Posttraumatic stress disorder in adults: Treatment overview

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a severe, often chronic, and disabling disorder, which develops in some persons following exposure to a traumatic event involving actual or threatened injury to themselves or others. PTSD is characterized by intrusive thoughts, nightmares, and flashbacks of past traumatic events, avoidance of reminders of trauma, hypervigilance, and sleep disturbance, all of which lead to considerable social, occupational, and interpersonal dysfunction.

Effective treatments for PTSD include psychotherapies and medications. However, some patients are unwilling to pursue treatment, and a substantial proportion of patients who do seek treatment have symptoms resistant to treatment. It is often necessary to switch or combine treatments to achieve a satisfactory therapeutic response.

This topic describes our approach to selecting treatment for PTSD in adults. This is also summarized in an algorithm (algorithm 1). The epidemiology, pathophysiology, clinical manifestations, assessment, diagnosis, psychotherapy, and pharmacotherapy for PTSD in adults are reviewed separately. Acute stress disorder and prevention of the development of PTSD, dissociative aspects of PTSD, and PTSD in children and adolescents are also reviewed separately.

- (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)

- (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions".)
- (See "Acute stress disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Dissociative aspects of posttraumatic stress disorder: Epidemiology, clinical manifestations, assessment, and diagnosis".)
- (See "Acute stress disorder in adults: Treatment overview".)
- (See "Posttraumatic stress disorder in children and adolescents: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Posttraumatic stress disorder in children and adolescents: Treatment overview".)

INITIATING TREATMENT

We prefer to begin treatment for posttraumatic stress disorder (PTSD) as soon as possible after the diagnosis is made. Early treatment of PTSD may prevent chronicity; however, more empirical data to support this are needed particularly for pharmacotherapeutic treatment [1]. Additionally, supportive interventions such as psychoeducation and case management appear to be helpful in acutely traumatized individuals [1]. While the diagnosis of PTSD is made after persistence of symptoms for at least four weeks following the trauma, most individuals present for treatment many months, or years, later.

Establishing treatment goals — We work with the patient and with permission, involve their chosen support (eg, family member, partner) to establish treatment goals. We review the goals of treatment at each visit through direct questioning during symptom review. (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis", section on 'Cardinal features' and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis", section on 'Assessment'.)

Specific treatment goals may vary between patients; however, for all individuals our goals include:

- Maintain the safety of the patient and others – We do this through assessments of suicidality and homicidality at regularly scheduled visits. (See "Suicidal ideation and behavior in adults".)

- Reduce symptoms of distress related to intrusive re-experiencing – Unwanted intrusive memories of the traumatic event vary widely from occasional unwanted thoughts to

frequent nightmares or flashbacks.

- Reduce hyperarousal – These can include symptoms such as insomnia, anger, irritability, and trouble concentrating and can be very distressing.
- Reduce avoidant behaviors – Avoidance of stimuli associated with the traumatic event may lead to behavior changes that affect psychosocial functioning.
- Lessen the risk of relapse of symptoms and diminish anxiety related to fear of recurrence.
- Address related comorbidities that may be present, for example, substance use disorder (SUD) or mood dysregulation.
- Improve adaptive and psychosocial functioning through psychotherapy often combined with pharmacologic management.

Trauma-focused psychotherapy as preferred treatment — For most adults diagnosed with PTSD, we suggest first-line treatment with a trauma-focused psychotherapy that includes exposure rather than other types of therapy, or medication (eg, selective serotonin reuptake inhibitor [SSRI] or serotonin-norepinephrine reuptake inhibitor [SNRI]).

However, in individuals with comorbid disorders (eg, depression, psychosis) that affect the person's ability to work in trauma-focused therapy (eg, concentration, motivation), we treat with pharmacologic management until the individual's symptoms are stable, then add psychotherapy. (See 'Serotonin reuptake inhibitors as alternative first-line or adjunctive treatment' below.)

