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Abstract

Purpose of review Posttraumatic stress disorder (PTSD) rarely occurs alone, with an approximate 80% syndromal comorbidity rate of which 50% is major depression. Evidence-based psychotherapy is the first-line treatment for PTSD and is very efficacious in some, but is directed toward PTSD symptomatology not depression, and many do not fully recover. This review presents the evidence for psychotherapy, pharmacotherapy, neurostimulation, and combinations of these modalities in treating PTSD with comorbid depression.
Recent findings Modifications to evidence-based psychotherapy for PTSD and comorbid depression can be made to involve comorbid traumatic brain injury and early childhood adversity, and although effective, some studies show such adaptations may not be necessary. Burgeoning neuromodulation research holds promise for possible additions to the current first-line treatment and new core treatment options.
Summary Cognitive processing therapy and prolonged exposure are the most cited effective treatments for PTSD; arguments for adding an antidepressant in cases of significant comorbid depression are supported by research. Treating PTSD first when comorbid with depression is supported by evidence that trauma-focused therapies reduce depressive

symptoms whereas depression-focused treatments do not show the same for comorbid PTSD. Future directions for study will involve new sequencing and combinations of current treatment modalities in addition to exploration of other factors including biomarkers, resiliency, and risk factors to inform novel treatment options for this population.

Introduction

Posttraumatic stress disorder (PTSD) is a complex syndrome involving pathological changes in arousal and cognitive schemas that impacts both veteran and civilian populations following trauma. In the USA, approximately 70% of the population have experienced a traumatic event at some point in their lives, with roughly 20% developing PTSD [1]. Comorbidity is considered the rule rather than the exception in PTSD with estimates of over 80% of patients with PTSD meeting criteria for at least one other syndromal psychiatric disorder [2]. Approximately 50% of adults with PTSD have comorbid depression [3]. This comorbidity results in increased morbidity and mortality for affected patients demonstrated in veterans with comorbid PTSD/MDD who were found to more likely be diagnosed with heart disease, migraines, fibromyalgia, and rheumatoid arthritis [4]. These veterans were also more likely to screen positive for suicidal ideation and were twice as likely to have a previous suicide attempt when compared with veterans with MDD only. Moreover, comorbid PTSD/MDD was associated with roughly a three-fold increase in disability compared with veterans with MDD alone [5]. Korean War veterans with comorbid depression and PTSD were found to have impaired life satisfaction, reduced quality of life, and greater severity of symptoms than those with either disorder alone, and this comorbidity was predicted by a more severe level of trauma exposure [6]. In a mostly civilian sample (2% had military-related trauma), Bedard-Gilligan et al. (2015) concurred that comorbid PTSD and depression resulted in more severe depression, dissociation, and social functioning. Within the comorbid group, a higher level of trauma exposure was predictive of worse outcomes and patients with comorbidity were more likely to have received inpatient psychiatric treatment [7].

Researchers have attempted to determine more about the interplay between depression and PTSD. Cluster classification has been examined; for example, Byllesby et al. (2017) determined the shared variance between depression and PTSD is accounted for by general distress and not by negative alterations in cognition and mood criteria [8]. Contractor et al. (2018) examined symptom clusters and reported for PTSD the dysphoric arousal cluster accounted for shared variance with somatic depression whereas negative affect, externalizing behaviors, and anhedonia clusters more strongly connected to the non-somatic subscale for depression [9]. It goes beyond the scope of the present review to further address the relationship between depression and PTSD. Several models exist: (1) a shared vulnerability model where depression may lead to vulnerability toward PTSD post trauma and PTSD may increase the probability of depression onset [3, 10]; (2) shared biological influences including genetics, epigenetics, and other biomarkers; (3) comorbidity existing due to symptom overlap between the two disorders; and (4) shared risk factors [11].

In this review, the major treatment options for comorbid PTSD and depression will be examined and categorized in terms of psychotherapy, pharmacotherapy, neurostimulation, and combination treatments. Variables affecting treatment outcomes and areas of future research and practice will be discussed.

