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**REVIEW ARTICLE**

# Current treatment of posttraumatic stress disorder – A review of therapeutic guidelines and good practice recommendations

**Octavian Vasiliu, Daniel Vasile, Andrei G. Mangalagiu, Bogdan M. Petrescu, Cristian A. Candea, Corina Tudor, Daniela Ungureanu, Madalina Miclos, Alina Draghici, Catalina Florescu, Roxana E. Bratu-Bazic**

**Abstract**: *A unique approach to the treatment of posttraumatic stress disorder (PTSD) is difficult to support, because of the complexity and heterogeneity of this pathology. Multiple evidence-based guidelines for PTSD treatment exist, elaborated by prestigious institutions around the world, but a certain level of the inconsistency of their recommendations appears when these sources are compared with each other. Therefore, a review of current guidelines and extraction of the most supported by evidence recommendations is considered important for clinical practice, due to the need to approach such complex cases as PTSD-diagnosed patients in a stepwise manner. Structured monitoring of the clinical status during the treatment is also an important and rather neglected aspect of the case management in PTSD, and the necessity of follow-up visits for efficacy and tolerability should be taken into consideration. Psychotherapy (especially cognitive-behavioral oriented therapies and eye movement desensitization and reprocessing therapy) is supported by evidence as a first-line approach, as well as certain antidepressants, like the selective serotonin reuptake inhibitors and venlafaxine. Many second-line pharmacological agents and psychotherapies are also available, but there is an obvious need for more pragmatic trials with PTSD patients.*

**Keywords**: *post-traumatic stress disorder, psychotherapy, case management, antidepressants, therapeutic guidelines, good clinical practice*

## BACKGROUND

While definitions of the diagnostic criteria for posttraumatic stress disorder (PTSD) are articulate and comprehensive in both the World Health Organization and American Psychiatric Association classifications of mental disorders [1-3], pragmatic recommendations for the treatment of this disorder are still lacking. Although there are several guidelines dedicated to this subject, they are based on randomized trials, and not on pragmatic, naturalistic studies, which leave some important questions unanswered. Even if the case management is based on these guidelines, there are several contradictions based on the different data they included. Therefore, we consider the first necessary step to be a critical analysis of these therapeutic guidelines, followed by the formulation of good practices and hierarchized recommendations, according to the GRADE level [4].

The diagnosis of PTSD could be formulated, according to ICD-11, if an extremely threatening or horrific event or series of events is followed by re-experiencing this trauma as intrusive memories, flashbacks, nightmares, accompanied

„Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania

by strong or overwhelming emotions and strong physical sensations; avoidance of thoughts and memories of the event(s), or avoidance of activities, situations, or people reminiscent of the events(s); persistent perceptions of heightened current threat, for example, indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises [1]. These symptoms have to persist for at least several weeks and to cause significant impairment in personal, family, social, educational, occupational, or other important areas of functioning to support a PTSD diagnosis [1]. The ICD-10 mentions the capacity of the stressful event to cause pervasive distress in almost anyone who has been removed from the latest edition of this classification [1,3]. Also, differences in the structure of the symptoms list necessary to establish the PTSD criteria have been formulated between the two editions of ICD, from 13 in the tenth edition, to only 6, by removing the non-specific manifestations [1,3]. In the latest edition of the American Psychiatric Association classification of mental disorders (2013), there are 4 clusters of symptoms needed for the diagnosis: (1) intrusion symptoms associated with the traumatic event, (2) persistent avoidance of stimuli associated with the traumatic event, (3) negative alterations in cognitions and mood associated with the traumatic event, (4) marked alterations in arousal and reactivity associated with the traumatic event, and the duration of these manifestations are more than one month [2].

Complex PTSD may develop following exposure to an event or series of events of an extremely threatening or horrific nature, commonly prolonged or repetitive events from which escape is difficult or impossible [1]. Complex PTSD is characterized by severe and persistent problems in affect regulation, beliefs about oneself as diminished, defeated, or worthless, accompanied by feelings of shame, guilt, or failure related to the traumatic event; difficulties in sustaining relationships, and feeling close to others [1]. These symptoms cause significant impairment in personal, family, social, educational, occupational, or other important areas of functioning [1].

