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Decreasing Suicidal Risks among Military Veterans with Posttraumatic Stress Disorder or Major Depression

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Decreasing Suicidal Risks among Military Veterans with Posttraumatic Stress Disorder or Major
Depression

by

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Abstract

Suicide is a major cause of death in the United States. Some populations, such as the veterans and active duty military personnel are at a higher risk of committing suicide compared to the general population. The risk is exacerbated by mental health conditions such as Posttraumatic Stress Disorder (PTSD) and major depression. Few reviews have explored the effects of the recommended psychotherapeutic interventions on suicidal ideations and suicide rates for these two disorders, focusing on the veteran population. To address this, a literature search was performed using a comprehensive search through electronic databases, applying the search criteria and keywords aimed at identifying appropriate journal articles. Treatment with CPT and PE for PTSD has been found effective in decreasing suicidal thoughts, intents, and attempts. On the other hand, CBT has been found effective in decreasing suicidal thoughts among veterans with various symptoms of depression. Given that the recommended PTSD and depression treatment can have the additional benefit of decreasing the risk of suicide, it is important for clinicians to always assess the risk of suicide for veterans diagnosed with these conditions. Future research should seek to explain the mechanism by which the explored psychotherapeutic interventions decrease suicidal thoughts, intents, and attempts in patients with PTSD or depression to address the inconsistencies in the present body of evidence.

INTRODUCTION AND BACKGROUND

Suicide is a serious public health problem and a major cause of mortality in the United States (U.S). According to the Centers for Disease Control and Prevention (CDC), about 48,000 deaths in 2018 were attributable to suicide, meaning that at least one person was committing suicide every 11 minutes in the U.S (CDC, 2020). The high incidences of suicide make it one of the top ten mortality causes in the U.S. Each year, many people contemplate or attempt suicide than they die by suicide. For instance, in 2018, about 10.7 million American adults seriously contemplated committing suicide, with 3.3 million making a plan and 1.4 million attempting suicide (CDC, 2020). A previous study by the National Comorbidity Survey follow-up revealed that 6.2% of the initial sample developed suicidal ideations. An additional 21% of the individuals who experienced suicidal ideations developed a suicide plan, with 15% making a suicide attempt (Husky et al., 2012).

Military service members or veterans are at an increased risk of committing suicide. For example, suicide rates among active service members in 2008 exceeded those of the general population for the first time (Nock et al., 2013). In spite of the heightened suicide prevention efforts by the Department of Veterans Affairs, rates of suicide among military personnel have remained elevated in the past few years. Suicide rates are still high among veterans, with an average of 20 deaths per day being recorded as a result of suicide (Office of Suicide Prevention, 2016). The data highlights the need to assess the effectiveness of existing treatment in decreasing suicidal ideations and suicide rates among service members. Timely intervention has been found effective in decreasing suicidal behaviors and can potentially result in more positive outcomes (Gradus et al., 2013).

Taking into account the high incidence of suicide rates, it is imperative to address the risk factors for committing suicide. A number of past studies have revealed that PTSD is a major risk factor for committing suicide. In a study by the National Comorbidity Survey, respondents with the condition had an adjusted odds ratio of 5.1 for suicidal ideations and odds ratio of 6 for suicidal attempts in comparison to those without PTSD (Pan et al., 2013). Likewise, Gradus et al. (2013) revealed 56% of the participants with PTSD reported suicidal ideations, suicide attempts,

and had developed suicide plans upon being exposed to trauma (Gradus et al., 2013). In the Canadian study by Sareen (2014), individuals with PTSD were 2.4 times more likely to attempt suicide compared to those without PTSD.

The risk factors are more common in certain populations. For instance, service members experience a high risk of suicide about 14% of the population reporting suicidal ideations, a well-known risk factor for committing suicide (Smith et al., 2016). A further associate of suicidal ideation is PTSD, which is common among military service members. Indeed, past studies have revealed that a diagnosis of PTSD among service members increases the risk of developing suicidal ideations by four times (Stayton et al., 2019).

Past studies have revealed a relationship between the onset of PTSD symptoms and suicidal behavior among military service members of all service eras (Stayton et al., 2019). A promising mechanism of action that has been offered for this relationship is depression symptoms, which usually coincide with PTSD and are among the recognized predictors of suicidal behaviors. Additional research has depicted that depression symptoms and PTSD have a synergistic impact on suicidal behaviors and intent such that the risk of committing suicide increases when the two conditions co-occur. A second mechanism that has been proposed between PTSD and suicidality is hopelessness, a major feature of PTSD and depression and a steady predictor of suicidal behavior (Smith et al., 2020).

A major empirical question is whether the treatment of PTSD and depression symptoms results in reductions in suicidal thoughts. In a study regarding PTSD and suicidal behaviors, Nock et al. (2013) noted that cognitive behavior therapy has the potential for decreasing the suicide risk in PTSD and depression patients. Information regarding the effects of PTSD treatment on suicidality could contribute to the existing body of knowledge regarding mechanisms of the relationship and would potentially have huge implications for the management of people with suicidal ideations among traumatized or depressed populations (Stayton et al., 2019). Moreover, reviews on the impact of trauma-focused PTSD treatment on suicidal ideations are lacking. Studies exploring the impact of psychotic interventions among veterans with PTSD or depression are limited; hence treatment recommendations remain speculative. The present study seeks to fill

the literature gap by investigating changes in suicidal ideations among veterans receiving psychotherapy in the form of cognitive processing therapy, cognitive behavioral therapy, and prolonged exposure.

Statement of the Problem

Rates of suicide among active service duty members have increased significantly, surpassing those of civilians in the past decade (Bryan et al., 2016; Office of Suicide Prevention, 2016). The high rates of suicide have persisted in spite of the various measures introduced to decrease suicide rates among active duty personnel. According to the Department of Veterans Affairs (2017), the risk of committing suicide is 22% higher among civilians upon controlling for age and gender. Depression and PTSD have been identified as prevalent conditions among veterans and have been recognized as the leading risk factors for suicide. Further research is needed to improve the current understanding of the effectiveness of various psychotherapeutic interventions in decreasing suicide rates among veterans.

Research Question

In veterans with PTSD or depression is CBT, or cognitive processing therapy more efficacious in reducing suicide rate and suicidal ideations?

RESEARCH METHODS

A literature search was conducted across various electronic databases including CINAHL, Embase, PubMed, Cochrane Library, and Scopus in an attempt to identify published data regarding psychotherapeutic techniques in addressing suicide behaviors among veterans with depression, and or PTSD. Key terms used in the search process included “Posttraumatic stress disorder, depression, treatment, suicide deaths, suicidal ideations, suicide, cognitive behavioral therapy, cognitive processing therapy, military personnel, veterans, active duty military, and prolonged exposure.” The initial search frame of articles published within the past five years yielded a limited amount of data. It was consequently expanded to accommodate articles published within the past ten years.