Clinical trials and meta-analysis have found trauma-focused therapies including trauma-focused cognitive-behavioral therapy (CBT; eg, cognitive processing therapy), exposure-based therapy (eg, prolonged and written exposure), and eye movement desensitization and reprocessing therapy to be effective in the treatment of PTSD in adults [2-5]. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions", section on 'Trauma-focused therapy as first-line treatment'.)

The choice of trauma-focused therapy is one of shared decision making and is based on patient presentation, patient preference, and therapist expertise. Choosing among trauma-focused therapies for individuals with PTSD is discussed further elsewhere. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions", section on 'Choosing among trauma-focused therapies'.)

Trauma-focused psychotherapies are the most extensively studied therapy for the treatment of PTSD [2-4,6].

In a meta-analysis of 14 trials including 649 individuals with PTSD, individuals treated with trauma-focused CBT or exposure therapy showed greater improvement in clinician-rated severity of PTSD symptoms (eg, Clinician-Administered PTSD Scale [CAPS] than individuals in wait list or usual care group at treatment end [standardized mean difference -1.4, 95% CI -1.89 to 0.91]) [2]. Furthermore, subgroup analysis (nine trials, n = 428) report individuals treated with exposure showed greater improvement on self-report measures (eg, Impact of Event Scale) of PTSD symptoms at treatment end than individuals in wait list or control group (standardized mean difference -1.68, 95% CI -2.14 to -1.22) [2]. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions", section on 'Trauma-focused therapy as first-line treatment'.)

Comparative clinical trials suggest that using monotherapy with SSRIs or trauma-focused therapy with exposure, are largely comparably effective for PTSD, with some advantage to psychotherapy and that the choice between the two should be based on patient preference [7-9].

- In a randomized trial including 200 individuals with PTSD, participants were first randomized either to treatment of choice (sertraline or prolonged exposure) or randomized treatment assignment. Those assigned to randomized assignment were then further randomized to prolonged exposure versus treatment with sertraline [7]. Efficacy of prolonged exposure and sertraline was, overall, equivalent across a range of outcomes, though some outcomes did favor prolonged exposure. There was a slight advantage (possibly mediated, in part, by better adherence) for patients who were randomized to their treatment of choice (irrespective of whether that treatment was prolonged exposure or sertraline), pointing to the importance of attending to patient preference in treatment selection.

- In a randomized trial including 207 patients with PTSD, participants were randomly assigned to receive sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, or prolonged exposure therapy plus sertraline and followed for 24 weeks [8]. All groups experienced reduced PTSD symptoms, but did not differ in the magnitude of symptom reduction.

Serotonin reuptake inhibitors as alternative first-line or adjunctive treatment — In individuals with comorbid disorders such as depression, we prefer to begin treatment with pharmacologic management with a serotonin reuptake inhibitor (SSRIs or SNRIs). This is

particularly true in individuals with depression who may have low motivation or poor concentration.

Our preference is to start with an SSRI such as sertraline or citalopram, rather than an SNRI such as venlafaxine, as there are more studies investigating SSRIs. However, SNRIs are a reasonable alternative option.

When these symptoms are less problematic (eg, they no longer interfere with the individuals ability to work in therapy), we begin trauma-focused therapy. (See 'Trauma-focused psychotherapy as preferred treatment' above.)

Additionally, in individuals who prefer pharmacologic management to trauma-focused therapy we begin with pharmacotherapy.

Administration — Serotonin reuptake inhibitors (SSRIs and SNRIs) are typically started at the low end of their therapeutic range and titrated up gradually until response is achieved. Usual starting doses, low starting doses, and therapeutic dose ranges for commonly used are shown in a table (table 1). Although there is not clear evidence of a dose-response relationship for serotonin reuptake inhibitors in PTSD, it is common practice to push the dose to the very high end of the therapeutic range (to the extent that this is tolerated by the patient) before concluding that a therapeutic trial has failed. We consider a therapeutic trial with a serotonin reuptake inhibitor to be a minimum of six to eight weeks at maximally tolerated dose within the therapeutic range, before concluding that the medication has failed.