A high rate of comorbid major depressive disorder (up to 50%) has been reported in PTSD patients, a phenomenon which underlines the necessity for a thorough psychiatric evaluation, both initially and during the monitoring period [5,6]. Also, there has been described as an overlap between PTSD and psychosis that may raise important diagnosis challenges and treatment dilemmas [7, 8]. Substance-related disorders have also been described with relatively high incidence in this population, and specific psychotherapy algorithms have been developed for these patients with dual diagnosis, based on imaginal and in vivo exposure for PTSD, applied concomitantly with cognitive-behavioral techniques for substance use disorders [9]. Also, the pharmacological treatment should be adjusted according to the existing comorbidities, and the case manager should integrate all the data, taking into account the risk of pharmacologic interactions, contraindications, and side effects (e.g., avoidance of drugs with the risk of addiction, like benzodiazepines, is recommended in PTSD patients) [10].

## ANALYSIS OF THE CURRENT THERAPEUTIC GUIDELINES FOR PTSD

Several prestigious institutions have elaborated evidence-based guidelines for the treatment of PTSD, therefore an important number of recommendations for approaching these patients to exist. While some therapeutic guidelines are focused on psychotherapy, others are based on pharmacological research, while still others encompass both types of treatment.

**American Psychological Association Clinical Practice Guideline for the Treatment of PTSD** (2017) strongly recommends as evidence-based psychotherapies in adults cognitive-behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and prolonged exposure therapy (PE), and suggests the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing therapy (EMDR), and narrative exposure therapy (NET) [11].

According to the **Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder** (2013), individual-trauma focused CBT, including exposure and/or cognitive therapy, should be recommended if symptoms are consistent with acute stress disorder or posttraumatic stress disorder in the initial 4 weeks after a potentially traumatic event (level C evidence) [12]. Individuals with posttraumatic stress disorder benefit from trauma-focused CBT or EMDR (level A recommendation), and if the symptoms did not respond to these interventions, non-trauma focused approaches may be considered (e.g., stress inoculation technique) [12]. Also, there is some evidence that supports the efficacy of in vivo exposure therefore, by expert consensus, it is recommended to include this method in the treatment [12]. Group CBT (trauma-focused or non-trauma focused) may be offered as an adjunctive to trauma-focused individual therapy [12].

Medication should not be used for the treatment of acute stress reaction or posttraumatic stress disorder within the four weeks of symptom onset unless the severity of such symptoms- associated distress cannot be managed by psychological means alone [12]. The pharmacological

approach may be continued while people are undertaking psychological treatments, but several agents, like benzodiazepines, may interfere with some effective psychological treatments [12]. SSRIs are considered the first line for the treatment of posttraumatic stress disorder [12].

According to the **Maudsley Prescribing Guidelines** (13th edition, 2018) patients diagnosed with posttraumatic stress disorder should be offered as the first line of treatment paroxetine, sertraline, fluoxetine (up to the maximum tolerated doses) or venlafaxine (37.5-300 mg/day) [13]. As second-line treatment the case manager could choose between antipsychotics (olanzapine 5-20 mg/day, risperidone 0.5-6 mg/day, quetiapine 50-800 mg/day), mirtazapine 15-45 mg/day, monoaminoxidase (MAO) inhibitors (phenelzine 15-75 mg/day), tricyclic antidepressants (amitriptyline 50-300 mg/day, imipramine 50-300 mg/day), and prazosin (2-15 mg nocte) for nightmare and sleep disturbances [13]. Possible choices if the first and second lines failed are duloxetine (60-120 mg/day), lamotrigine (up to 500 mg/day), phenytoin, valproate, or i.v. ketamine, and as non-drug therapies- eye-movement desensitization and reprocessing (EMDR) and trauma-focused CBT [13].