Eligible studies included those evaluating the effectiveness of psychotherapeutic interventions in decreasing suicidal rates and ideations among veterans with PTSD and or

depression. Suicidal ideations are the thoughts regarding taking action to end one's life while suicide attempt refers to the self-inflicted potentially injurious behaviors with non-fatal outcomes but with the intention of ending one's life (Gould et al., 2015; Stayton et al., 2019). The search was limited to papers available in English language due to the lack of translation capacity. Exclusion criteria included studies not involving veterans, those not available in English language, and those published before 2010. Editorials, opinion essays, and periodicals, and dissertations were not eligible. The focus of the review was on identifying peer reviewed journal articles (Table 1).

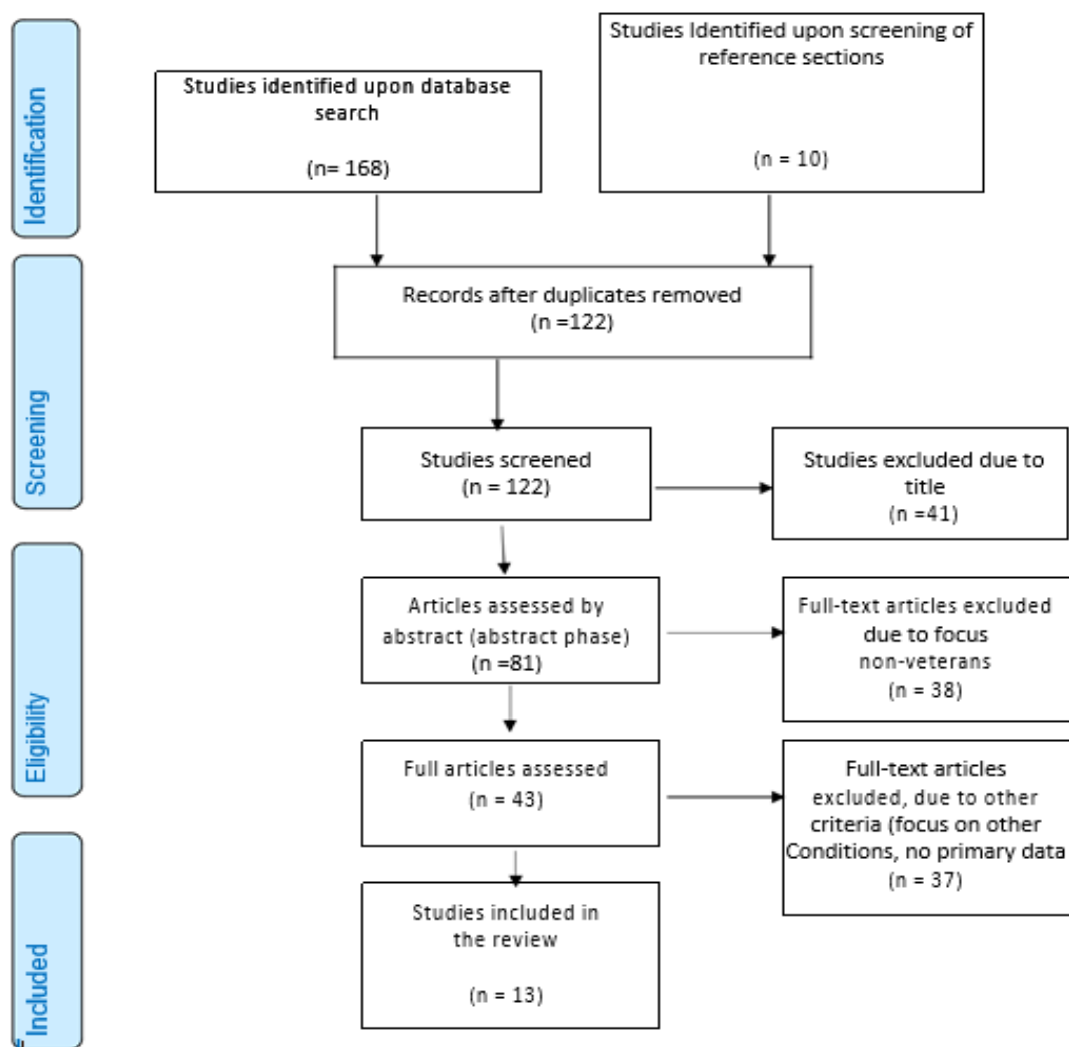
Table 1. Inclusion and exclusion criteria

Inclusion criteria	Primary research studies Studies involving active military service members or veterans Suicide rates, PTSD, Depression
Limiters	Available in full text Peer reviewed Available in English language Published within the past ten years
Exclusion criteria	Editorials, opinion essays, and periodicals, and dissertations Studies not involving military personnel

Advanced literature search techniques were used. Footnote chasing technique was applied in screening for the referencing sections of the included articles to identify other eligible and appropriate articles. Boolean operates (AND, OR) and truncation techniques were applied to broaden the literature search process or narrow it depending on the outcomes obtained. The application of the criteria led to the identification of 168 studies (Figure 1). The articles were evaluated for duplicate articles and quality of the research methods. Relevant data, including psychiatric diagnoses, main results, psychotherapeutic strategy, methods used, and sample size, were extracted and summarized in a tabular layout.

In searching for the relevant articles, a total of 168 studies were identified relating to psychotherapeutic interventions aimed at decreasing suicidal ideations and suicide rates among military service members. All the articles were published between 2010 and 2020 and the studies were conducted in the U.S. A total of 13 articles remained upon applying the inclusion and exclusion criteria and removing duplicates. Six articles were retrieved from PubMed, three from Cochrane Library, one from CINAHL, two from EMBASE, and one from Scopus. Interventions of interest included cognitive processing therapy, cognitive behavioral therapy, and prolonged exposure therapy. Study designs employed in the included studies include randomized controlled trials, non-randomized experimental studies, and cohort studies. The articles are carefully reviewed for any duplication from different search engines to Cochrane review website. The criteria above yielded a total of 13 correlating studies, which are discussed below. The introductory section will include the prevalence of PTSD and depression among veterans, suicide rates in the Veteran population, and treatment of PTSD and depression.

Figure 1: Literature Search Flow Chart



Prevalence of PTSD among veterans

PTSD is a common mental disorder that is marked by trauma, intrusive thoughts, flashbacks, and negative changes in cognition and mood. Individuals who have experienced traumatic events are at higher risk of developing PTSD. Other risk factors to developing PTSD include sexual assault, domestic violence, exposure to combatants, and natural disasters such as hurricanes (U.S. Department of Veterans Affairs, 2018). The prevalence of PTSD is higher among veterans compared to the members of the public, with data by U.S. Department of Veterans Affairs (2018) indicating that 11-20 of every 100 military personnel who served in the gulf war experienced PTSD, suggesting that the prevalence of PTSD is 11-20% in any given year. A lower prevalence rate was reported by Cameron et al. (2019), who observed that the lifetime incidence rate of PTSD among active service members is 3.84 incidences per 1000 person-years. However, the incidence rate of PTSD increased by seven times from 2008, and this was attributed to the aftermath of the gulf war.

