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Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future☆

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a serious psychiatric consequence of trauma that occurs in a proportion of individuals exposed to life-threatening events. Trauma-focused psychotherapy is often recommended as first choice for those who do not recover spontaneously. But many individuals require medications. In the US, only paroxetine (PRX) and sertraline (SRT) are FDA approved for PTSD. But response and remission rates with these medications are low, so numerous other pharmacologic interventions have been tried. To date, there has not been a systematic review of the data on what are the best next-step pharmacologic strategies for individuals who fail standard treatments. To that end, we review 168 published trials of medications other than PRX or SRT and provide a detailed analysis of the 88/168 studies that describe alternative pharmacologic interventions in patients refractory to other treatment. We also review clinical factors relevant to treatment-refractory PTSD; the neurobiology of extinction, as well as evidence-based psychotherapy and neuromodulation strategies for this condition.

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1. Introduction

More than half of the world's population experiences stressful events that would qualify for the "A Criterion" for a DSM-IV TR diagnosis (American Psychiatric Association, 2000) of posttraumatic stress disorder (PTSD) (McLaughlin et al., 2015). The lifetime prevalence of PTSD in the US is 6.8% (Kessler et al., 2005). Thus, trauma exposure, while necessary, is not sufficient for development of the disorder, and the modal long-term outcome is recovery. Solomon et al. (2012) found a 55% spontaneous remission rate 35 years after combat exposure in 349 Israeli military personnel who were initially diagnosed with PTSD an average of 18 years after trauma exposure. Rona et al. (2012) found a 39% spontaneous remission rate at 5 years among 9395 UK Iraq veterans in whom initial PTSD diagnosis was made at 12 months post-trauma. Most recently, Morina et al., (2014) conducted a meta-analysis of 42 studies of PTSD from a variety of traumata, and included only those in which patients were initially diagnosed using a standardized measure and re-assessed a minimum of 10 months afterward without receiving formal treatment in the interim. They found a mean recovery rate (no longer meeting criteria for PTSD diagnosis) of 44% at a mean 40 months after initial assessment. Among numerous clinical and demographic variables assessed, only two stood out as predicting remission: rates

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were higher in subjects who received initial assessment within 5 months post-trauma (51.7%) as opposed to >5 months after trauma (36.9%); and remission rates were lowest in those with PTSD related to physical illness (31.4%) and highest in those with PTSD related to natural disaster (60%). Interestingly, the authors found no studies on long-term spontaneous remission in individuals with PTSD due to childhood abuse; and did not include the only two studies found on combat PTSD, although those studies contributed to "war-related PTSD" which also included people who developed PTSD after exposure to war as non-combatants.

Overall, these results have at least two important implications for understanding treatment refractory PTSD, the focus of the present article. First, it must be said that the first step in considering treatment-refractoriness should be that sufficient time has elapsed for spontaneous recovery to occur—acknowledging that this involves personal patient efforts, choices, resiliency and a variety of non-clinical environmental factors. On the other hand, the spontaneous recovery rates also mean that 45–60% of individuals with PTSD do not recover spontaneously even many years after diagnosis. In fact, Morina et al. (2014) found that the rates of remission did not increase as duration of follow-up increased (range 10–204 months). Chronic PTSD is associated with less life satisfaction and happiness (Koenen et al., 2008), increased rates of major depression (Breslau et al., 2000), impaired family functioning (Riggs et al., 1998), marital problems (Cohen et al., 2009), occupational disability (Koenen et al., 2008; Alonso et al., 2011), substance use disorders (Mills et al., 2006), general medical illness and medical illness-related morbidity (Cohen et al., 2009) and suicide risk (Kang and Bullman, 2008; Panagioti et al., 2012) compared with the general population.

For these individuals, both psychotherapy and medication treatment can be effective, but even in specialized treatment centers, it has long been known that a substantial minority of individuals still fail to recover despite the best of treatments. One sobering study found a 17% mortality rate in 51 veterans over a 6-year follow-up period despite treatment at the National Center for PTSD in New Haven (Johnson et al., 2004). It is these patients we refer to as having treatment-refractory PTSD (TRPTSD). It has been more than 10 years since the last published review of the literature explicitly reviewing the topic of treatment-refractory PTSD (Hamner et al., 2004). Those authors concluded that because of the complexity of PTSD, including variations in symptom severity across symptom clusters, co-morbidity, and heterogeneity in treatment response based on trauma subtype, combination pharmacotherapy based on targeting individual symptom patterns should be considered for patients who fail an initial antidepressant trial. They noted the dearth of empirical evidence on specific treatments in patients who fail antidepressants, outlining several specific areas in which such research was merited. They noted the promise of trauma-focused psychotherapy as the likely treatment of choice, although they acknowledged the limited empirical data supporting the efficacy of trauma-focused psychotherapy in patients who failed a medication trial.