According to the **VA/DOD Clinical Practice Guideline for the Management of PTSD and ASD** (2017) pharmacotherapy in PTSD is classified as follows: sertraline, paroxetine, fluoxetine, venlafaxine as monotherapy (moderate evidence), nefazodone (low evidence), imipramine, phenelzine (very low evidence) [14]. The Work Group recommended against the use of atypical antipsychotics, benzodiazepines, and Divalproex as augmentation therapy due to low-quality evidence and potential adverse effects [14]. Also, prazosin is not supported by this guideline for the use in monotherapy or combination with other agents [14]. Individual trauma-focused psychotherapy for PTSD are Prolonged Exposure, Cognitive Processing Therapy, and EMDR, which are supported by the strongest evidence, but other therapies like specific cognitive therapies for PTSD, Brief Eclectic Psychotherapy, Narrative Exposure Therapy, written narrative exposure may be recommended [14]. If individual trauma-focused psychotherapy is not available, Stress Inoculation Therapy, Interpersonal Therapy, or Present-Centered Therapy may be recommended [14].

The **International Society for Traumatic Stress Studies new guidelines for the Prevention and Treatment of Posttraumatic Stress Disorder** (2019) has formulated the following recommendations according to their evidence-based status: (1) strong support for cognitive processing therapy, cognitive therapy, EMDR, individual CBT with a trauma focus, prolonged exposure; (2) standard recommendations for CBT without a trauma focus, guided Internet-based CBT with a trauma focus, narrative exposure therapy, present-centered therapy; (3) emerging evidence-couples CBT with a trauma focus, group and individual CBT with a trauma focus, reconsolidation of traumatic memories, single-session CBT, written exposure therapy, and virtual reality therapy [15].

Individual trauma-focused CBT intervention may be useful for adults who have acute stress disorder or clinically important symptoms of PTSD and have been exposed to 1 or more traumatic events within the last month- cognitive processing therapy, cognitive therapy, narrative exposure therapy, prolonged exposure therapy, according to the **NICE Guidelines** (2018) [16]. In adults with PTSD symptoms should be offered trauma-focused CBT, during 8-12 sessions, accompanied by psychoeducation about reactions to trauma, strategies for managing arousal and flashbacks, safety planning, or EMDR for patients with PTSD symptoms, if the patient has a preference for this method [16]. Trauma-focused computerized CBT for adults with a diagnosis of PTSD or clinically important symptoms of PTSD more than 3 months after a traumatic event, who do not want to be engaged in trauma-focused CBT or EMDR [16]. Symptom-specific CBT interventions for adults with a diagnosis of PTSD or clinically important symptoms of PTSD more than 3 months after traumatic events who are unable or unwilling to engage in a trauma-focused intervention that targets PTSD or have residual symptoms after a trauma-focused intervention [16].

Medication should not include benzodiazepines for the prevention of PTSD in adults, but venlafaxine or an SSRI may be chosen [16]. Antipsychotics may be offered if patients have disabling symptoms (psychotic) or if their symptoms have not responded to other drug or psychological treatments [16].

For patients with complex PTSD the case manager should help the patient control any symptoms (e.g. dissociation or emotional dysfunctions) that might interfere with engaging in trauma-focused therapies; ensure adequate time for the construction of the therapeutic relationship; to increase the number of trauma-focused therapy sessions according to the person's needs; plan any ongoing support the person needs and has implications in the therapeutic management [16].

## DESCRIPTION OF THE MAIN PSYCHOTHERAPEUTIC METHODS IN PTSD

Cognitive-behavioral therapy (CBT) in PTSD is focused on the relationship among thoughts, feelings, and behaviors that are present-oriented and target current problems and

symptoms [17]. CBT is based on emotional processing theory and social cognitive theory, therefore it claims that changing associations between reminders of the traumatic event and responses will lead to healthier behaviors while reframing the relation between trauma and existing beliefs about self, others and the world will also help decrease self-blame and improve the processing of the trauma [17].

Cognitive distortions in PTSD include perceiving the world as dangerous, seeing him/herself as powerless, and feeling guilty about surviving while other significant ones have died [18]. Cognitive therapy fosters the development of more realistic and adaptive cognitions, by successful processing of the traumatic event, with engaging and organization of the trauma narrative [18, 19].