Psychotherapy

According to recent treatment guidelines [12•, 13, 14], trauma-focused psychotherapy is the first-line treatment for PTSD in both civilian and military populations. Prolonged exposure (PE) and cognitive processing therapy (CPT) are

the most cited and rigorously studied [15•], with eye movement desensitization and reprocessing (EMDR) with more modest evidence of efficacy. These therapies reduce PTSD symptoms primarily by cognitive restructuring and emotional processing via exposures, which both serve to reduce avoidance. Studies have demonstrated that trauma-focused psychotherapies also confer secondary improvement in depression [16, 17]. As these therapies are designed to treat PTSD and not depression specifically, no meta-analyses exist that directly assess depression as a primary outcome measure in this population. Consequently, studies that show a reduction in depression are limited to patient self-report measures, such as the Patient Health Questionnaire (PHQ9) and the Beck Depression Inventory (BDI). It is paramount in future research on trauma-focused psychotherapies to begin to utilize clinician-measured tools to more accurately assess depression when comorbid with PTSD.

Cognitive processing therapy

Randomized clinical trials of PTSD and comorbid depression have demonstrated that CPT produced improvements with large effect sizes in both PTSD and depression [18, 19]. Bryan et al. (2016) reported that patients treated with CPT exhibited a significant reduction in suicide risk [20]. Walter et al. (2012) found participants with borderline personality disorder and PTSD had greater depressive symptoms compared with non-personality disordered participants prior to CPT and had a greater reduction in depressive symptoms than those without a personality disorder [21]. An Australian study validated the effectiveness of CPT in a veteran population demonstrating greater improvements in PTSD, depression, and substance use compared with those receiving treatment as usual [22].

Prolonged exposure

Prolonged exposure has been shown to be efficacious with large effect sizes both for the treatment of PTSD [23, 24] and for depression [24]. Foa et al. (1999) demonstrated PE had large effect sizes (ITT: 1.46 for the PSS-I, 1.42 for the BDI; for the completers:1.92, 1.47, respectively) when compared with stress inoculation training (SIT), PE-SIT, and wait list conditions [25]. McLean et al. (2017) studied 61 female adolescents using the Child PTSD symptom scale and the BDI and compared PE with Client-Centered Therapy (CCT). Both treatment arms lead to significant improvement in PTSD symptoms with PE showing greater improvements in PTSD, functioning, and depression over CCT. Significant reductions in PTSD symptom severity were associated with greater reductions in depressive symptoms than vice versa [26]. This finding aligns with a prior study of adults treated with PE where PTSD symptom reduction accounted for 80% of depression symptom reduction, whereas depression symptom reduction accounted only for 45% of PTSD symptom reduction [27].

Eye movement desensitization and reprocessing

A recent meta-analysis [28] demonstrated moderate effect sizes for EMDR in the treatment of PTSD and depression and large effect sizes for subjective distress based on the SUD instrument. Studies with EMDR therapists experienced in group PTSD treatment and where sessions lasted longer than 60 min

demonstrated better outcomes.

Psychotherapies: head to head comparisons

Resick et al. (2002) compared CPT directly with PE and reported that both significantly reduced PTSD symptoms relative to wait list; CPT showed significantly greater improvements in guilt-related cognitions [29]. CPT has been shown to improve other depressive symptoms such as suicidal ideation and hopelessness in comparison with PE [30, 31].

Jayawickreme et al. (2014) pooled data from 4 RTCs of evidence-based psychotherapy for PTSD (PE, CPT + A (CPT version with a trauma account), EMDR, and a wait list condition), using a relatively homogenous sample of female assault victims, and reported that all of the active treatments reduced PTSD and depressive symptoms. Worsening of symptoms was absent for active treatment participants in terms of PTSD and very low in terms of depression, significantly lower than that of wait list participants. Clinician-administered measures (CAPS and PSS-I) were used to measure PTSD symptom severity and BDI was used for depressive symptoms [32].