As examples:

- Paroxetine can be started at 20 mg/day orally. If minimal or no clinical response is seen after three to four weeks, we typically increase the dose in 10 to 20 mg/day increments with at least two weeks between dosing increases, up to 60 mg/day.
- Sertraline can be started at 25 or 50 mg/day orally. If minimal or no clinical response is seen after three to four weeks, we typically increase doses in 25 to 50 mg/day increments with at least two weeks between dosing increases, up to 250 mg/day.

Efficacy of serotonin reuptake inhibitors — Clinical trials have found serotonin reuptake inhibitors (SSRIs and SNRIs) to reduce PTSD symptoms compared with placebo [10-13]. Clinical trials have not compared the efficacy of different medications for PTSD.

- **SSRIs** – In a meta-analysis of 12 trials [10] including 1909 individuals with PTSD, treatment with SSRIs led to a greater decline on the Clinician Administered PTSD Symptoms Scale, a structured interview for PTSD, than treatment with placebo (mean difference -5.6, 95% CI

-8.6 to -2.6). Furthermore, indirect comparisons showed greater improvement on CAPS score with SSRIs than other medications (eg, venlafaxine, risperidone).

- **SNRIs** – Although there are fewer studies assessing the efficacy of SNRIs for PTSD compared with SSRIs, two randomized trials found venlafaxine extended-release (ER) to be effective in reducing PTSD symptoms compared with placebo [12,13]. As an example, 329 adults with PTSD were randomly assigned to receive venlafaxine ER or placebo for 24 weeks. Patients receiving venlafaxine ER were more likely to experience remission of PTSD symptoms compared with patients receiving placebo (50.9 versus 37.5 percent) [12].

Response to pharmacologic treatment of PTSD varies greatly with few robust individual predictors of response available [14,15]. Symptoms associated with PTSD, such as sleep disturbance, can be particularly difficult to treat, and are among the symptoms that result in the use of polypharmacy that is common in the treatment of PTSD [16,17].

Side effects of SSRIs and SNRIs are reviewed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects' and "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

Additional considerations for specific populations or symptoms

Substance use disorders — We treat individuals with PTSD and an active SUD with a hybrid approach known as COPE (Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure) [18-20]. Current substance use does not necessarily require delay of psychotherapy for PTSD. Discussion of concurrent treatment for PTSD and SUD may be found elsewhere. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions", section on 'Comorbid substance use disorder' and "Substance use disorders: Psychosocial management".)

Borderline personality disorder — We treat individuals with co-occurring PTSD and borderline personality disorder with a modified treatment that combines prolonged exposure and dialectical behavior therapy. This is particularly useful if chronic suicidality and self-harm behaviors are prominent [21]. Further discussion of the treatment of comorbid borderline personality disorder and PTSD may be found elsewhere. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions", section on 'Comorbid personality disorders' and "Borderline personality disorder: Psychotherapy", section on 'Dialectical behavior therapy'.)

Comorbid traumatic brain injury — Hybrid psychotherapeutic approaches may offer additional improvements over standard therapy in the treatment of PTSD with comorbid

moderate to severe traumatic brain injury (TBI) in military personnel returning from combat [22]. For example, in an individual with PTSD and comorbid moderate to severe TBI, our preference is to use a hybrid approach that offers cognitive processing therapy with compensatory cognitive training. Most patients with mild TBIs do well with evidence-based approaches to PTSD without the requirement for the modification of those approaches. Further discussion of treatment of combined PTSD and TBI is found elsewhere. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions", section on 'Comorbid TBI'.)

Prominent sleep disturbance or nightmares — We suggest treatment with prazosin for individuals with PTSD who experience significant sleep disturbance, most typically nightmares. In our clinical experience, prazosin appears to reduce overall PTSD symptoms, nightmares, and sleep disturbance in approximately 50 percent of patients with PTSD.

Alpha-adrenergic receptor blockers — We typically use prazosin as an augmenting agent for individuals being treated with serotonin reuptake inhibitors (SSRI or SNRI); however, in some cases it is given as monotherapy or combined with trauma-focused therapy.