Cognitive processing therapy (CPT) is an efficient method for treating PTSD as demonstrated by a recent meta-analysis (n=11 studies, N=1130 participants), outperforming inactive control conditions on PTSD outcome measures at posttreatment and follow-up, but also other active treatments at posttreatment but not at follow-up [20]. Effect sizes of CPT were superior to 89% of the inactive control conditions at posttreatment and 82% at follow-up, which indicates a large and sustained effect of the CPT [20].

Veterans who were diagnosed with both PTSD and alcohol use disorder (AUD) completed a 6-week CPT-based program had significantly better outcomes, including trauma-related cognitive distortions, PTSD symptoms, depressive symptoms, and trauma-cued substance craving [21]. In another study that included veterans (n=465), enrolled in CPT plus a written trauma account either group format or individual, the PTSD and depressive symptoms decreased significantly, with medium effects for the first option, and large effects for the second treatment [22].

Cognitive therapy (CT) has proven efficient in a group of 20 patients diagnosed with PTSD, as it decreased core PTSD features, but also depressive and anxiety symptoms [23]. Good treatment outcomes were related to more changes in dysfunctional cognitions related to the trauma [23]. Intensive CT was applied in 14 patients diagnosed with PTSD, in an 18-hour format during 5-7 working days, followed by one session a week later and up to 3 follow-up sessions; intensive CT led to similar outcomes as weekly-administered CT, but the intensive treatment improved the key PTSD symptoms over a shorter period and led to greater reductions in depression [24].

Prolonged exposure therapy (PE) is another trauma-focused CBT effective for improving PTSD, with response rates in 60-65% of trauma victims suffering from this disorder [25]. PE is based on two types of exposure techniques, imaginal exposure, and in vivo exposure, and it is used for enhancing emotional processing through systematic confrontation with trauma-related stimuli [26-28]. Intensive PE therapy (12 sessions, 90 minutes each, during 4 days) followed by four weekly 90-minute booster PE sessions in an open trial (n=73) patients diagnosed with PTSD who presented multiple interpersonal trauma had positive results after repeated treatment attempts [29]. Exposure therapy has an impact on the fear and contextualization circuits by facilitating communication between the ventromedial prefrontal cortex, hippocampus, and the amygdala [30].

Brief eclectic psychotherapy (BEP) for PTSD is a manualized technique that combines elements from psychodynamic, cognitive-behavioral, and directive psychotherapy [31]. Psychoeducation with the participation of the spouse, and exposure used to help the patient to access his or her feelings related to the traumatic event are also used during BEP [31]. A 16-session protocol of BEP in PTSD includes the following steps: psychoeducation for the development of self-control and motivation for therapy (the patient is invited to call up his memories and related emotions one last time); imaginal exposure or guidance (brief periods of muscle relaxation, relieving of the traumatic experience by imaginal exposure of 20-30 minutes); writing tasks and mementos (for uncovering the difficult feelings that may be related to the traumatic experience); meaning and integration (exploring and accepting a new view of the world and the self); farewell ritual (symbolic ritual created to encourage the expression of the sorrow the patient may still feel, and then to leave behind these feelings) [31, 32].

The first randomized clinical trial for BEP in patients with PTSD included 42 police officers who received 16 weekly sessions (60 minutes each) of psychotherapy [32]. At posttest and follow-up (at 3 months) BEP had produced significant improvement in PTSD symptoms, work functioning, and several comorbid conditions (e.g., agoraphobia) [32].

Another clinical trial included patients diagnosed with PTSD (n=24) randomly assigned to BEP or a waitlist group for 4 months, with superior efficacy on PTSD core symptoms and general anxiety symptoms in the active intervention group [33]. In this trial, BEP consisted of 16 weekly sessions (45-60 minutes each), and a high rate of the dropout was recorded (25% for the treatment group) [33].