Novel psychotherapy

Virtual reality exposure

In a recent review, limited by studies with small sample sizes and pilot data, virtual reality demonstrated a reduction in PTSD and depressive symptoms with medium effect sizes in contrast to large effect sizes for the most evidence-based manualized treatments for PTSD [33]. Suggested advantages to virtual reality exposure (VRE) include being more palatable to a more technically savvy population, objective data about what patients are exposed to in treatment (not reliant on patient imagination), and it allows for pacing by the clinician in terms of exposure and the ability of patients to avoid aspects of their trauma [34]. For more information on VRE digital interventions for PTSD, please see the article by Kuhn and Owen in this issue.

Psychotherapy summary

The most evidence-based trauma-focused psychotherapies (PE, CPT, EMDR) all have been shown to reduce comorbid depression with VRE to a lesser, but still significant, degree.

Pharmacotherapy

Implementation of effective pharmacotherapy in patients with PTSD and depression can be challenging given the plethora of options and relatively modest impact of these agents on symptoms of PTSD. Of the pharmacological classes, only the SSRIs sertraline and paroxetine have been FDA approved for the treatment of PTSD in addition to depression. Several large meta-analyses investigating the effect of pharmacotherapies for PTSD have consistently demonstrated superiority of SSRIs, namely paroxetine and fluoxetine, and the SNRI venlafaxine over placebo for the treatment of PTSD with concurrent improvements in depressive symptoms evaluated as a

secondary outcome measure (standardized mean difference – 0.23, 95% CI – 0.33 to – 0.12) [35]. Aripiprazole, divalproex, guanfacine, and olanzapine are no more effective than placebo when combined with an antidepressant for symptomatic treatment of PTSD [36]. Sertraline has also been found to improve symptoms of PTSD and depression; however, other studies have found no difference between sertraline vs. placebo for symptoms of PTSD [35, 37, 38]. Small RCTs examining quetiapine and mirtazapine monotherapy for treatment of PTSD found significant improvements in CAPS (Clinician Administered PTSD Scale) and Hamilton Depression Scale [37, 39]. Puetz et al. (2015) evaluated predominantly male combat veterans with depression/PTSD comorbidity and found a significantly greater benefit for both SSRIs and TCAs for PTSD symptoms and a significant improvement in depressive symptoms compared with other medications for up to approximately 14 weeks, after which time observed differences between TCAs/SSRIs and other medications (mood stabilizers, antipsychotics, or antihypertensives) were no longer significant [40].

Alternative pharmacotherapy options

Ketamine

With the recent FDA approval of intranasal esketamine for treatment-resistant depression (TRD), we anticipate the use of the agent to increase in the general population including those with comorbid PTSD and depression. Intravenously administered ketamine has been previously investigated in the treatment of PTSD with observed superiority in trauma and depressive symptom reduction when compared with active-control (midazolam, $n = 41$). However, these results were obtained no later than at a 2-week follow-up and meaningful clinical significance should be interpreted with caution [41]. Ketamine has also been reported to reduce hospital admission duration by 70% in patients with comorbid PTSD and depression [42]. Further studies are needed to investigate the durability of symptom improvement and examine side effect burden. Given these limitations, current support for indefinite treatment with ketamine/esketamine in patients with PTSD/depression comorbidity remains unclear [43].

3,4-Methylenedioxymethamphetamine

3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treatment of PTSD is currently in phase 3 clinical trials following compelling phase 2 trial data ($n = 72$) showing significantly greater reductions in trauma symptoms via CAPS-IV (– 22, $P < 0.001$, Cohen's d effect size 0.8) and reductions in depressive symptoms via BDI-II (– 6.0, $P = 0.053$) following 3 treatments with MDMA and 12 MDMA-specific manual based psychotherapy sessions focusing on trauma, relaxation, and reflective integration before, during, and following MDMA treatment [44, 45•]. Although the results of this study are promising, they are limited by a relatively small sample size and challenges in participant blinding. Ongoing phase 3 trials investigating MDMA for PTSD will help provide further clarity regarding the therapeutic potential of this treatment.

Other medications

Medications found to not improve symptoms of PTSD or depression include benzodiazepines and cannabis. These compounds can perpetuate avoidance and potentially worsen symptoms of anxiety associated with PTSD [46, 47].