Our preference is to start prazosin at 1 mg 30 to 60 minutes before bedtime and gradually increase to 3 to 15 mg over several months. We are cautious in treating individuals with hypotension (eg, due to being on other medications). Sudden discontinuation of prazosin must be avoided, as this can result in rebound hypertension.

Clinical trials of prazosin for sleep disruption in PTSD have found mixed results [23-25]. Possible reasons for the discrepancies include methodologic differences and heterogeneity in patient populations [26]:

- A meta-analysis of six randomized clinical trials including 240 subjects (mostly military veterans or active-duty service members) with PTSD showed moderate to large effects of prazosin in reducing overall PTSD symptoms and nightmares and improving sleep quality [24].

- In a trial involving 67 active-duty United States Army personnel with PTSD returning from combat deployments from Iraq or Afghanistan, subjects were randomly assigned to treatment with prazosin versus placebo [25]. Prazosin was superior to placebo in reducing nightmares, improving overall sleep quality, and improving overall clinical symptoms. The study was stopped early because of the early benefit observed with prazosin.

- A subsequent randomized trial in 304 veterans with PTSD failed to show benefits of prazosin compared with placebo in alleviating distressing dreams or improving sleep

quality [23].

Further research is needed to identify whether specific subgroups of patients with PTSD are uniquely responsive to prazosin.

Psychosis — In individuals with PTSD who have prominent psychotic symptoms we typically begin treatment with an SSRI and augment with a second-generation antipsychotic (SGA) medication [27].

Second-generation antipsychotics — Our preference is to treat individuals with prominent psychosis in the context of PTSD with an SGA. For example, if we are augmenting an SSRI with risperidone, we would begin with 0.5 mg orally at night. After one week we increase in weekly increments of 0.5 mg or 1 mg increments to a maximum of 4 mg/day. An alternative option is quetiapine which we would start at 25 mg orally at night and increase one week later if the response is inadequate. We titrate weekly in 50 mg increments up to 800 mg/day.

If no clinical benefit is seen after two to three weeks of treatment at the maximal tolerated dose, we gradually discontinue the medication to lessen the risk of side effects.

Randomized clinical trials provide some evidence of efficacy for SGAs in PTSD as monotherapy or augmenting serotonin reuptake inhibitors [28-34].

- In a randomized clinical trial 80 United States military veterans with chronic PTSD were treated with quetiapine versus placebo monotherapy [28]. Quetiapine was started at 25 mg/day and increased to an average of 258 mg/day (range, 50 to 800 mg/day). After 12 weeks, mean reductions in CAPS total score were greater among the quetiapine-treated group than among those in the placebo group (mean change 21.5 versus 4.9, respectively). Additionally, subscores of hyperarousal and re-experiencing were greater for quetiapine-treated group than the placebo-treated group.

- A large trial involving SGA augmentation randomly assigned 247 United States military veterans who responded inadequately to two or more trials with an SSRI or SNRI to receive adjunctive risperidone (up to 4 mg once daily) or placebo [29]. Patients continued to receive other medication and psychosocial interventions for PTSD. After six months, no meaningful difference was seen in overall CAPS score (the primary outcome) compared with placebo, or in symptoms of anxiety, depression, or quality of life. Risperidone led to small, mean reductions in re-experiencing and hyperarousal symptoms. Participants receiving risperidone were more likely to experience weight gain, fatigue, somnolence, and hypersalivation compared with patients receiving placebo.

- Other, smaller trials showed mixed results [31,32,34]. Most of the patients in these studies were treated for combat-related PTSD; it is not clear whether the results are generalizable to the civilian population.

Side effects, including weight gain and other metabolic abnormalities, make SGAs a less desirable option than serotonin reuptake inhibitors (SSRI or SNRI). Side effects of SGAs are shown in a table (table 2) and reviewed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

DURATION OF TREATMENT

We continue medications that are effective for posttraumatic stress disorder (PTSD) for at least six months to one year in order prevent relapse or recurrence. A clinical trial randomly assigned 96 patients with PTSD who had completed 12 weeks of acute treatment with sertraline to either 28 weeks of maintenance treatment with sertraline or to placebo. Patients who continued sertraline were less likely to relapse than patients receiving placebo (5 versus 26 percent) [35].