1.1. Definition of TRPTSD

The treatment literature in PTSD commonly states that as many as a third of patients with PTSD fail to respond to treatment. Despite this, there has to date been little attention paid to creating a framework for defining what might constitute TRPTSD, analogous to the concept of treatment-resistant depression (TRD) which has received relatively greater attention (eg Trevino et al., 2014).

Dunlop et al. (2014a) have published the most recent attempt to characterize TRPTSD: the Emory Treatment Resistance Interview for PTSD (E-TRIP). Focusing on receipt of pharmacologic or psychotherapeutic treatments with adequate randomized controlled trial (RCT) efficacy that have been tolerated by the patient and adhered to at a minimally effective dose and duration, this structured interview tool permits a numeric continuous measure description of the degree to which a given adult patient, at a given time, has failed to respond to treatments of proven efficacy. To date, only one citing article (Dunlop et al., 2014b) was found on our search. However, systematic use of this instrument could permit better future understanding in the research literature of efficacy of new treatments for TRPTSD, and in individual patients, decision making about alternative treatments for a clinician to recommend. The authors noted that limiting the E-TRIP to treatments of proven efficacy—i.e., receipt of treatments with at least one positive RCT involving ≥16 patients/arm and using validated outcome measures may underestimate the level of treatment resistance. They address this by suggesting that the E-TRIP can be periodically updated as new treatments accrue RCT data supporting efficacy. Another limitation of the E-TRIP addressed by the authors is that it fails to take into consideration the effect of pretreatment clinical variables on treatment resistance.

The E-TRIP (Dunlop et al., 2014a) assesses treatment response based solely on total symptom reduction in RCTs. While this provides a reliable standard for comparing patients with each other and assessing TRPTSD across time for individual patients, it overlooks two important aspects of PTSD that have substantial clinical utility and merit inclusion in a focused assessment of the meaning and nature of TRPTSD: 1) While it is has been validated that the definition of PTSD based on intrusive, avoidant and hyperarousal symptom clusters in DSM-IV corresponds to typical manifestations of the condition, treatments have variable impact on different symptom clusters; 2) PTSD response to treatment varies across trauma etiologies. In this respect, TRPTSD may differ from other treatment-refractory psychiatric disorders like TRD, since only in PTSD is a specific causative factor required for the diagnosis.

In their recent review comprising 51 trials of pharmacologic intervention in 13,634 subjects, Hoskins et al. (2015), for example, found SSRIs as a group, and paroxetine, fluoxetine and venlafaxine XR as individual agents, to be more effective than placebo for overall PTSD symptom reduction measured with subjective and/or objective rating scales. But they did not measure treatment effects by trauma subtype or individual symptom clusters. Meanwhile, in a recent meta-analysis of atypical antipsychotic trials in PTSD, Liu et al. (2014) found atypical antipsychotics > placebo for total Clinician Administered PTSD Rating Scale (CAPS; Blake et al., 1995) as well as recurrence (intrusion) and hyperarousal clusters, but NOT the avoidance/numbing cluster when given as monotherapy; and only for total CAPS but not any individual cluster when used as adjunctive therapy with antidepressants. For the subgroup of trials done in combat PTSD (the only trauma subtype with sufficient data to assess subtype response), atypical antipsychotics did better than placebo for overall symptoms, as well as the intrusive cluster, but were not better than placebo or either avoidance or hyperarousal symptoms. Thus an important issue for understanding and treating TRPTSD is assessing both overall symptom reduction and improvement on individual clusters.

Notably, the DSM-5 diagnostic criteria for PTSD (American Psychiatric Association, 2013) include a fourth cluster—negative alterations in cognition and mood–based on well replicated evidence that these clinical phenomena characterize patients with PTSD and are not well-represented in DSM-IV criteria (Friedman, 2013). Studies incorporating this symptom cluster in the assessment of PTSD relevant to treatment-refractoriness have not yet been published. No doubt, this will be relevant in a future review of this topic. On the other hand, most pharmacotherapy trials in PTSD include significant proportions of subjects who meet criteria for co-morbid major depression, and assess changes in depression severity as secondary outcomes. While a recent meta-analysis of 93 RCTs of PTSD treatment found that treatments effective for PTSD are also effective for improving co-morbid depressive symptoms with good correlation ($r = 0.56$) between the two (Ronconi et al., 2015), these changes may not serve as a proxy measure for the DSM-5 cluster D symptoms for at least the following reasons: 1) Only a variable proportion of subjects met diagnostic criteria for major depression in published studies; and 2) other aspects of the DSM-5 Cluster D criteria are not captured by depressive syndrome scales, particularly D1 and D3, and also to some extent D2 and D6.

Another issue not addressed with the E-TRIP of paramount importance in the care of patients with TRPTSD is that of functional outcome. While chronic PTSD is associated with tremendous negative impact on quality of life and social and occupational function, clinical experience