of PTSD.^[30] Most studies have not found a relation between severity of injury^[30-35] and risk for development of PTSD. Intentional or assaultive injury has shown to be a risk factor for onset of PTSD.^[30] There has also been some evidence suggesting that TBI, especially mild TBI, is specifically linked to PTSD.^[31-33] There has been some work suggesting that self-perceived fear of death during the traumatic event has been associated with PTSD.^[34] Peritraumatic dissociation has also been shown to be a consistent risk factor for PTSD.^[35] Numerous posttrauma risk factors for PTSD have been identified. Multiple studies have shown that a high heart rate (>95 bpm) at first presentation to an emergency department is a risk factor for PTSD among people with physical injury.^[36] Acute high levels of pain have been linked to PTSD among patients with severe physical injury.^[37] There is a substantial body of evidence that PTSD and pain are often comorbid through mutual maintenance. Asmundson et al^[38] suggest that pain is a reminder of the

traumatic event that triggers flashbacks. PTSD symptoms, such as insomnia, reduce the threshold for pain.^[39] Further, although length of hospitalization has not been shown to be a strong predictor of mental health problems^[40], admission to an intensive care unit^[40] has been indicated in one study to be a risk factor for PTSD. The level of physical disability and lack of ability to return to work have been shown to be associated with increased risk for PTSD.^[41-45] Social supports during the posttrauma period have been shown to be a protective factor in PTSD.^[44] Financial stress and legal involvement owing to trauma have been shown to be important in risk for PTSD.

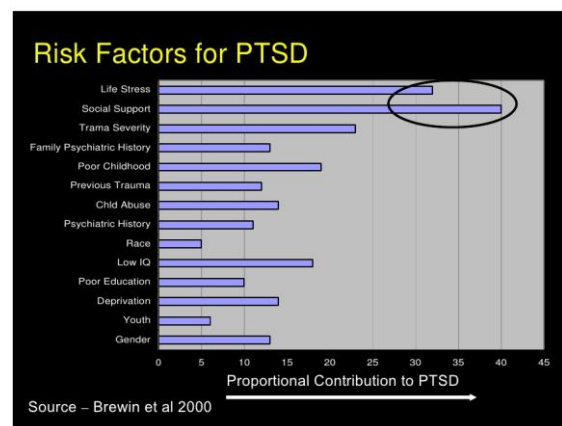


Figure 4:

6. DIAGNOSTIC CRITERIA

The DSM-III diagnostic criteria for PTSD were revised in DSM-III-R (1987), DSM-IV (1994) and DSM-IV-TR (2000). A very similar syndrome is classified in ICD-10 (The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines). One important finding, which was not apparent when PTSD was first proposed as a diagnosis in 1980, is that it is relatively common. Recent data from the National Comorbidity Survey Replication indicates lifetime PTSD prevalence rates are 3.6% and 9.7% respectively among American men and women. Rates of PTSD are much higher in post-conflict settings such as

Algeria (37%), Cambodia (28%), Ethiopia (16%) and Gaza (18%).

DSM-IV Diagnostic criteria for PTSD included a history of exposure to a traumatic event and symptoms from each of three symptom clusters: intrusive recollections, avoidant/numbing symptoms and hyper-arousal symptoms. A fifth criterion concerned duration of symptoms; and a sixth criterion stipulated that PTSD symptoms must cause significant distress or functional impairment.

The latest revision, the DSM-5 (2013), has made a number of notable evidence-based revisions to PTSD diagnostic criteria, with both important conceptual and

clinical implications. First, because it has become apparent that PTSD is not just a fear-based anxiety disorder (as explicated in both DSM-III and DSM-IV), PTSD in DSM-5 has expanded to include anhedonic/dysphoric presentations, which are most prominent. Such presentations are marked by negative cognitions and mood states as well as disruptive (e.g. angry, impulsive, reckless and self-destructive) behavioural symptoms. Furthermore, as a result of research-based changes to the diagnosis, PTSD is no longer categorized as an Anxiety Disorder. PTSD is now classified in a new category, Trauma- and Stressor-Related Disorders, in which the onset of every disorder has been preceded by exposure to a traumatic or otherwise adverse environmental event.