Additionally, in individuals that respond favorably to psychotherapy with an evidence-based treatment for PTSD, we find that treatment gains are generally maintained [36], with studies suggesting continued maintenance for 12 months [37] but even more enduring outcomes likely for many patients.

MANAGEMENT OF SUBOPTIMAL RESPONSE

Our preference for psychotherapy, medication, or their combination in patients who experience a suboptimal (eg, poor or partial response) to initial treatment is made on the basis of treatment availability and/or patient preference. There are no clinical trials comparing medication with psychotherapy in posttraumatic stress disorder (PTSD) patients who do not respond to initial treatment.

We assess for and address underlying or untreated psychiatric comorbidities in individuals that have a suboptimal (poor or partial response) to a therapeutic trial of medication (eg, eight weeks at therapeutic dose) or psychotherapy (eg, eight sessions, acceptable engagement in treatment, and adherence to treatment recommendations).

Our preference for subsequent treatment is described below.

Individuals who prefer psychotherapy — For individuals who prefer psychotherapy, our choices for treatment of suboptimal response to initial psychotherapy are:

- For poor response to initial psychotherapy, our preference is to switch to another trauma-focused therapy (eg, cognitive processing therapy).
- For partial response to initial psychotherapy, our preference is to augment with another trauma-focused therapy (eg, trauma processing therapy).

We choose subsequent psychotherapy based on the clinical presentation. As an example, if a patient is not willing or able to engage emotionally with the trauma memory and reminders, we change from exposure therapy to a combined cognitive therapy/exposure therapy.

We often use assessment tools such as the Emory Treatment Resistance Interview for PTSD (E-TRIP) to help inform subsequent treatment decisions. The E-TRIP includes clinician-administered questions used to assess the adequacy and benefit derived from past treatment trials [38]. (See "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions".)

Individuals who prefer medication — For individuals preferring medication management, our choices after suboptimal response to initial treatment (with psychotherapy or pharmacotherapy), are as follows:

- For individuals with poor response to trauma-focused therapy our preference is to discontinue the therapy and switch to pharmacologic management with a selective serotonin reuptake inhibitor (SSRI).
- For individuals with poor response to initial medication management our choice is to switch to another SSRI. A trial of a serotonin-norepinephrine reuptake inhibitor (SNRI) is an acceptable option; however, SNRIs have been less extensively studied than SSRIs in the treatment of PTSD [10,12,13]. We typically taper the first medication over two weeks while titrating the second one at the same time. While directly switching to a new SSRI at equivalent dose of the current SSRI is typically well tolerated, it is less preferred.
- For individuals who have failed to respond to two prior serotonin reuptake inhibitors (SSRI or SNRI) our preference is to treat with a second-generation antipsychotic (SGA) medication. (See 'For individuals refractory to two or more serotonin reuptake inhibitors' below.)

Individuals agreeable to combined modalities — In our clinical experience, augmentation of psychotherapy with an SSRI (or augmentation of an SSRI with psychotherapy) may be helpful for some. However, clinical trials have provided little direct evidence supporting greater

improvement with the combination of cognitive-behavioral therapy and an SSRI/SNRI than either modality alone [8,9,39-41]. As examples:

- Eighty-eight patients with PTSD who were initially treated with sertraline for 10 weeks and did not achieve a full response [40] were randomly assigned to continue to receive sertraline alone or sertraline augmented with prolonged exposure for an additional five weeks. No difference in PTSD symptom reduction was seen between the two groups.

- Seventy-eight patients with PTSD who were initially treated with eight sessions of prolonged exposure and experienced a partial response [41] were randomly assigned to continued prolonged exposure with either controlled-release paroxetine or placebo. No difference was seen between the two groups.

- Two hundred twenty-three patients with combat-related PTSD were randomized to receive up to 13 sessions of prolonged exposure plus placebo pills, sertraline with enhanced medication management, or the combination of prolonged exposure and sertraline, with outcomes assessed by blinded raters at 24 weeks. No difference in change in PTSD symptoms or symptom severity at 24 weeks was found between sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline [8].