Eye movement desensitization and reprocessing therapy (EMDR) is a type of psychotherapy developed by F.Shapiro for intervention in emotional trauma and other negative life experiences [34]. This psychotherapy consists of a protocol with 8 phases and bilateral stimulation targeting patient

desensitization from the discomfort induced by traumatic memories [35]. The final objective of the EMDR is to achieve the reprocessing of these memories and to integrate them within the autobiographical memory [35].

According to a review of 24 randomized controlled trials, EMDR is an evidence-based approach for this kind of disorder, with 7 out of 10 studies reporting EMDR to be faster acting and/or more effective than trauma-focused CBT [34]. Two meta-analyses supported the efficacy of EMDR in treating PTSD, with results superior to various interventions and control conditions, and showed the efficacy of this psychotherapy over symptoms of depression, anxiety, and subjective distress [36,37]. A review of the trials published between 2014 and 2017 regarding the efficacy of EMDR in PTSD further supported this method, because it improved core symptoms over time, compared to relaxation therapy and a waiting-list control group [38].

Narrative exposure therapy (NET) is a psychotherapeutic intervention dedicated to the treatment of survivors of multiple and severe traumas, and 3-6 sessions may be sufficient to provide significant relief [39]. It is a short-term approach based on CBT and testimony therapy [40]. NET was evaluated in a group of 59 political detainees, 18 of which had full PTSD criteria, who were allocated in a randomized manner to either one session of psychoeducation or five sessions of NET [41]. After 6 months, NET but not psychoeducation produced a significant reduction in PTSD symptoms and depression scores, although four out of the nine patients receiving NET and eight out of the nine patients undergoing psychoeducation still had PTSD symptoms at 6 months [41]. In another trial, NET was compared to supportive counseling and psychoeducation (4, 4 and one sessions, respectively) in a group of Sudanese refugees (n=43), and the results after one year of treatment were superior for NET (29% vs. 79% vs. 80% still had PTSD criteria) [40].

Interpersonal therapy (IPT) is a time-limited focused on the patient's actual events and reframing of the social functioning as a way to tackle the symptoms and may be recommended where the patient does not want to be exposed to exposure-based approaches [42]. In a case study, IPT proved itself efficient comparative to the other two psychotherapies, after 14 weekly sessions [42]. In a 14-week randomized trial, IPT was compared to prolonged exposure and relaxation therapy in 110 unmedicated patients with chronic PTSD and the response rates were 63% for IPT, 47% for prolonged exposure, and 38% for relaxation therapy, without significant differences between groups [43]. IPT and exposure therapy improved the quality of life and social functioning more than relaxation therapy [43].

Group Interpersonal Therapy (G-IPT) was evaluated in 13 patients diagnosed with chronic PTSD, in an 8-week treatment program, with favorable results [44]. The improvement was significant in social functioning, general wellbeing and depressive symptoms, and a moderate reduction in the avoidant symptom cluster of PTSD [44]. These positive effects were stable at 3 months and associated with perceived intra-therapy progress in solving problematic domains identified during IPT [44].

Present-Centered Therapy (PCT) for PTSD is a manualized psychotherapy originally designed as a treatment comparator in studies focused on the effectiveness of trauma-oriented CBT [45]. A systematic review of the randomized trials (n=12, N=1837 participants) states that moderate-quality evidence supports a superior efficacy of PCT in reducing PTSD severity compared to control conditions, and PCT was associated with lower drop-out rates comparative to trauma-focused CBT [45].

Stress inoculation training (SIT) is derived from CBT and proved itself efficient in veterans with PTSD [46]. According to this model, PTSD symptoms are maintained by an imbalance between perceived situational demands and perceived resources to fulfill the environmental and personal demands [47, 48]. The purpose of SIT is to increase the patient's feeling of self-confidence by helping him or her to control anxiety and related symptoms and to inoculate patients against possible future episodes of severe anxiety [48].

In a population with PTSD and traumatic brain injury (n=65 veterans), SIT was applied for 18 months in an outpatient clinic and the results supported the efficacy of this psychotherapy because significant reductions in PTSD and depressive symptoms were detected, as well as increases in perceived stress tolerance and performance in multiple life domains [46]. Improvements in social and occupational functioning were also reported [46].