Although several aforementioned agents have the potential for therapeutic benefit, pharmacological therapies in the treatment of PTSD and depression are overall limited in variety and efficacy. It is important to recognize recommendations for trauma-focused psychotherapy as a first-line intervention cited in major treatment guidelines when creating individualized treatment plans for patients [12•, 13, 14]. In cases of concerning comorbid depression and PTSD, we recommend considering incorporation of an SSRI or the SNRI venlafaxine over a TCA given the improved tolerability and reduced lethality in overdose. Realistic expectations regarding the moderate impact of these agents should be communicated to patients emphasizing the potential for symptom reduction but not for symptom remission, especially in terms of PTSD. Furthermore, critically evaluating side effect burden relative to symptomatic improvement and minimizing polypharmacy can help guide clinicians in selecting appropriate pharmacotherapy regimens for patients.

Pharmacotherapy summary

When considering effect size and side effect burden, antidepressants, namely paroxetine, fluoxetine, and venlafaxine, have demonstrated the greatest impact for patients with comorbid PTSD and depression. Preliminary data for MDMA is compelling and supports further consideration and research into its potential role in treating patients with comorbidity.

Improvements in depressive symptoms with psychotherapy or medication

Ronconi et al. (2015) completed a meta-analysis of depressive symptom outcomes in RCTs for PTSD including those using medication or psychotherapy. Ninety-three studies with depressive symptom outcomes were examined; all effective treatments for PTSD were also effective for depression. Direct comparisons were less accurate due to the nature of differences in trials involving medications vs. psychotherapies; however, most treatments had overlapping 95% confidence intervals evidencing they were not significantly different. In the treatment of depressive symptoms, paroxetine had the greatest effect size (1.18; 95% CI, 0.4–2.04), next was CPT (1.12; 95% CI, 0.53–1.7), followed by PE (0.92; 95% CI, 0.64–1.19), and then EMDR (0.92; 95% CI, 0.43–1.42) [48•]. See Fig. 1 for details.

Combined treatments: psychotherapy with pharmacotherapy or neurostimulation

Combination treatments of trauma-focused psychotherapy administered in conjunction with medications or neurostimulation for treatment of PTSD have become popular not only in research but also in clinical practice. Kozel and colleagues found veterans ($n = 103$) who received rTMS compared with sham in
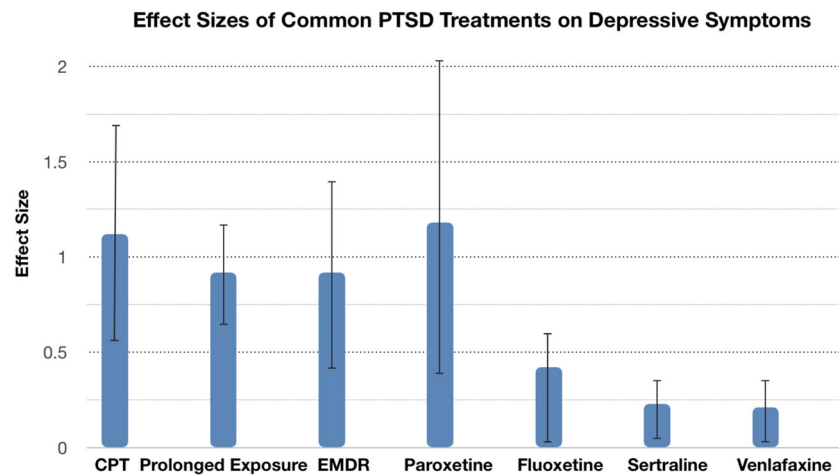
Effect Sizes of Common PTSD Treatments on Depressive Symptoms

Fig. 1. Comparison of depressive symptoms effect size for treatments known to be effective for PTSD. Adapted from Ronconi et al. [48•].

addition to cognitive-based trauma-focused therapy had significant improvement in trauma symptoms measured by CAPS and PCL scores (≤ -2.01, $p \leq 0.023$; ≤ -2.14, $p \leq 0.017$, respectively), with differences occurring early in treatment with a sustained posttreatment effect observed at 6 months. Improvements in depressive symptoms, measured via the QIDs, were observed in sham+CPT and rTMS+CPT groups [49]. Investigations exploring exposure-based therapies with neurostimulation targeting fear-processing centers show promise in their potential for reducing intrusive and hyperarousal symptoms of PTSD; however, improvements in depressive symptoms have not been demonstrated [50, 51]. Future larger scale studies are needed to further substantiate these findings.