The administration, dosing, and side effects of serotonin reuptake inhibitors are reviewed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects' and "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

For individuals refractory to two or more serotonin reuptake inhibitors — For individuals preferring medication management who have not adequately responded to two or more trials of serotonin reuptake inhibitors (SSRI or SNRI) our preference is treatment with an SGA.

- For individuals with a partial response to serotonin reuptake inhibitor treatment we prefer to augment with quetiapine or risperidone.

- For individuals with minimal to no response to serotonin reuptake inhibitor treatment we use quetiapine or risperidone monotherapy.

Randomized trials provide some evidence of efficacy for SGAs in the treatment of PTSD as monotherapy [28-30] or as augmentation [31,32]. However, the side effect burden including weight gain and other metabolic abnormalities make SGAs a less desirable option than serotonin reuptake inhibitors. Side effects of SGAs are shown on the table (table 2).

Based upon the absence of other medications proven to be effective and our clinical experience that some patients appear to benefit from SGAs, they are an option for patients failing previously suggested treatment. (See 'Second-generation antipsychotics' above.)

Administration and monitoring of individuals on SGAs may be found elsewhere. (See 'Second-generation antipsychotics' above and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

MEDICATIONS WITH LIMITED SUPPORTING EVIDENCE

We do not recommend the following agents due to limited evidence supporting their use in the treatment of posttraumatic stress disorder (PTSD).

- **Benzodiazepines** – Based on the absence of clear benefit and the possibility of worsening PTSD, we suggest not using benzodiazepines to treat patients with PTSD. Benzodiazepines have not been studied in adequately powered randomized clinical trials in PTSD, yet they are frequently used to treat symptoms of anxiety and hyperarousal [16,17]. Some data suggest that benzodiazepines may impair the therapeutic effects of treatments, such as exposure therapy that rely on extinction learning [42], but further study is needed to confirm this adverse effect.

  Additionally, given the high prevalence of comorbid substance use disorder (SUD) in patients with PTSD, we avoid using benzodiazepines in patients with an active SUD or a history of a benzodiazepine use disorder or alcohol use disorder. (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis", section on 'Co-occurring conditions'.)

  We monitor all patients prescribed benzodiazepines for PTSD for signs of misuse or abuse. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management", section on 'Sedatives-hypnotics'.)

- **Beta-adrenergic blocking agents (eg, propranolol)** – Although early reports proposed a potential use for beta-adrenergic blockers such as propranolol in the early prevention or subsequent treatment of PTSD, subsequent studies have not supported this claim, and further research is needed [43].

- **Mood stabilizers** – Anticonvulsant medications with mood-stabilizing properties in other psychiatric disorders have insufficiently tested in clinical trials for their ability to reduce

PTSD symptoms. Few adequately powered, randomized trials have been conducted, and findings have been mostly negative [14,44-49].

- **Ketamine** – Ketamine is an N-methyl-D-aspartic acid antagonist used as an anesthetic and is an emerging treatment for depression and PTSD. Based on clinical trials, treatment with ketamine combined with psychotherapy appears to reduce PTSD symptoms [50-52]. In a meta-analysis of trials, 34 subjects with PTSD treated with a combination of ketamine infusion (various protocols) and psychotherapy for PTSD (psychotherapy protocols included 10 weeks Trauma Interventions Using Mindfulness-Based Extinction and Reconsolidation of Memories [TIMBER] therapy, 10 weekly sessions of prolonged exposure therapy, 5 daily sessions exposure therapy) showed greater improvement on PTSD symptoms than those treated psychotherapy and placebo [52]. Improvements are reported on the Clinician-Administered PTSD scale (standardized mean difference -7.26, 95% CI -12.28 to -2.35) and the PTSD checklist (standardized mean difference -5.17, 95% CI -7.99 to -2.35). Further investigation of the potential of ketamine-assisted psychotherapy for PTSD are warranted.