6.1. DSM-5 Criteria for PTSD diagnosis

DSM-5 Criteria	Operationalization
Criterion A Exposure to traumatic event threatening death or serious injury of self or others.	Direct exposure; witnessing event, learning that event occurred to close other, experiencing repeated exposure to details of event.
Criterion B Intrusion	Intrusive recollections Repetitive play with event – related themes Distressing dreams Frightening dreams without recognizable content Flashbacks / recurring of the event Trauma – specific re-enactment in play Internal / external cues triggering Psychological distress
Criterion C Avoidance	Effortful avoidance of memories, thoughts, feelings, about event Effortful avoidance of external reminders about event
Criterion D Negative alterations in cognition and mood	Inability to remember aspect of event Persistent negative beliefs about self, other, the world Persistent distorted cognition about cause / consequence of event; blame of self or others Persistent negative emotional state Diminished interest in activities Feelings of detachment Persistent inability to experience positive emotions
Criterion E Alterations in arousal and reactivity	Irritability or outbursts of anger Reckless/ self-destructive behaviour Hypervigilance Exaggerated startle response Concentration difficulty Difficulty falling or staying sleep
Criterion F Duration of disturbance	Symptoms persist more than one month
Criterion G Functional impairment	Significant distress or impairment in social, occupational, or other important areas of functioning
Criterion H Exclusion	Disturbance not attributable to physiological effects of substance or medical condition

6.2. Assessing PTSD

Since 1980, there has been a great deal of attention devoted to the development of instruments for assessing PTSD. Keane and associates, working with Vietnam war-zone Veterans, first developed both psychometric and psychophysiological assessment techniques that have proven to be both valid and reliable. Other investigators have modified such assessment instruments and used them with natural disaster survivors, rape/incest survivors and other traumatized individuals. These assessment techniques have been used in the

epidemiological studies mentioned above and in other research protocols.

6.3. Neurobiology

Neurobiological research indicates that PTSD may be associated with stable neurobiological alterations in both the central and autonomic nervous systems. Psychophysiological alterations associated with PTSD include hyperarousal of the sympathetic nervous system, increased sensitivity and augmentation of the acoustic-startle eye blink reflex and sleep abnormalities.

Neuropharmacological and neuroendocrine abnormalities have been detected in most brain mechanisms that have evolved for coping, adaptation and preservation of the species. These include the noradrenergic, hypothalamic-pituitary-adrenocortical, serotonergic, glutamatergic, thyroid, endogenous opioid and other systems. Structural brain imaging suggests reduced volume of the hippocampus and anterior cingulate. Functional brain imaging suggests excessive amygdala activity and reduced activation of the prefrontal cortex and hippocampus.

6.4. Longitudinal expression

Longitudinal research has shown that PTSD can become a chronic psychiatric disorder and can persist for decades and sometimes for a lifetime. Patients with chronic PTSD often exhibit a longitudinal course marked by remissions and relapses. There is also a delayed variant of PTSD in which individuals exposed to a traumatic event do not exhibit the full PTSD syndrome until months or years afterward. DSM-IV's "delayed onset" has been changed to "delayed expression" in DSM-5 to clarify that although full diagnostic criteria may not be met until at least 6 months after the trauma, the onset and expression of some symptoms may be immediate. Usually, the prompting precipitant is a situation that resembles the original trauma in a significant way (for example, a war Veteran whose child is deployed to a war zone or a rape survivor who is sexually harassed or assaulted years later).

6.5. Co-occurring conditions

If an individual meets diagnostic criteria for PTSD, it is likely that he or she will meet DSM-5 criteria for one or more additional diagnoses. Most often, these comorbid diagnoses include major affective disorders, dysthymia, alcohol or substance abuse disorders, anxiety disorders, or personality disorders. There is a legitimate question whether the high rate of diagnostic comorbidity seen with PTSD is an artifact of our current decision-making rules for the PTSD diagnosis since there are not exclusionary criteria in DSM-5. In any case, high rates of comorbidity complicate treatment decisions concerning patients with PTSD since the clinician must decide whether to treat the comorbid disorders concurrently or sequentially.

6.6. Biologic Characteristics

There is increasing evidence that PTSD is associated with biological alterations or abnormalities. Individuals with PTSD have an atypical stress response. Instead of producing increases in cortisol, a stress related hormone, the usual hypothalamic-pituitary axis mechanisms are disrupted and result in lower than expected levels of the hormone. It is possible to induce PTSD symptoms in diagnosed individuals with injection of relatively benign chemical stimuli. Decreased brain volume or volume of specific brain structures have been documented in some adults and children with PTSD. The biologic correlates

have not yet been fully explored, nor are the implications for intervention established.

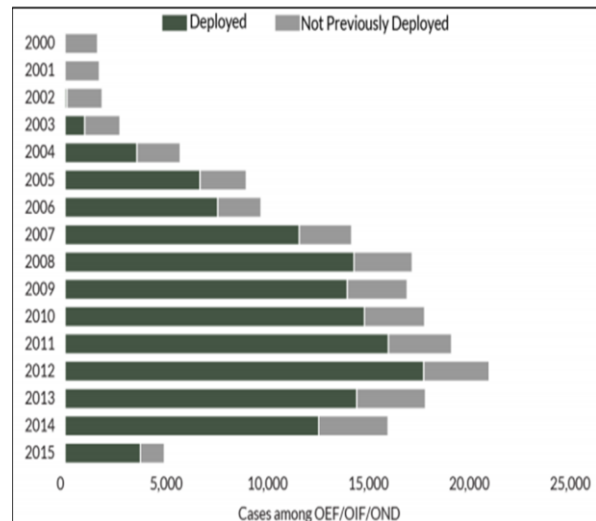


Figure 5: Annual post – traumatic stress disorder diagnoses in all services 2000-2015

7. TREATMENT FOR PTSD

The goal of PTSD treatment is to reduce the emotional and physical symptoms, to improve daily functioning and to help the person better cope with the event that triggered the disorder. Treatment for PTSD may involve psychotherapy (a type of counselling), medication or both.