Numerous factors have been correlated with an increased incidence of PTSD among veterans. Examples of these factors include combat exposure, history of physical assault, disabling injury or illness, and lack of social support (Armenta et al., 2018). Persistent PTSD has been correlated with long-term neurobiological changes that impact the mental as well as physical functioning of the affected person. The changes affect one's quality of life and increases the risk of developing physical health conditions such as cardiovascular disease and immune-mediated disorders. Moreover, the condition co-occurs with anxiety, depression, and substance

misuse, all of which are conditions that have been correlated with suicidal behaviors (CDC, 2020).

Prevalence of depression among veterans

Depression is a major mental health disorder marked by loss of interest in activities that people once enjoyed, withdrawal, and decreased energy. The condition makes people feel hopeless about the future and even contemplate suicide. According to the National Institute of Mental Health (2020), major depression is one of the most prevalent conditions in the U.S. It is the leading cause of disability among mental and behavioral disorders. It is estimated that about 17 million people in the U.S experience at least one major depressive episode annually (National Institute of Mental Health, 2020). The occurrence of mental health disorders such as major depression have been found to be high among veterans, with the Veterans Administration estimating that close to 1 in 3 veterans seen in primary care settings had some symptoms of depression, with 1 in 5 requiring further assessment for major depression, and 1 in 8 receiving a diagnosis of major depression (U.S Department of Veterans Affairs, 2016).

A study by Gould et al. (2015) found 11% of the veterans experienced depression, a rate that was comparable to that of the general population. However, a diagnosis of depression was two times likely among war veterans involved in the Vietnam War compared to the veterans who did not take part in such major wars (OR = 2.15, 95% CI: 1.54–3.00). Risk factors for depression included lower educational levels, ethnic minority, increased age, and exposure to combatants. Nevertheless, the prevalence rate reported in Gould et al. (2015) study is likely to be an underestimate of the actual prevalence of depression due to missing data. An examination of missing data by the investigators showed that older people were less likely to complete questionnaire items. Veterans seeking care from the VA Health Care System are likely to have

more mental health disorders unlike those recruited from community settings; hence the study did not indicate the true prevalence of depression in veteran healthcare clinics. Depression is a serious condition among the veterans as it has been found to limit their daily functioning and has been associated with increased risk of committing suicide (Hepner et al., 2018).

Suicide rates among veterans

There is increasing evidence that veteran suicide is a continuous and worrying public health phenomenon regarding the high incidences of suicide among the U.S military veterans compared to the general public. For instance, in 2012 alone, about 7,500 veterans died by suicide, with more active service duty personnel (177) succumbing to suicide in comparison to 176 who were killed in combat, suggesting that suicide kills more soldiers than they are killed in wars (Pilkington, 2018). The U.S Department of Veteran Affairs study showed that close to 22 service members died by suicide each day or one veteran committed suicide each hour (Department of Veterans Affairs, 2016). Other researchers disputed the analysis arguing that they were an underestimate of the problem, considering that the administration relied on data from 21 states and did not include two of the largest states; Texas and California. Besides, the organization relies on the reported deaths and this is a major challenge considering that some families conceal suicide as the cause of death to avoid the stigma associated with mental illnesses and suicide. Their reports indicating the incidence maybe as high as 30 per 100,000 population in comparison to 14 per 100,000 among civilians per year (Gibbons, Brown, & Hur, 2012).

Recent reports have shown that the rate of suicide among veterans is decreasing. According to the U.S. Department of Veterans Affairs (2019), about 45,390 American adults committed suicide in 2017, including 6,139 veterans, suggesting that close to 14% of the

individuals who committed suicide in that year were veterans. Veterans contribute to about 7.9% of the American adult population, suggesting that they are disproportionately affected by suicide rates. Among Americans adults, the average number of daily incidences of suicide increased from 86.6 in 2005 to 124.4 in 2017. The numbers included an average of 15.9 veteran suicide incidences per day to 16.8 daily incidences by 2017. In 2017, the suicide rate was 1.5 times higher among veterans compared to the general population, upon adjusting for population differences in terms of sex and age. Firearms were the most commonly used approach to committing suicide by male veterans, with 70.7% of the male suicide deaths been accomplished via this method. Firearms are also commonly used by female soldiers who commit suicide, with the approach been used by about 43% of the female soldiers who commit suicide. Among veterans dying by suicide each year, more than a half (58%) have a diagnosis of a mental health disorder or substance use disorder. Suicide rates are high among those with PTSD, bipolar disorder, and depression (Department of Veterans Affairs, 2016).

Treatment of PTSD and depression

The number of Veterans Affairs patients receiving a diagnosis of PTSD and depression has increased dramatically since the commencement of the gulf wars, with an average of 15% of the veterans having PTSD and 10% major depression (U.S Department of Veterans Affairs, 2016). Major depression and PTSD have been recognized as key suicide risk factors among veterans. Evidence-based psychotherapies have led to inordinate strides in the management of suicide in the past few years, with Veteran Administration making it a requirement for patients with PTSD and depression to receive evidence-based psychotherapeutic treatment. Evidence-based psychotherapeutic interventions for management of these two conditions of interest in this

paper include cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), and prolonged exposure therapy (PE).

PTSD treatment and change in suicidal ideation

The recommended first-line treatment for PTSD is trauma-focused psychotherapy, including CPT and PE. A prospective observational study by Horwitz et al. (2019) indicated that CPT was effective in decreasing PTSD symptoms. The study showed concurrent reductions in suicidal ideations with decreased PTSD symptoms following provision of trauma-focused treatment. Participants in this prospective study included 160 veterans (63% Caucasian, 87% male, and 64% combat trauma) who took an evidence-based course focused on trauma management in Veteran Affairs hospital. Bonferroni tests suggested that those with decreased suicidal ideation had a significant reduction in hyperarousal and mood alterations compared to those with heightened or no change in their symptoms. The researchers concluded that veterans with suicidal ideations might benefit from psychotherapeutic treatment process emphasizing on addressing cognitive or mood symptoms.

Consistent findings were reported by Cox et al. (2016) interventional study investigating changes in suicidal ideations at a multi-site sample from three different Veterans Health Administration (VA) medical centers. In total, 289 veterans took part, and the received PE therapy for the management of PTSD. Suicidal ideations and PTSD symptoms were evaluated using self-report tools used in routine clinical care. Both PTSD and suicidal symptoms decreased during the treatment process (d-type effect sizes of 1.47 and .27, respectively). Further analysis of the data indicated that suicidal ideations were correlated with PTSD symptoms, with reductions in the intensity of PTSD symptoms being predictive of future reductions in suicidal ideations. The findings suggest that treating PTSD symptoms with PE Therapy is a promising

approach to decreasing suicidal ideations. A key strength of this study was that it used a prospective study design, minimizing challenges relating to missing data and recall bias. However, there was no randomization or comparison group making it challenging to attribute the improvements in suicidal symptoms to the administered intervention.