In another trial, 96 female assault victims with chronic PTSD were randomized on prolonged exposure, SIT, combined prolonged exposure-SIT, or wait-list control [49]. All active treatments (9 twice-weekly individual sessions) decreased PTSD and depression symptoms compared to wait-list but did not differ significantly from each other, and these results persisted at follow-ups (3, 6, and 12 months) [49].

**GOOD CLINICAL PRACTICE RECOMMENDATIONS**

Therapeutic guidelines offer various and sometimes contradictory recommendations, therefore a critical analysis of the literature is granted to find common management strategies. While several guidelines are more cautious when

recommending pharmacotherapy [12] and support a psychotherapeutic-based approach especially in the first stage of the PTSD, others are more focused on drug therapy [13], and still, others consider the type of approach should be selected according to the individual variables, including patient's preference, availability, etc [14].

We formulated GRADE recommendations according to 4 levels: A= high quality, defined as the level to what future research are very unlikely to change the validity of these recommendations; B= moderate quality, meaning that future research is likely to have an important impact on the appreciation of the recommendations; C=low quality, which means that it is very likely that future research will have an important impact over the confidence in the estimate of effect and is likely to change the recommendations; D= very low quality, defined by the uncertainty of any estimate of the effect [4].

A wide range of psychotherapies have been studied for patients with PTSD, but CBT and related techniques (CPT, CT, PE), as well as EMDR, are the most evidence-based approaches [11-15]. We consider a GRADE level A for these therapies is granted, based on the existing evidence. Level B evidence exists for BEP, NET, IPT, PCT, and SIT [31-33, 39-49].

The same level of evidence exists for SSRIs and venlafaxine, as these are the most supported by evidence pharmacological agents in PTSD patients [12-15]. If the first-line agents fail, then second-line agents may be used-mirtazapine, MAO inhibitors or tricyclics, or add-ons like atypical antipsychotics (level B of evidence) [13].

A structured diagnostic approach is strongly encouraged and adequate instruments should be used. Structured interviews (e.g., Mini-International Neuropsychiatric Interview, Composite International Diagnostic Interview, or Schedules for Clinical Assessment in Neuropsychiatry) are considered useful because of the high comorbidity rate met in PTSD patients [50-52]. Because the evolution of PTSD is not linear, even under treatment, detection of new-onset psychiatric disorders is also important because of their high impact over the treatment plan. Therefore, using structured clinical interviews during the first 6-12 months of the treatment is also recommended.

Monitoring treatment efficacy in PTSD using standardized instruments is strongly encouraged. For this purpose, we recommend validated scales, inventories, or structured interviews, like the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), PTSD Symptom Scale Interview (PSS-I), Mississippi Scale for Combat-related PTSD (MISS) [53-55]. This is considered a good clinical practice because it may increase the objectivity of the psychiatric evaluation, although it is not specifically recommended in all the reviewed therapeutic guidelines.

We consider good clinical practice in the PTSD treatment to actively monitor the tolerability of the pharmacological treatment, to detect early adverse events that may decrease therapeutic adherence [56]. For this purpose, the administration of the Treatment Satisfaction Questionnaire for Medication (TSQM) [57] or a simpler visual analogic scale for self-evaluation is considered useful.

## CONCLUSIONS

A review of the existing therapeutic guidelines focused on PTSD management detected several common recommendations. These refer to the use of CBT and related therapies and EMDR as a first-line approach and SSRIs or venlafaxine as the main pharmacologic agents [1-5, 11]. Our team has added as good practice recommendations the necessity to use validated instruments for initial and follow-up diagnostic evaluations, as well as the monitoring of treatment tolerability and efficacy. Because of the high rate of comorbid disorders in PTSD patients, the case manager should be alert to new-onset psychiatric disorders that may appear as complications or just comorbidities in this population.

An integrated, psychological, and pharmacological approach should be considered for these patients, with frequent follow-up visits, and emergent disorders have to be integrated into the case management plan as soon as they are detected.

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