Studies evaluating the effect of combining medication (SSRIs) and psychotherapy for the treatment of PTSD are limited in quantity and vary in design. Rauch et al. (2019) evaluated the effect of sertraline with and without prolonged exposure ($n = 149$), and found no difference in the change of combat-related PTSD symptoms at 24 weeks between exposure therapy plus sertraline, sertraline plus enhanced medication management, or exposure therapy plus placebo [38]. A Cochrane review evaluating combined medication and psychotherapy for treatment of PTSD found no strong evidence to show a significant difference between combination and single-intervention groups [52]. While these findings do not unequivocally support the use of antidepressants in combination with psychotherapy for PTSD, the evidence in favor of combined treatment improving outcomes in patients with comorbid PTSD/depression, and evidence supporting improvements in depressive symptoms of patients with PTSD treated with SSRIs (namely, paroxetine), favors the use of combination treatment for patients with PTSD/depression comorbidity when clinically appropriate [53, 54].

Neurostimulation treatments

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is known to be an effective treatment for patients with unipolar depression and is becoming increasingly researched

as an intervention for patients with refractory PTSD. Utilizing a known side effect of ECT (effects on memory consolidation), investigators have evaluated the plasticity of memory permanence positing that, via memory reactivation and treatment with ECT, memory traces resume a more fluid state susceptible to disruption. This recent study tasked 42 depressed patients to learn two emotionally aversive visually aided stories, then 1 week later recall details of one story, after being prompted via an incomplete visual aid from that story prior to receiving ECT or sham treatment. The treatment group demonstrated alterations in episodic emotional reconsolidation at 24 h only in the specific story triggered before the stimulation, indicating reactivated emotional memories may be specifically sensitive to disruption [55].

Research investigating outcomes for patients with comorbid PTSD and depression treated with ECT is more robust than in other areas of neurostimulation. Multiple retrospective analyses examining the impact of ECT in patients with comorbidity have demonstrated reductions in depressive symptoms independent of PTSD symptoms, and reduction of PTSD symptoms independent of depressive symptoms [56–58]. In the largest retrospective case-controlled study identified examining the efficacy of ECT on PTSD and depression comorbidity ($N = 22{,}164$; $n = 3485$ with comorbid MDD and PTSD $n = 18{,}679$ without MDD and PTSD, $n = 92$ with ECT, $n = 3393$ without ECT), ECT was associated with a reduction in both depressive and PTSD symptoms, with the latter improving independent of depressive symptoms. Researchers also found a reduction in suicidality as well as cardiovascular and all-cause mortality in patients with PTSD [59]. This research highlights the benefit ECT can provide patients with comorbid depression and PTSD and contributes to the growing evidence supporting its use in patients with refractory PTSD. For more information regarding treatment options for patients with refractory PTSD, please see " Predicting and Managing Treatment Non-response in Posttraumatic Stress Disorder" by Fonzo et al. in this issue.

Repetitive transcranial magnetic stimulation

In the treatment of major depression, the FDA-approved repetitive transcranial magnetic stimulation (rTMS) has become increasingly investigated for the treatment of PTSD as well as comorbid PTSD and depression with positive sham-control emerging in the literature. Generalizability of these results is limited by undefined and non-unified pulse sequence protocols, variability in selection of neuroanatomical stimulation zones, and small sample sizes [60]. In veteran populations where placebo response rates tend to be high, observed effect sizes of rTMS diminish. A recent multisite study investigating rTMS for US military veterans with treatment-resistant depression ($n = 164$) found an overall remission rate of 40% with no significant difference between sham and active groups [61]. Those with MDD and comorbid PTSD had significantly lower rates of remission to both sham and rTMS treatment groups when compared with patients with MDD alone. Although this study was conducted with only male veterans with depression, it does reflect the challenges posed in interpretation of efficacy data in the context of high placebo response rates. Other

investigations in civilian populations have found rTMS superior to sham for comorbid PTSD and depression; however, sample sizes in these studies remain small [62].