- **Cannabis and synthetic cannabinoids** – With the passage of legislation legalizing use of medical cannabis in many states in the United States and other countries, some researchers have questioned whether cannabis could be a useful treatment for PTSD [53-55]. A role for specific components of cannabis (eg, cannabidiol versus tetrahydrocannabinol) or other cannabinoids (synthetic and naturally occurring) in the treatment of PTSD remains to be determined with further research. A review of open label and observational trials has concluded that cannabis use is associated with worse treatment outcomes in some naturalistic studies and concluded that "known risks of marijuana thus currently outweigh unknown benefits for PTSD" [53]. Further study of cannabinoids and other drugs that enhance the function of endocannabinoids is warranted.

- **Riluzole augmentation** – The glutamatergic modulator riluzole, has been shown to improve hyperarousal symptoms associated with PTSD but not overall PTSD symptoms. Further study of riluzole and other glutamatergic modulators is warranted [56].

- **Other antidepressants** – There is insufficient evidence of effectiveness of antidepressants other than selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors in PTSD, including tricyclic antidepressants, monoamine oxidase inhibitors, serotonin modulators (eg, trazodone), or atypical antidepressants (eg, mirtazapine) [57-59].

- **Other investigational treatments**

  - **3,4 methylenedioxymethamphetamine (MDMA**) – MDMA ("ecstasy"), a synthetic stimulant with potential for misuse, has been studied clinical trials as a treatment for PTSD and appears to be effective when combined with a very specific, intensive form of psychotherapy [60,61]. In a trial, 104 participants with moderate or severe PTSD (moderate: Clinician Administered PTSD Scale for DSM-5 [CAPS-5] 28 to 34; severe: CAPS-5 ≥35) were randomly assigned to treatment with MDMA-assisted therapy (MDMA-AT) versus placebo with therapy [61]. At 18-week assessment, subjects in the MDMA-AT treatment had a greater reduction in CAPS-5 score, as compared with subjects who received placebo plus therapy (least squares mean change: 23.7 versus 14.8, respectively). At study end, a greater percentage of subjects in the treatment group no longer met criteria for PTSD as compared with the placebo-therapy group (71.2 versus 47.6 percent, respectively). Treatment-emergent adverse effects were more prevalent in the group treated with MDMA-AT; however, no deaths or serious side effects were reported in either group. (See "MDMA (ecstasy) intoxication".)

    While research combining MDMA-AT is promising, at present we do not recommend this treatment. MDMA is not yet legally available in the United States for this purpose. Additionally, the intensive form of psychotherapy used in the trial is also not widely available. Furthermore, it is currently unknown if MDMA will be effective for PTSD in combination with other available trauma-focused therapies. Further trials are warranted.

  - **D-cycloserine** – Use of D-cycloserine to enhance trauma-focused psychotherapy for PTSD has been mixed. The use of D-cycloserine is not recommended at this time.

  - **Propranolol and trauma memory reactivation** – Although research on the combination of propranolol and trauma memory reactivation is promising, it is too preliminary to recommend the use of this approach to treatment of PTSD. A randomized clinical trial found that trauma memory reactivation preceded by treatment with propranolol demonstrated an advantage compared with placebo-pretreatment of trauma memory reactivation in reducing PTSD symptoms (as measured by the Clinician Administered PTSD Scale) [62].

  - **Stellate ganglion blockade** – Stellate ganglion blockade involves injection of local anesthetic into the stellate ganglion of the sympathetic chain in the neck. Randomized trials have shown mixed results in the treatment of PTSD symptoms [63,64]. As examples:

- In a trial 42 military service members (active-duty or retired) with PTSD were randomly assigned to stellate ganglion blockade using either local anesthetic or sham injection. Participants were reassessed after one week, one month, and three months. Reduction of PTSD symptoms (as measured by the Clinician-Administered PTSD Scale) and self-reported scores for depression and anxiety were similar between groups across time. No differences were seen in complication rates between active and control groups.