A randomized controlled trial (RCT) by Bryan et al. (2016) reported similar findings. The purpose of the study was to establish if CPT is effective in decreasing suicidality in a sample of active U.S service members with a diagnosis of PTSD. The intervention group received CPT while the comparison group were administered with present-centered therapy. A total of 100 men and eight women with a diagnosis of PTSD were randomized into the intervention or control groups. There were substantial reductions in rates of suicide among both groups. The severity of suicidal ideations decreased substantially across both groups. The onset of suicidal ideations was rare, and there were no suicide attempts throughout the study period. A potential explanation for the reductions in suicidal ideations and attempts can be attributed to the changes in depression symptoms such as hopelessness (Smith et al., 2020). Subsequent mediation analysis suggested that even though PTSD was indirectly related to consequent suicidal ideations, changes in the suicidal ideations were not due to the reductions in PTSD symptoms but changes in depression symptoms. The observation has been supported by some past studies attributing reductions in suicidal ideations to the changes in depression symptoms rather than PTSD (Bryan & Corso, 2011; Nock et al., 2014). Although the RCT design allowed Bryan et al. (2016) to decrease bias in the study, participants were active military service members thus the findings may not apply to those no longer in service.

Consistent findings were reported by Bryan et al. (2018) study seeking to explore the effectiveness of CPT for PTSD when administered daily for a period of two weeks. Compared to

the baseline data, PTSD symptom severity and PTSD diagnosis were substantially decreased at six-month follow-up. This was an open-label, prospective cohort study involving American military personnel and veterans diagnosed with PTSD. The findings of Bryan et al. (2018) indicated that administration of CPT daily is a promising approach for rapidly and effectively treating service members with PTSD. The participants demonstrated large and statistically significant reductions in the severity of suicidal ideations. The investigators assessed depression symptoms, and the intervention was not associated with a substantial decline in depression severity; thus, the effectiveness of the interventions may not be attributable to changes in depression symptoms as it was the case for Bryan et al. (2016) study. The findings should be understood in the context of the various limitations of the study. A small sample size was used; thus, there is a possibility of the overestimation of the positive effects of the treatment. There were no randomization or comparison groups; the study cannot indicate the effectiveness of the intervention compared to others. A comparison group would have been necessary to control for the confounding variables (Smith et al., 2020).

Cognitive processing therapy has been found effective in decreasing suicidal ideations among military service members, whether administered to individuals or a group of active duty military personnel. An RCT by Resick et al. (2017) indicated that improvements in CPT were greater when CPT was administered individually in comparison to the group format. Substantial improvements were maintained with the individual and group mean with no differences being observed in terms of severity of PTSD remission within six months. The trial involved 268 service members seeking care in an army medical center. Individual treatment sessions were associated with substantial improvements in PTSD symptoms, while depression and suicidal symptoms improved equally among both formats. The investigators involved a small sample size

of female participants which prevented examinations in terms of sex differences. While this is the case in military service where the majority of the people are males, further research is needed to establish how the participants could have responded in terms of gender. The use of a RCT design and the presence of intervention and comparison groups allowed the investigators to reduce the possibility of bias in the selection of participants as well as analysis of the findings.

Stayton et al. (2019) sought to establish the effectiveness of CPT in decreasing suicidal ideations among veterans in residential settings. Participants were 303 veterans admitted to a residential PTSD treatment in VA medical centers. Post-treatment assessment revealed that suicidal ideations decreased significantly over course of the treatment process ($B = -0.153$, $SE = 0.028$, $95\%CI = [-0.21, -0.10]$, $t = -5.40$, $p < .001$). The researchers observed that the changes did not differ in terms of demographic details such as race, marital status, and sex. The findings indicate that CPT among veterans in residential care centers can expect to experience substantial decrease in suicidal ideations, regardless of their ethnicity, sex, marital status, or even race. The study was carried out in the right setting; individuals in residential programs are likely to have higher PTSD severity compared to those in outpatient settings. This is an indication that the findings of the current study may generalize to veteran patient populations with severe PTSD. However, a comparison group was missing making it a challenge to control for confounding variables; it cannot be determined to what extent the findings may be attributed to the intervention alone. In addition, the researchers used PHQ-9 tool, an instrument that has been found to have poor specificity in identifying people with suicidal ideations (Smith et al., 2016)

Consistent findings were reported by Smith et al. (2020) study investigating the effectiveness of CPT and PE in the reduction of suicidal ideations among veterans receiving residential PTSD treatment. Suicidal ideations were established using the Patient Health

Questionnaire (PHQ-9), a validated tool for screening of depression. The interventions led to significant reductions in suicidal ideations with majority of the participants being discharged from the residential PTSD treatment program without suicidal ideations. In total, 23% of the veterans remitted suicidal ideations by discharge with statistical analysis indicating that the changes were significant ($p < .05$). The findings suggest that treating PTSD symptoms has the potential to decrease suicidal ideations and intents. While the intervention led to statistically significant improvements, it is important to highlight that 43% of the participants reported suicidal ideations at the end of the intervention, highlighting the need for more effective interventions. A major limitation of this study is the lack of a control and a comparison group. The study generally focused on psychotherapeutic interventions including CPT, PE and others and the approach used did not allow the investigators to establish the role of each type of intervention in decreasing suicidal thoughts.

Norr, Smolenski, and Reger (2018) explored the impact of PE on suicidal ideations as well as the potential mechanisms among active service members. Participants in this study included 162 active service members from a military base in the U.S. An RCT design was used with the interventions of interest including virtual reality exposure and prolonged exposure for PTSD stemming from deployment to the gulf war. Diagnosis of PTSD was made using DSM-IV criteria, and the outcome measures were evaluated using clinician interviews and self-reports. The findings indicated that PE decreased post-treatment suicidal ideations significantly in comparison to the waitlist. The study demonstrated that PE was effective in reducing suicidal ideations in active duty military personnel with a diagnosis of PTSD. The study provides supporting evidence that PE is effective in decreasing suicidality among military personnel with a diagnosis of PTSD. However, the findings of the study should be considered in the context of

its limitations, such as a high dropout rate before the completion of the study. More than a third of the participants dropped out, and the authors have not provided clear reasons for the high dropout rates.