When comparing rTMS trials, improvements in depression and PTSD symptoms are observed in patients receiving inhibitory or excitatory stimulation (1 Hz, vs. 5–20 Hz, respectively), indicating symptom improvement may be independent of stimulation intensity [63], and although the dorsolateral-prefrontal cortex (DLPFC) has been the primary stimulation target in the majority of PTSD/depression investigations, preferred laterality of stimulation has remained debated with a recent meta-analysis indicating a potential for right-sided superiority [64]. Evolving research exploring stimulation of other neuroanatomical regions, namely the medial prefrontal cortex, has also shown positive results indicating the need for further research exploring the therapeutic utility of this neuroanatomical region [65].

When exposed to PTSD-related script-driven imagery or shown fearful stimuli, patients with PTSD demonstrate an increased amygdala response [66]. Following rTMS treatment administered to the right DLPFC, patients with PTSD exhibited a reduction in amygdala activation after exposure to threatening stimuli [67]. A potential mechanistic explanation for the improvements observed in rTMS involves increasing metaplasticity and altering the thresholds required for inducing future synaptic changes with greater prefrontal cortex functionality and altered connectivity with deeper limbic structures [49, 68, 69]. For patients with comorbid depression and PTSD, rTMS has shown largely positive results and future trials investigating circuitry and implementing standardized protocols will continue to help guide clinicians in interpreting results and utilizing rTMS.

Intermittent theta burst transcranial magnetic stimulation

Intermittent theta burst transcranial magnetic stimulation (iTBS), a form of TMS which utilizes short bursts of high-frequency (50-Hz) stimulation repeated at 5 Hz (200 ms), has been investigated for the treatment of PTSD with comorbid depression [70]. iTBS offers advantages over traditional rTMS treatments allowing for shorter duration treatments (5 min vs. 30 min); and based on results from a recent sham-controlled trial of 50 veterans, iTBS demonstrated improvements at 2-week and 1-month follow-up assessments in social-occupational functioning and depression [70].

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS), not currently FDA approved, has been investigated for the treatment of depression and PTSD. A recent randomized sham-control trial for tDCS in patients with PTSD found improvements in cognitive and hyper-arousal symptoms, as well as improvements in depressive and anxiety symptoms after 10 sessions of bilateral DLPFC tCDS delivered at 2 mA [71]. Another recent study examining tDCS with virtual reality ($n = 12$) found reduction in physiological arousal and improvement in PTSD symptoms; depression symptoms were not assessed [51]. TDCS studies for PTSD are similarly limited by small sample size, impacting generalizability, but do offer a framework for the feasibility and potential therapeutic benefit of tDCS treatments in the future.

Deep brain stimulation

Deep brain stimulation (DBS) has been investigated for both treatment-resistant depression and PTSD independently in small case series demonstrating variable effects. No studies exist examining treatment in patients with comorbidity and at this time there is insufficient data to recommend this treatment [72, 73].

Neurostimulation summary

ECT has demonstrated reductions in symptoms of PTSD and depression, and suicidal ideation, and reductions in cardiovascular and all-cause mortality in patients with PTSD. Other forms of neurostimulation like rTMS have compelling evidence for treating patients with comorbidity; however, rTMS protocols are still diverse and require further investigation and standardization.