- In a trial 113 active-duty service members with PTSD symptoms (clinical threshold and subthreshold) were randomly assigned to treatment with two stellate ganglion blockades or sham injections. At eight-week follow-up, the mean change (as measured by the Clinician-Administered PTSD Scale for DSM-5) was greater in the group receiving active treatment than in the treatment receiving sham treatment (mean change -12.2 and -5.8, respectively). Note is made of the mild to moderate level of PTSD symptom severity and the short follow-up time which may limit generalizability.

Further trials investigating the use of stellate ganglion blockade as an adjunctive PTSD treatment are warranted.

SUMMARY AND RECOMMENDATIONS

- **Initiating treatment** – We prefer to begin treatment for posttraumatic stress disorder (PTSD) as soon as possible after the diagnosis is made. (See 'Initiating treatment' above.)

  - **Goals** – The goals of treatment include maintaining safety of the patient and others, reduce distressing symptoms, reduce avoidant behaviors, diminish anxiety, and improve adaptive and psychosocial functioning, and lessen the risk of relapse. (See 'Establishing treatment goals' above.)

  - **Trauma-focused psychotherapy as first line** – For most adults with PTSD we suggest first-line treatment with a trauma-focused psychotherapy that includes exposure rather than a serotonin reuptake inhibitor (selective serotonin reuptake inhibitor [SSRI] or serotonin-norepinephrine reuptake inhibitor [SNRI]) (**Grade 2C**). (See 'Trauma-focused psychotherapy as preferred treatment' above.)

- **SSRIs as alternative first line** – SSRIs are an appropriate alternative to psychotherapy and are preferred in patients with comorbid depression or other anxiety disorder,

particularly if their symptoms interfere with psychotherapy. (See 'Serotonin reuptake inhibitors as alternative first-line or adjunctive treatment' above.)

- **Considerations for specific populations or symptoms** – We use modified psychotherapeutic approaches that incorporate treatment for PTSD as initial management for individuals with substance use disorders, personality disorders, and moderate-to-severe traumatic brain injury. (See 'Additional considerations for specific populations or symptoms' above.)

  For individuals with PTSD who experience significant sleep disturbance, typically nightmares, we suggest treatment with prazosin (**Grade 2C**). We use prazosin as an augmenting agent with serotonin reuptake inhibitors or in some cases as monotherapy or combined with trauma-focused therapy. (See 'Prominent sleep disturbance or nightmares' above.)

  For individuals with PTSD with prominent psychotic symptoms, we suggest treatment with a combination SSRI and second-generation antipsychotic (SGA) medication (**Grade 2C**). (See 'Psychosis' above.)

- **Duration of treatment** – We continue medications that are effective for PTSD for at least six months to one year in order prevent relapse or recurrence. (See 'Duration of treatment' above.)

- **Management of suboptimal response** – Our subsequent choices are as follows:

  - **Individuals with preference for psychotherapy** – For partial response to initial psychotherapy our preference is to augment with another trauma-focused therapy. (See 'Individuals who prefer psychotherapy' above.)

    For poor response to initial psychotherapy, our preference is to switch to another trauma-focused therapy.

  - **Individuals with preference for medication** – For individuals with poor response to initial trauma-focused therapy our preference is to discontinue therapy and start pharmacologic management with an SSRI. An SNRI is an acceptable, though less studied, option. (See 'Individuals who prefer medication' above.)

    For individuals with poor response to medication management who do not want further psychotherapy, our next choice is to switch to another serotonin reuptake inhibitor (SSRI or SNRI).

- **For individuals willing to use combined modalities** – In our clinical experience, augmentation of psychotherapy with an SSRI (or augmentation of an SSRI with psychotherapy) may be helpful for some. However, clinical trials have provided little direct evidence supporting this option. (See 'Individuals agreeable to combined modalities' above.)

- **For individuals who have not responded to two or more serotonin reuptake inhibitors (SSRI or SNRI)** – Our preference is to try an SGA. If no clinical benefit is seen after two to three weeks of treatment at the maximal tolerated dose, we gradually discontinue the medication to lessen the risk of side effects. (See 'For individuals refractory to two or more serotonin reuptake inhibitors' above.)

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