Likewise, Brown et al. (2019) pursued to explore the effects PE on suicidal ideations among active duty military personnel with PTSD. A total of 335 service members were randomized to PE group versus Present Centered Therapy. PE was associated with substantial decrease in suicidal ideations during treatment compared to Present Centered Therapy (PCT) and minimal contact control (MCC). More service members in the PE group in comparison to the control group had substantial improvements. PE led to decreased PTSD symptoms and this was associated with significant decrease in suicidal ideations compared to PCT and MCC. The findings suggest that PE improves PTSD symptoms and decreases suicidal ideations, although the mechanism remains largely unclear. In addition, the investigators involved participants with low intensity suicidal ideations; thus, there might be a possibility that the effectiveness of PE may be altered in a population of service members with severe suicidal ideations. The presence of a control and a comparison group in this study decreased bias because the investigators were able to control for confounding variables; that is, other factors that may have impacted the severity suicidal ideations. In addition, random selection of the participants removed bias in the group allocation processes; thus, improving the validity and reliability of the findings.

Depression treatment and change in suicidal ideation

The literature search led to the identification of a number of studies exploring the effectiveness of psychotherapy in decreasing suicidal ideations and suicide among veterans with depressive symptoms. Brown et al. (2016) interventional study sought to examine the impact of CBT on suicidal ideations among veterans with a clinical diagnosis of depression. The

researchers involved 902 depressed veterans receiving treatment through the Department of Veterans Affairs healthcare system. Beck Depression Inventory (BDI) scale was used to determine the severity of depression symptoms, with special attention being paid to hopelessness and suicidal ideations of the participants. Out of the 902 patients, 405 (45%) had suicidal ideations but no suicidal intents, 26 (3%) had suicidal ideations and desire to kill themselves, and 8 (1%) had suicide intents prior to the intervention while 36 (4%) did not answer questions relating to suicidality. The incidence of suicidal ideations reduced by 64% from 1.03 at the beginning of the sessions to 0.37 at the end of the assessment (95% CI: 0.31, 0.43).

Further analysis of the findings showed that for veterans with suicidal ideations prior to the intervention, the average BDI test scores reduced by 33.4 pre-intervention to 20.8 post-intervention, representing a 38% reduction in the total BDI-II total scores. Each single point reduction in BDI total scores was associated with a 4% reduction in suicidal ideations by the end of the intervention upon controlling for baseline suicidal ideations and the reductions were clinically significant. The above findings depict that CBT was effective in decreasing depression symptoms and this consequently led to decreased suicidal ideations in the course of treatment. A major strength of Brown et al. (2016) is that a national sample of veterans receiving treatment for depression were involved, suggesting that the findings are applicable countrywide considering that a huge sample size was used. Another strength is that the study involved participants seeking care in mental health clinics for veterans, an indication that the findings apply to the real world settings. However, this was not a randomized trial thus the investigators did not manage to control for all the confounding variables that maybe correlated with the decrease in suicidal ideations such as concurrent treatment or interventions such as family support.

In a different form of a study, Trockel et al. (2015) explored the effectiveness of CBT for insomnia on suicidal ideations among depressed veterans. The setting was outpatient and residential of the Department of Veterans Affairs healthcare system. Participants in this study included 405 veterans and the intervention provided was CBT. Suicidal ideations decreased from 32% at the baseline to 21% following the provision of the intervention [$\chi^2 (df = 1) = 125$; $P < 0.001$]. Upon adjusting for demographic details and the severity of insomnia, each 7-point reduction in the Insomnia Severity Index score during CBT treatment decreased the odds of suicidal ideations by 65%. The decrease in suicidal ideations as a result of CBT were statistically and clinically meaningful among veterans receiving CBT. Just like Brown et al. (2016), Trockel et al. (2015) involved a large sample of participants and was carried out in real clinical settings, aspects that improve the applicability of the findings to the US veteran population receiving CBT. However, even though the study employed a longitudinal design, they were unable to explain fully the mechanism by which effective treatment of insomnia in depressed veterans leads to decreased suicide risk.

Kumpula et al. (2019) investigated the effects of evidence-based psychotherapeutic interventions for depression on suicidal ideations with a focus on the role of gender. Mental health providers providing psychotherapeutic interventions such as CBT for depression provided data regarding depressive symptoms and suicidal ideations of both male and female veterans receiving care. CBT and other psychotherapeutic interventions were associated with statistically significant reduction in the severity of suicidal ideations ($\chi^2 (2) = 224.01$, $p = .0001$), with the decrease being larger among female veterans ($\chi^2 (2) = 9.26$, $p = .001$). The study demonstrated the effectiveness of CBT among depressed veterans as a means of reducing suicidal ideations, particularly among female veterans. While the study was unique in the sense that it explored the

effectiveness of the treatment approaches with regards to gender, there was no intervention or control groups making it hard to control for confounding variables. There is a possibility that the decrease in suicidal ideations was due to other factors besides those explored in this study. Nevertheless, the study was carried out in routine clinical settings and it provided consistent findings with those of past studies showing that CBT is an effective intervention in decreasing suicidal ideations among military veterans.

In a similar study, Rudd et al. (2015) assessed the effectiveness of CBT in preventing suicide attempts among active military duty personnel using an RCT design. Unlike other past interventional studies reviewed in this paper, the investigators employed a randomized controlled trial design with the participants being randomly allocated to various study groups. This was important because the approach reduces bias in the participant selection and allocation to control or study group processes; thus, improving the validity of the findings. All participants in this study had experienced suicidal ideations or had attempted suicide and were located to the usual treatment group (n=76) or the usual treatment group together with CBT (n =76). Participants were followed for two years with eight military personnel (13.8%) ($p=0.02$, $HR=0.38$, 95% CI =0.16–0.87) in the CBT group attempting suicide in comparison to 18 subjects in the usual treatment group (40.2%). In total, 26 participants made 31 suicide attempts leading to two deaths by suicide with the CBT and usual care group experiencing one suicidal death.

The findings of Rudd et al. (2015) suggest that service members in the usual care and CBT group were 60% less likely to express suicidality during the study period as compared to those in the usual care group. Soldiers in the CBT group had statistically significant less chances of attempting suicide even after controlling for other variables. Participants were randomly placed into treatment and control groups, minimizing selection bias. The findings are consistent

with those of past studies showing that CBT is an effective intervention in decreasing suicide attempt rates and ideations among military service members diagnosed with depression. Unlike Kumpula et al. (2019), the sample size in the Rudd et al. (2015) study was predominantly male meaning that conclusions regarding the effectiveness of CBT among female service members may not be made from this study. In addition, although the researchers made efforts to follow-up with the participants, there was a high attrition rate but this problem can be attributed to the high mobile nature of military personnel as they get deployed or reassigned to another base.

DISCUSSION

All the 13 studies included in this review were published between 2011 and 2020. All the included literature materials were primary studies and satisfied the inclusion criteria stated in this paper. Sample ranged between 20 and 3,703 and the age of the participants ranged from 25 to 70 years. Nine studies explored the effectiveness of psychotherapeutic interventions for PTSD, four focused on depression. All the studies were conducted in the US and study settings were mostly clinics for veterans under the Department of Veteran Administration. The characteristics of the included studies have been summarized in the Appendix.