7.1. PSYCHOTHERAPY

This involves meeting one on one with a licensed Psychologist, Social Worker or Mental Health Counsellor. Typically these meetings are once a week for an hour and focus on talking about the events, your reactions to them and means of mitigating the effects on your life. The types of modalities therapists use may include:

7.1.1. Cognitive Behavioral Therapy (CBT)

This treatment approach looks at ways in which a person thinks about a problem, their learned responses to certain triggers associated with that problem and ways in which their thinking affects their emotional state. This treatment often uses a combination of exposure (deliberately thinking about an event or confronting a trigger) and relaxation training along with cognitive restructuring or changing one's thoughts or beliefs about an event or trigger. This process tends to "desensitize" a person's response to reminders of the event so that it no longer carries the same emotional impact. CBT has been well researched and has been shown to be an effective treatment for PTSD.

7.1.2. Prolonged Exposure (PE)

Prolonged Exposure is a standard technique that has been used with various anxiety disorders and has now been adapted for PTSD in rape victims (Foa & Rothbaum, 1998). PE involves repeated imaginal re-living of the

traumatic experience. Then it is followed up with subsequent real life exposure to situations that are unpleasant reminders of the cause of the fear. The theory posits that repeated pairing of the emotional memories, with a non dangerous environment will lead to reconditioning of the emotionally aversive associations to trauma memories. Gradually being reminder or remembering the trauma will lose the intense negative quality. Breathing retraining to assist with relaxation is an initial component of the approach. Foa and Rothbaum (1998) offer a detailed treatment rationale and manual that specifies the techniques on a session by session basis. The treatment ordinarily is carried out over ninety minute sessions that may occur twice a week. PE has been proven effective with female victims of rape, with at least 90 days of sobriety if there has been a substance abuse issue. High-risk concerns such as psychosis, homicidal or suicidal tendencies should be addressed. Neither depression nor its management with antidepressants, nor co-morbid personality disorder precludes effective treatment. (Foa, E.B. & Rothbaum, B.O. (1998).

7.1.3. Cognitive Processing Therapy (CPT)

Cognitive Processing Therapy is an approach that focuses primarily on trauma-related attributions and cognition that are maladaptive. There is exposure to the trauma, but it occurs in a modulated fashion and is accomplished through having victims write descriptions of the trauma that are repeatedly reviewed and read. The description is analyzed to identify blocks and dysfunctional cognitions and cognitive therapy techniques are used to challenge and replace these distortions with more appropriate, accurate and adaptive views. Themes of safety, trust, power, esteem and intimacy are specifically addressed. Coping skills are taught to assist victims in predicting and managing stress responses. CPT has been proven effective with female rape victims. Resick and Schnicke (1995) provide the theory underlying the approach and a detailed description of the various techniques. The treatment occurs over 12 sessions. (Resick, P. A. & Schnicke, M.K. (1993).

7.1.4. Stress inoculation training (SIT)

SIT is a CBT approach that has a primary focus on teaching the identification and management of anxiety reactions to stressful situations. Michenbaum (1985) first developed this intervention for use with a wide variety of populations suffering from anxious response including trauma. he has since published a manual (Michenbaum, 1994) that is specifically devoted to PTSD. SIT involved explaining the physical, cognitive and behavioral components of fear and anxiety reactions. Then victims are taught various coping strategies to address dysfunctional thoughts and unpleasant feelings that come up with exposure to certain trauma reminders. These include relaxation, shifting attention and self-coaching dialogues. The goal is that victims learn to manage trauma related anxiety with confidence and efficacy.

SIT has been found effective with various stress-related conditions and for female rape victims. Typically this approach consists of 8-14 sessions. (Meichenbaum, D. (1985) and 1994).

7.1.5. Eye Movement Desensitization and Reprocessing (EMDR)

Shapiro (1995) developed the Eye Movement Desensitization and Reprocessing (EMDR) approach. Like SIT, this approach has been advocated as a treatment for a variety of psychological problems involving intense emotions and intrusive thoughts. It is generally considered a form of imaginal exposure accompanied by cognitive re-framing, which are standard elements of CBT. Victims are encouraged to imagine a stressful scene and replace dysfunctional cognitions with more adaptive ones while engaging in lateral eye movements. Therapists move fingers back and forth to facilitate this process. The unique aspect of the treatment is the eye movement component. The currently available research has established.