Variables affecting treatment response

Length of treatments

Due to practical life barriers such as parenting, educational, and employment time burdens, quick re-deployment cycles, and high dropout rates from treatment in general, investigations of condensed time courses for PTSD evidence-based treatments are underway. In a retrospective data analysis, Gutner et al. (2016) concluded that session frequency of CPT moderated PTSD outcomes, suggesting that closer spacing of sessions yielded better results [74]. In terms of reducing comorbid depression in particular, Bryan et al. (2018) in an expedited CPT trial where CPT was performed over a 2-week period demonstrated significant reduction of PTSD symptoms and improved suicidality, but with no significant improvement in depression [75]. The results may suggest that length of time of trauma-focused psychotherapy may predict secondary benefit in depression outcomes. Foa et al. (2018) examined active duty military with massed PE (10 sessions over 2 weeks) vs. spaced PE (10 sessions over 8 weeks) vs. present-centered therapy (PCC) over 8 weeks vs. a minimal contact control (MCC) and found massed PE decreased PTSD symptoms more than MCC and was noninferior to spaced PE which was equivalent to PCT. The reductions in PTSD symptoms for all treatments were modest, so further research is needed to determine effectiveness of massed PE in this active duty population; depression change was not reported in this sample [76].

Veteran vs. civilian

Some evidence exists that civilians respond better to evidence-based PTSD therapies [37, 77]. In a community-based sample, Dillon et al. (2019) demonstrated that military patients undergoing CPT showed significant improvements in both PTSD and depressive symptoms, but improved less when compared with civilians [78]. Gobin et al. (2018) studied differences in outcomes using CPT in female veterans and civilians with similar baseline PTSD symptoms. Veterans had less reduction in CAPS posttreatment linked to higher pre-treatment posttraumatic cognitions and lower treatment expectations among the veteran sample [79]. Psychologically, combat veterans in particular may be reluctant to give up hypervigilance that is ingrained in warrior training and needed for survival in the field. In contrast to feeling detached from others post

trauma, the team unity of combat may reduce one's willingness to be rid of combat memories [80]. As it is posited that a reduction in PTSD symptoms leads to a reduction in depressive symptoms, if veterans show less improvement in PTSD symptoms, similarly, they may have more treatment-resistant depressive symptoms. Further research is needed to clarify these outcomes and to help more clearly define risk factors that could be associated with differential treatment outcomes between these populations.

Traumatic brain injury

Particularly in the military, the role of traumatic brain injuries (TBIs) affecting treatment outcome has been a focus largely in part due to the increase in TBIs in this population. The Department of Defense numbers for TBI worldwide between 2000 and 2018 reached 383,947 [81]. Comorbid PTSD and TBI occurs in approximately 42–73% of Iraq/Afghanistan era veterans [82–84]. Several studies have examined the effectiveness of CPT or PE for PTSD and comorbid TBI. Chard et al.(2011) demonstrated CPT reduced PTSD symptoms in veterans with mild to moderate TBI in a residential program [85]. Jak et al. (2019) found components of compensatory cognitive training from Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) combined with CPT (SMART-CPT) resulted in clinically significant reductions in post-concussive symptoms and PTSD symptoms similar to that of CPT alone in veterans with comorbid PTSD and mild to moderate TBI. SMART-CPT additionally improved attention/working memory, novel problem solving, and verbal learning over CPT alone [86]. A more recent study by Crocker et al. (2019) examined CPT and SMART-CPT and five TBI injury variables of lifetime TBI, time since injury, loss of consciousness (LOC) or not, posttraumatic amnesia or not, and blast or other type of injury, and found that no injury component predicted dropouts or moderated outcomes in terms of PTSD or depressive symptom improvement. Veterans showed a clinically significant decrease in PTSD symptoms and a significant decrease in depressive symptoms, and if there was no LOC, greater reductions in PTSD and depression were found in the CPT vs. SMART-CPT, implying that TBI without LOC may not need added treatment components [82]. A significant reduction in PTSD symptoms in veterans with mild to moderate TBI treated with PE was reported by Wolf et al. (2012) when minor modifications to PE such as behavioral memory enhancers of calendars and smartphones, increasing structure, and increasing session time for cognitive deficits were added [87]. Wolf et al. (2015) demonstrated that neither TBI severity nor inpatient vs. outpatient status affected treatment response to PE. Moreover, more severe TBI patients had a more rapid reduction in PTSD and depressive symptoms [88]. Ragsdale et al. (2016) reported positive treatment outcomes for PTSD using CPT or PE were not prevented by the presence of TBI in a veteran sample [89].