Effectiveness of interventions targeting PTSD

Suicide is a substantial public health problem with major risk factors among veterans including PTSD and depression. The current study sought to evaluate the effectiveness of CPT, CBT, and PE in the reduction of suicidal symptoms among veterans with PTSD or depression. Eight studies included in this review reported that a reduction in PTSD symptoms in the course of treatment led to a subsequent decrease in suicidal ideations with the reductions being maintained for long periods of up to ten years. However, not all the studies were able to explain

the methodology by which the reductions in PTSD symptoms were taking place following administration of CPT, CBT, and PE.

A potential explanation of the reductions in PTSD treatment following the administration of the psychotherapeutic interventions is that PTSD decreases hopelessness, which in turn, leads to reduced suicidal ideations. In past studies regarding other mental disorders such as major depression, therapy have been shown to decrease feelings of hopelessness, a key predictor of suicidal ideations (Brown et al., 2016; Stayton et al., 2019). However, research by Gradus et al. (2013) reported that changes in hopelessness in the course of the treatment process did not account for the relationship between PTSD and reductions in PTSD symptoms as well as suicidal ideations. The authors instead argued that the decrease in PTSD symptoms may decrease the suicidal ideations and suicide rates through other mechanisms, such as decrease in distress that is correlated with re-experiencing and hyper-arousal of PTSD symptoms.

Reductions in suicidal ideations were noted in the treatment groups receiving CPT, CBT, and PE. Regarding the superiority of the interventions, the included studies favored CPT to PE in decreasing suicidal ideations. Consistent findings have been reported by Gradus et al. (2013), an intervention study that explored the effectiveness of CPT and PE among a non-veteran population of women who had developed PTSD upon experiencing major life events such as rape and assaults. The argument is in accord with a report by Gallagher and Resick (2012), another study involving a non-veteran sample. The reductions in PTSD symptoms and decrease in suicidal ideations were significant in the CPT group but not for the PE group.

The differences between CPT and PE on the reductions in suicidal ideations is surprising taking into account that the treatment effects have been found effective in treating PTSD and a number of other mental health conditions. The findings of the included studies showed that CPT

has the potential to lead to more decreases in suicidal ideations among veterans compared to PE or CBT. Although there some overlaps, CPT is a form of cognitive therapy involving teachings of people with PTSD about how to recognize and challenge maladaptive thinking patterns regarding the role of trauma in addition to their overall thinking patterns regarding the world. It is likely that individuals receiving CPT develop skills that enable them cope with suicidal thoughts in a better way compared to those of PE (Brown et al., 2016; Gradus et al., 2013). However, future research is needed to explore this relationship further.

Not all studies managed to compare the effectiveness of two or three interventions. Cox et al. (2016) reported that reductions in suicidal ideations among veterans receiving outpatient care in a VA medical center was correlated with decreased suicidal ideations. PE was the intervention administered and even though there were substantial reductions in suicidal ideations, the evidence was questionable because some reductions in PTSD symptoms took place prior to the intervention, a clear indication that the findings were affected by confounding factors. There was no control or comparison groups as well as randomization of the participants, making it challenging to attribute the improvements in suicidal ideations to PE therapy alone. In addition, 59% of those who commenced PE treatment with SI reported at least some form of SI at the end of the treatment sessions. Suicidal ideation reduction effect size was small compared to the entire sample ($d = .27$).

Significant reductions in suicidal ideations was reported in Norr et al. (2018) study. Analyses revealed statistically significant reductions in suicidal ideations following the implementation of PE therapy for the management of veterans with PTSD in comparison to the waitlist control. The findings are consistent with those of Brown et al. (2019) and Cox et al. (2016) studies, with the difference being that the reductions in suicidal ideations were significant

in this study. The researchers attributed the decrease in suicidal ideations to decreased PTSD symptom severity. The findings of Cox et al. (2016) and Norr et al. (2018) are congruent with those of past studies reporting that PE may be a strong intervention in decreasing suicidal ideations among veterans diagnosed with PTSD. However, the results do suggest that PE is still a relevant part of the clinical services for managing SI in patients with PTSD, although the effect size may not be as strong as that of CPT.

The effectiveness of CPT was endorsed in other studies evaluating the effectiveness of CPT alone or in comparison to other treatment approaches. Horwitz et al. (2019) reported significant reductions in suicidal ideations upon implementation of CPT. The effectiveness of the intervention was attributed to the decrease in the intrusive and cognitive mood alterations among PTSD patients. On the other hand, Bryan et al. (2016) revealed that trauma focused treatment in form of CPT does not increase the risk of committing suicide but it is correlated with a reduction in suicide risk of service members diagnosed with PTSD. There were also comparable reductions in suicidal ideations in the PCT group. The proportion of participants reporting reductions in the two groups did not differ significantly ($p = 0.543$), an indication that the two types of interventions are effective in decreasing suicidal ideations. There were substantial decrease in the probability of endorsing suicidal ideations in the CPT group ($B = -.24$, $SE = .06$, $F [1, 615] = 13.81$, $P < 0.001$), a clear indication that the intervention is effective in decreasing suicidal ideations. There were no suicidal attempts during the treatment phase.

Contrary to the findings of past studies (Cox et al., 2016; Horwitz et al., 2019; Norr et al., 2018), Bryan et al. (2016) RCT attributed the reductions in suicidal ideations to decreased symptoms of comorbid depression rather than PTSD symptoms. Mediation analyses conducted by the investigators suggested that PTSD was indirectly related to the severity of suicidal

ideations, although the changes were not directly related to PTSD symptoms. The argument for the reductions in PTSD symptoms diverged from those of past research showing that diminished suicidal ideations during CPT are as a result of reductions in PTSD symptoms. Consistent findings were reported by Stayton et al. (2019) who observed statistically significant reductions in suicidal ideations following the provision of CPT and attributed the changes to the reductions in maladaptive beliefs associated with depression rather than the reductions in PTSD severity.

Resick et al. (2017) reported similar findings to Bryan et al. (2016) and Stayton et al. (2019) studies although their research was unique in the sense that it focused on comparing two types of CPTs. Individual CPT was found more effective compared to group PTSD in terms of decreasing PTSD severity and suicidal ideations, with those in the individual therapy sessions experiencing twice improvements. However, the significant differences between the two groups warrants further investigation, considering that it is easy to follow-up an individual and reschedule an appointment when they do not attend a session unlike group sessions where individual who miss sessions lose content. It may also be due to the personalized nature of the individual sessions where a healthcare provider is able to understand the unique needs of an individual unlike in group sessions where the focus is on group therapy. An observation made in all studies evaluating the effectiveness of CPT in decreasing suicidal ideations is that there were no clinical worsening of suicidal ideations or intents unlike it had reported before in studies involving the general population (Gallagher & Resick, 2012; Gradus et al., 2013). The findings mean that mental health providers should administer CPT with confidence because it decreases the severity of suicidal ideations and intents.