EMDR is as effective as CBT treatments. However, the eye movements have not been found to be necessary and they do not explain symptom reduction. Initially, it was claimed that EMDR could cure PTSD in one or two sessions. The developer of the method now takes the position that up to 12 sessions may be necessary in some cases to achieve full effects. (Shapiro, F. (1995).

7.2. MEDICATION

People are often very leery of about medication feeling it signifies that they are “crazy” or out of control. This is, of course, not the case and many people take medication for varying lengths of time following particularly stressful life events. Traumatic events can influence the neurochemistry of the body and brain impacting a person in many ways. Excessive stress hormones can make it difficult to concentrate, relax or even sleep. They can increase blood pressure, muscle tension, skin conductance and general arousal levels. It can impair immune system functioning, making people more vulnerable to illness. Fairly often these changes can lead to depression or anxiety. Medication can be effective in resetting the levels in the brain and may prove to be very helpful for a period of time. Some types of medication may include:

7.2.1. Anxiolytic (Anti-anxiety) Medication

Include medications such as Xanax or Ativan. These tend to be short lasting medications that help to reduce physiological and emotional arousal and irritability associated with PTSD.

7.2.2. Antidepressants

These are medications such as Prozac, Paxil or Zoloft. Research has shown these medications to be effective in helping to reduce overall PTSD symptoms including irritability, depressed or anxious moods, anger, impulsivity and obsessive thoughts.

7.2.3. Adrenergic agents

This class of medication includes Propranolol and Clonidine. These act on the adrenal system and help to

lower overall arousal levels, control intrusive images, memories and nightmares.

8. Current Recommended Drugs And Dosage Form to Treat Post-traumatic stress disorder (PTSD)

Symptoms	Drug	Class	Brand Name	Administration route	Dosage form
PTSD, panic disorder, social anxiety and obsessive compulsive disorder.	Sertraline	Selective serotonin reuptake inhibitor	Zoloft	Oral	Tablet, Oral solution
PTSD, panic disorder, social anxiety and obsessive compulsive disorder.	Paroxetine	Selective serotonin reuptake inhibitor	Paxil, Pexeva	Oral	Tablet, capsule, suspension
Major depressive disorder, bulimia nervosa, panic disorder and obsessive compulsive disorder.	Fluoxetine	Selective serotonin reuptake inhibitor	Prozac	Oral	Tablet, capsule, oral solution
Antidepressant and anxiolytic.	Phenelzine	Monoamine oxidase inhibitor	Nardil	Oral	Tablet
Major depressive disorder and anxiety disorder.	Amitriptyline	Tricyclic anti depressant	Elavil	Oral	Tablet
Major depression and enuresis (bedwetting)	Imipramine	Tricyclic anti depressant	Tofranil	Oral	Tablet, capsule
anxiety disorder and trouble sleeping	Lorazepam	Benzodiazepine	Ativan	Oral, intramuscular, intravenous	Tablet, injection, oral solution
Anxiety disorder and seizures	Diazepam	Benzodiazepine	Valium	Oral, intramuscular, intravenous, suppository	Tablet, injection, oral solution, rectal gel.
Hypertension and angina	Propranolol	Benzodiazepine	Inderal	Oral, intravenous.	Tablet, capsule, injection, oral solution
Neuropathic pain and epilepsy	Carbamazepine	Anticonvulsant	Tegretol	Oral	Tablet, capsule, suspension
Bipolar disorder and epilepsy	Lamotrigine	Anticonvulsant	Lamictal	Oral	Tablet
Bipolar mania, schizophrenia and irritability associate with autistic disorder.	Risperidone	Atypical antipsychotic	Risperidal	Oral, intramuscular	Tablet, injection, oral solution
Bipolar disorder, schizophrenia and resistant depression.	Olanzapine	Atypical antipsychotic	Zyprexa	Oral, intramuscular	Tablet, injection, suspension
Hypertension, anxiety and ptsd	Prazosin	Alpha-1 receptor antagonist	Minipress	Oral	Capsule
Anxiety	Clonidine	Alpha-2 adrenergic antagonist	Catapres	Oral, intravenous, topical, transdermal	Tablet, injection, patches.

9. CONCLUSION

PTSD is common and severe problems in veterans and military service members and merit intervention. Fortunately, a number of psychological treatments and medications have been demonstrated as effective for each problem and should be incorporated into clinical practice whether the conditions occur independently or together. There is increasing evidence that PTSD is associated with suicidal behaviour and comorbidity with mental and physical health conditions. Finally, a large body of literature has distinguished the pretrauma, trauma and posttrauma risk factors for PTSD.

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