Early childhood trauma

It is well established that childhood trauma confers increased risk for major psychiatric disorders. In a meta-analysis, Nanni et al. (2012) concluded that childhood trauma confers poorer remission and response rates to psychotherapy, pharmacotherapy, and their combination in patients with major depression [90]. In studies of adult soldiers, exposure to childhood adversity was

associated with an increased risk of PTSD and depression in adulthood [91••, 92, 93]. Many in the field feel that phase-based treatment with stabilization before trauma-focused therapy is necessary for complex trauma. Others argue that delaying evidence-based trauma-focused therapy prolongs what could be more immediate benefit. Cloitre et al. (2017) found childhood abuse survivors with severe depression and PTSD had the most significant reductions and long-lasting effects in both disorders when Skills Training in Affect and Interpersonal Regulation (STAIR) and Narrative Therapy (a version of prolonged exposure) were combined compared with either modality paired with supportive counseling [94]. Rosner et al. (2019) found developmentally adaptive CPT, with additions for motivation enhancement, emotion regulation, and developmental tasks, was more effective in reducing PTSD and depression than a waitlist condition for adolescents with abuse histories. Interestingly, in the motivation and emotional regulation portions, outcomes did not differ from waitlist. The CPT portion came afterwards which was where the marked improvement occurred, bringing into question the notion that a stabilization phase is needed in this population [95]. In a meta-analysis by Ehring et al. (2014) of 16 RCTs, trauma-focused treatments were more efficacious than non-trauma-focused in adult survivors of childhood abuse in terms of symptoms of PTSD, anxiety, depression, and dissociation [96]. Chen et al. (2018), based on a systematic review limited by small samples, showed EMDR successfully treated PTSD and depression in adults and children with childhood trauma [97]. If childhood trauma occurs in particular sensitive periods in development, it is postulated to have a more detrimental impact on functioning. Wagenmans et al. (2018) stratified patients into childhood sexual abuse (CSA), adolescent sexual abuse, sexual abuse after 18, and no sexual abuse, and found all groups improved equally well with EMDR and PE without a stabilization phase; however, CSA patients may need more sessions to reach the same level of improvement [98]. This finding aligns with prior studies that demonstrated that patients with and without a history of CSA respond well to trauma-focused treatments [99, 100]. Even if PTSD and depression can be successfully treated with PE, CPT, or EMDR, the long-term effects of childhood maltreatment in terms of inflammation, neuroendocrine axis activity, the interactions between genetic polymorphism and vulnerability, and attachment and relational skills cannot be ignored, especially for those who do not respond to evidence-based treatments or for those who need sequential psychotherapy to address residual, non-PTSD symptoms.

Conclusion

Although the literature is rich with data demonstrating that evidence-based psychotherapies are effective for many patients with PTSD, there are still too many patients who are non-responders, and many responders have significant residual symptoms. Insomnia and hyperarousal, including irritability and difficulty with focus and concentration, are two of the most common residual PTSD symptoms which are also often components of depression [101, 102]. The combination of medication with these therapies in treating PTSD is minimally additive, but may be more effective in reducing comorbid depression. Logically, if one is no longer burdened by PTSD symptoms, hopefulness and

general life outlook may improve even with comorbid depression. As research demonstrates a reduction in depression with trauma-focused therapies and no such reduction in PTSD has been shown in depression-only–focused therapies, treating PTSD first and evaluating for residual depression is a reasonable approach. As we wait for further research to continue to aid in defining optimal treatment choices for individual patients, attention should be paid to other comorbidities including substance abuse and psychosis. Unavailability of first-line psychotherapy may dictate other treatment options; therefore, educating patients so they can participate in shared decision making and ultimately feel in control of choosing their own treatment is paramount. Due to length constraints, the growing advances in research involving epigenetics, genomics, and brain imaging findings poised to advance novel treatment and prevention approaches in the future were not reviewed here. The next phase of treatment improvements for comorbid PTSD and depression will likely involve exploring novel combinations and sequencing of treatment modalities with more personalized medicine approaches based on individual genetic and environmental predispositions or vulnerabilities.

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Papers of particular interest, published recently, have been highlighted as:
- •   Of importance
- ••   Of major importance

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