Effectiveness of interventions targeting depression

The review found few empirical studies investigating the effectiveness of depression treatment in decreasing suicidal ideations and attempts, with five studies employing RCT design (Bryan et al., 2016; Norr et al., 2018; Resick et al., 2017; Rudd et al., 2015). All the studies assessed the effectiveness of CBT and no study was found assessing the effectiveness of PE or CPT in the treatment of depression among soldiers. Nine studies involved military veterans with four studies involving active duty military soldiers. All the studies reported decrease in suicidal ideations and attempts following the provision of CBT intervention. The degree of reductions in suicidal ideations varied, although statistically significant and clinically meaningful reductions in suicidal ideations from the baseline were reported in all the studies. The findings of the current review are consistent with those of past reviews involving non-veteran population. Büscher et al. (2020) reported significant reductions in suicidal ideations following administration of CBT in depressed members of the population. The researchers concluded that CBT is an effective intervention in decreasing the severity and intensity of suicidal ideations in depressed people.

Despite the promising findings regarding the effectiveness of CBT in decreasing suicidal ideations, intents, and attempts in depressed veterans, the mechanism by which this happens remains a controversial area. Researchers are yet to agree on exactly how suicidal symptoms decrease following the provision of CBT. In Brown et al. (2016), reductions in the severity of depression was associated with significant reductions in suicidal ideations during CBT therapy even upon controlling for baseline suicidal symptom scores. However, the researchers did not explain further how the reductions in depression symptoms decreased suicidal ideations and intents among the participants.

Kumpula et al. (2019) showed that CBT was an effective intervention in decreasing suicidal ideations among male and female veterans, although there were sharper declines in suicidal ideations among women. The researchers did not were not able to justify the gender differences in terms of reductions in suicidal ideations and did not shed light on the mechanism by which CBT decreased suicidal ideations. This is probably due to the research design employed; there was no control or comparison group and the follow-up was done within a short period (six months). Longitudinal studies employing an RCT design may be needed to shed light on the mechanism.

Rudd et al. (2015) argued that the primary goal of CBT is emotional regulation and development of problem solving skills and this is what supported reductions in suicidal thoughts. Although there were reductions in depression symptoms such as hopelessness, the reductions were not statistically significant hence the decrease in suicidal ideations in this study cannot be attributed to reductions in depression symptoms alone. The researchers attributed the reductions in suicidal ideations and intents to the development of core skills in areas such as cognitive restructuring, interpersonal functioning, and emotion regulations following administration of CBT. The mechanism of this study contradict those of Bryan et al. (2016), who reported that reductions in the risk of suicide could be attributed to the improvement of depression symptoms such as hopelessness

On the other hand, Trockel et al. (2015) found that reductions in suicidal ideations was associated with decreased insomnia, a major symptom of depression. A feasible mechanism of action in this case includes serotonergic dysfunction and changes in the hypothalamic-pituitary-adrenal axis. According to McCall and Black (2013), irregular sleep patterns results in the desensitization of serotonergic 1A receptor system, offering a viable mechanism for the

relationship between poor sleep, depressed mood, and suicidality. Moreover, Yoo et al. (2007) reported that impaired regulation of suboptimal decision and affective stability is correlated with poor sleep quality, a major risk factor for increasing suicidal ideations and suicide. However, the reductions in suicidal symptoms may be due to improvements in depression symptoms making one feel better thus increasing a sense of self-efficacy to manage life difficulties leading to decreased risk of committing suicide (Asarnow & Manber, 2019; Trockel et al., 2015). While the findings are promising on the effectiveness of CBT, the study did not have a comparison group, meaning that the reductions in suicidal ideations could have occurred due to antidepressants among other factors, further complicating the debates regarding the mechanism by which suicidal ideations and intents decreased.

Implications for Clinical Practice and Future Research

The overarching aim of this review was to establish the effectiveness of PTSD and depression psychotherapeutic treatments in decreasing suicide rates and suicidal ideations. The review found evidence supporting the effectiveness of CPT and PE in decreasing suicidal ideations among veterans or active military soldiers with suicidal ideations. Among comparative studies, CPT was generally found more effective compared to PE in decreasing suicidal symptoms. Likewise, there were significant reductions in suicidal thoughts and attempt rates among veterans receiving CBT for depression or various symptoms of depression. The findings of these studies supported the effectiveness of evidence-based practice for depression in decreasing suicidal thoughts among veterans and active duty military personnel.

The included studies provided evidence regarding the effectiveness of psychotherapeutic interventions in the treatment of patients diagnosed with PTSD or depression and with active suicidal ideations. The findings suggested that CPT and PE decreased the risk of suicide among

military personnel with a diagnosis of PTSD. CPT did not raise suicidal thoughts or lead to other adverse effects in spite of the treatment process addressing trauma aspects. On the other hand, evidence was found regarding the safety of CBT in treating depressed patients with active suicidal ideations.

The positive findings of the above psychotherapeutic interventions have implications for practice because they show the interventions do not increase suicidal ideations as previously thought (Bryan et al, 2016) and instead decreases the risk of committing suicide among veterans and active duty military service members. This means that the interventions are safe and are effective in decreasing suicidal ideations. Clinicians should always assess suicidal thoughts and ideations in patients with PTSD or depression, and address the ideations through evidence-based interventions. Nevertheless, the mechanism by which the treatment for the two conditions decrease suicidal thoughts and intent large remains poorly understood, highlighting the need for further research to elucidate the pathways as they appear inconsistent across the identified studies. The studies should be randomized controlled trials and longitudinal in nature to empower the researchers to control for confounding variables. Future studies should also consider having a larger sample of women to allow possibilities in exploring the effectiveness of the treatment approaches in terms of gender. Majority of the included studies had a very small sample size of women. While this is reflective of the U.S military population, there is a need for further research to explore the differences in reductions of suicidal ideations with regards to gender.

CONCLUSION

Veterans are at a higher risk of committing suicide compared to the general population, with mental health conditions such as PTSD and major depression increasing the risk of

developing suicidal thoughts and attempting suicide. Treatment with CPT and PE for PTSD has been found effective in decreasing suicidal thoughts, intents, and attempts. On the other hand, CBT has been found effective in decreasing suicidal thoughts among veterans with various symptoms of depression. Given that the recommended treatment for PTSD and depression can have the added benefit of decreasing the risk of suicide, it is important for clinicians to always assess the risk of suicide for veterans diagnosed with these conditions. Referrals can always be to trauma-focused PTSD centers as appropriate. Future research endeavors should seek to explain the mechanism by which the explored psychotherapeutic interventions decrease suicidal thoughts, intents, and attempts in patients with PTSD or depression to address the inconsistencies in the present body of evidence.

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Citation	Research aims	Research design	Sample and instrument	Key findings	Strengths and limitations
Bryan et al., 2016	To determine whether group cognitive processing therapy-cognitive only version (CPT-C) is associated with iatrogenic suicide risk in a sample of active duty US Army personnel diagnosed with PTSD	Randomized controlled trial (RCT)	100 men and eight women Columbia Suicide Severity Rating Scale (CSSRS) Beck Depression Inventory Second Edition (BDI-II) PTSD Checklist (stressor-specific version; PCL-S)	Among soldiers with pretreatment suicide ideation, severity of suicide ideation significantly decreased across both treatments and was maintained for up to 12 months posttreatment.	Strengths RCT design No selection bias Limitations Findings may not be generalized to military personnel not in service
Bryan et al. (2018)	To examine the effectiveness of cognitive processing therapy (CPT) for posttraumatic stress disorder (PTSD) when administered on a daily basis during a 2-week period of time.	Prospective cohort pilot trial,	20 veterans Clinician Administered PTSD Scale for DSM-5 TSD Checklist for DSM-5 scores Patient Health Questionnaire-8 and Beck Scale for Suicide Ideation (BSSI) scores.	PTSD symptom severity and rates of PTSD diagnosis were significantly reduced at posttreatment and 6-month follow-up. Depression symptom severity did not significantly improve, but suicide ideation significantly decreased at 6-month follow-up.	Strengths Prospective design (no recall bias) Limitations No randomization Small sample size
Brown et al. (2016)	To examine suicidal ideation and depression outcomes among Veterans receiving CBT-D for depression	Non-randomized experimental study Pretest posttest	902 patients, 427 (47%) had no SI, 405 (45%) had SI but no suicidal intent, 26 (3%) indicated suicidal desire, 8 (1%) Beck Depression Inventory-II (BDI-II)	The odds of SI decreased by 64% from 1.03 at session one to 0.37 at final assessment (OR ¼ 0.36; 95% CI: 0.31, 0.43). Findings reveal that CBT-D was associated with significant decreases	Strengths Veterans in routine clinical settings national sample of patients Limitations Confounding variables

				in SI and depression among Veterans	
Cox et al. (2016)	To investigate changes in suicidal ideations in a multi-site sample of veterans receiving evidence-based treatment for PTSD.	Non-randomized experimental study	289 veterans at VA medical centers Clinician administered PTSD scale Beck Depression Inventory Second Edition (BDI-II)	PTSD and suicidal symptoms decreased during the treatment process (d-type effect sizes of 1.47 and .27, respectively)	Strengths Prospective study design Real clinical setting Limitations No randomization or comparison group
Horwitz et al. (2019)	To prospectively examined associations between PTSD symptom clusters and SI to better specify mechanisms of change during treatment	Prospective cohort study	160 veterans (87% male, 63% Caucasian, 64% combat trauma) Patient Health Questionnaire–9 and Posttraumatic Stress Disorder Checklist–5 were used	Concurrent reductions in suicidal ideations with decreased PTSD symptoms following provision of trauma-focused treatment	Strength Prospective study design Real clinical setting Limitations No randomization or comparison group
Kumpula et al. (2019)	To examine the impact of evidence-based psychotherapies for depression on suicidal ideations	Non-randomized experimental study	3, 703 veterans Beck Depression Inventory Second Edition (BDI-II)	Significant reduction in the severity of suicidal ideations ($\chi^2(2) = 224.01$, $p = .0001$)	Strengths Prospective study design Real clinical setting Limitations Confounding variables
Norr et al. (2018)	To investigate the effects of exposure therapy on suicidal ideation (SI), as well as potential mechanistic pathways of SI reduction among active duty military personnel	RCT	162 active service members Clinician Administered PTSD Scale (CAPS) Beck Depression Inventory-II	Analyses revealed that PE/VRE had a lower probability of post-treatment suicidal ideation (OR = 0.23, 95% CI [0.06, 0.86]) compared to the waitlist control.	Strengths Randomization Limitations High dropout rate
Resick et al. (2017)	To determine the effects of CPT on PTSD and co-occurring symptoms and whether they differ when administered	RCT	268 active-duty service members consented Posttraumatic Symptom Scale–Interview Version (PSS-I)	Improvement in PTSD severity at posttreatment was greater when CPT was administered individually compared with the group format (mean [SE] difference	Strengths Randomization Reduced bias Limitations Small sample size

	in an individual or a group format.		Beck Depression Inventory–II (BDI-II) Beck Scale for Suicidal Ideation (BSSI)	on the PSS-I, -3.7 [1.4]; Cohen $d = 0.6$; $P = .006$)	
Rudd et al. (2015)	To evaluate the effectiveness of brief cognitive-behavioral therapy (CBT) for the prevention of suicide attempts in military personnel	RCT	Treatment as usual (N=76) or treatment as usual plus brief CBT (N=76) Beck Depression Inventory–II (BDI-II)	8 participants in CBT (13.8%) and 18 participants in treatment as usual (40.2%) made at least one suicide attempt	Strengths Randomization Reduced bias Limitations High dropout rate
Smith et al. (2020)	To examine the prevalence and correlates of four courses of suicidal (SI) among veterans receiving residential PTSD treatment	Prospective cohort study	1,807 veterans receiving residential PTSD PHQ-9 PTSD checklist for DSM-5	Remitted SI course was associated with greatest pre-posttreatment PTSD improvement, followed by No SI, Chronic SI, and SI Onset.	Strengths Prospective study design Real clinical setting Limitations PHQ-9 does not discriminate between passive morbid ideation/death ideation
Stayton et al. (2019)	To examine changes in suicidal ideation across a residential CPT treatment program and (b) the influence of demographic variables on change in suicidal ideation across treatment.	Non-randomized experimental study Pretest posttest	303 veterans were admitted to a residential PTSD treatment Clinician-Administered PTSD Scale for DSM 5 PHQ-9	23% of the veterans remitted suicidal ideations by discharge with statistical analysis indicating that the changes were significant ($p < .05$)	Strength Real clinical setting Limitations PHQ 9 has poor specificity
Trockel et al. (2015)	To examine the effects of cognitive behavioral therapy for insomnia (CBT-I) on suicidal ideation among Veterans with insomnia	Longitudinal data collected in the course of an uncontrolled evaluation	405 Veterans presenting for treatment of insomnia Outpatient and residential treatment facilities Beck Depression Inventory-II (BDI-II) Scale for Suicide Ideation	CBT-I treatment was associated with a 65% (odds ratio = 0.35; 95% confidence intervals = 0.24 to 0.52) reduction in odds of suicidal ideation.	Strength Large sample size and study of patients in real, ongoing clinical treatment settings Limitations Lack of data available on comorbid conditions

Appendix