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THE EFFECTIVENESS OF DBT COMPARED TO OTHER PSYCHOLOGICAL THERAPIES IN PATIENTS WITH A DUAL DIAGNOSIS OF PTSD AND BPD: A SYSTEMATIC REVIEW

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Abstract:

Objectives: The goal of this study was to assess the effectiveness of dialectical behavioral therapy (DBT) in treating post-traumatic stress disorder (PTSD) symptoms in patients with borderline personality disorder (BPD) compared to other interventions.

Background: PTSD and BPD are often comorbid, and effective treatment options are limited. DBT has shown promise in treating BPD, but its efficacy in treating PTSD symptoms in this population is unclear. This research aimed to deal with this gap in the literature.

Methods: The PRISMA guidelines were followed in conducting this systematic review. For this systematic review, papers published in Cochrane, Science Direct, PubMed, Google Scholar, and gray literature were considered without any exclusions based on country, setting, and date of publication. However, these studies were restricted to English and clinical trials involving human participants. Randomized controlled trials comparing DBT to other interventions in patients with PTSD and BPD were included.

Results: Four trials were included in this review. The findings showed a significant improvement in PTSD and BPD symptoms in those who received DBT intervention compared to those who received other interventions. However, one study showed that the DBT prolonged exposure protocol yielded better results than the regular DBT protocol. Notably, one study showed that NET was slightly more effective than DBT therapy after 12 months.

Conclusion: This study provides evidence that DBT can be used to treat PTSD symptoms in individuals with BPD. It suggests that the use of a prolonged exposure protocol may lead to better outcomes than the standard DBT approach. Practitioners should consider these findings when deciding on options for treating patients with both PTSD and BPD diagnosis. Further research is needed to determine if other interventions beyond DBT, are effective in this population over an extended period.

1. Introduction

The simultaneous occurrence of post-traumatic stress disorder (PTSD) and borderline personality disorder (BPD) is a common phenomenon that has been extensively studied. According to various population and clinical samples, individuals with BPD are affected by PTSD at rates ranging from 30% to 50%(1)(2)(3)(4). To be diagnosed with PTSD, one must exhibit ongoing symptoms for a minimum of one month, including intrusion, avoidance, depressive symptoms, changes in cognition, and arousal reactivity(5). The fundamental psychopathological characteristics of borderline personality disorder (BPD) include widespread emotional instability, identity problems, impulsive behavior, pronounced self-harm, and unstable relationships (6). Current therapies typically focus on either PTSD alone or BPD combined with purposeful self-harm, but not on all three issues at once. The majority of PTSD treatment recommendations state that such care is not recommended for patients who are immediately suicidal. Several evidence-based BPD treatments available typically concentrate on the present rather than the past, including past trauma (7). Only Dialectical Behavior Therapy has been studied for its effect on comorbid PTSD among these therapies. DBT is a comprehensive treatment approach that is often delivered in outpatient settings over a course of 12 months and necessitates the uses of therapists who are highly skilled and trained(7)(8).

According to estimates, BPD affects 1.5% of the general population but can affect up to 20% of psychiatric inpatients and inmates. Among those with BPD, 30.2% also had PTSD diagnosis, whereas 24.2% of those with PTSD also had BPD diagnosis. In comparison to people with either illness alone, those with co-morbid PTSD–BPD had a poorer quality of life, more comorbidity with other Axis I conditions, higher odds of making a suicide attempt in their lifetime, and a higher prevalence of recurrent childhood traumatic events(3). It is primarily identified in women (9). Numerous studies have investigated the effects of various treatments. Schema therapy (ST) and dialectical behavior therapy (DBT) have proven to be effective in lowering BPD symptoms and expenses (10). Post-traumatic Stress Disorder (PTSD), on the other hand, is commonly treated with trauma-focused exposure therapies as well as cognitive restructuring-based treatments and stress inoculation therapy. While only two medications are FDA-approved for PTSD treatment currently available, many off-label drugs can address specific PTSD symptoms effectively(11). PTSD treatments based on mindfulness have shown promise as complementary or alternative intervention strategies (12). A strategy that concurrently treats both conditions is essential, because borderline personality disorder and posttraumatic stress disorder are comorbid among half of the cases and increase the already high symptom load (2)(3). Furthermore, studies suggest that, before PTSD is effectively treated, comorbid conditions are not altered (13).

As treating either condition alone does not produce effective results, we sought to determine which therapy is most effective in treating patients with both PTSD and BPD. To develop a comprehensive treatment strategy in the future, we also sought to assess the advantages and disadvantages of DBT in contrast to other therapies in this systematic review.

2. Methods

The PRISMA guidelines were followed in conducting this systematic review (14) and has been registered on PROSPERO (registration number: CRD4202348746).

2.1. Search Strategy:

For this systematic review, papers published in Cochrane, Science Direct, PubMed, Google Scholar, and gray literature were considered without any exclusions based on country, setting, and date of publication. All databases were searched from the date of inception to April 10, 2023. However, these studies were restricted to English and clinical trials involving human participants. Additionally, bibliographies of relevant past reviews, meta-analyses, conference proceedings, and trial information present on clinicaltrials.gov were assessed. Keywords used were "Dialectical Behavioral Therapy",

"Post Traumatic Stress Disorder" and "bipolar disorder." The detailed search strategies are included in the supplementary file in Table S1.

2.2. Study Selection and Screening.

Only studies that met the following criteria were considered eligible to be part of this review [1] participants were aged 18 years and above; [2] study design was a clinical trial, randomized control trial (RCT), or pilot RCT; [3] patients had a combined diagnosis of BPD and PTSD; [4] DBT was given as an intervention and compared with another therapy as a control [5] assessed either improvement of PTSD or BPD symptoms as an outcome

Studies were excluded if they [1] were study designs other than a clinical trial, RCT, or pilot RCT; [2] were in a language other than English; [3] had participants with BMI less than 16.5; [4] had an intellectual disability and mental retardation; [5] had a medical condition contraindicating the exposure protocol; and [6] had schizophrenia or substance dependence.

In this study, the process of data extraction was carried out by two reviewers (ZT and MZB) who worked independently. Any disagreements that arose during the screening process were resolved through mutual agreement. In cases where a consensus could not be reached, a third reviewer (RK) was consulted to provide an unbiased perspective. Initially, both reviewers screened articles based on their titles and abstracts to determine their relevance for inclusion in this research project. All reference lists were uploaded onto Mendeley(15), and duplicates were removed after merging them together. Finally, full-text versions of all relevant articles underwent scrutiny according to pre-defined inclusion/exclusion criteria before being included in the analysis phase of our investigation.

2.3 Data Extraction and Quality Assessment

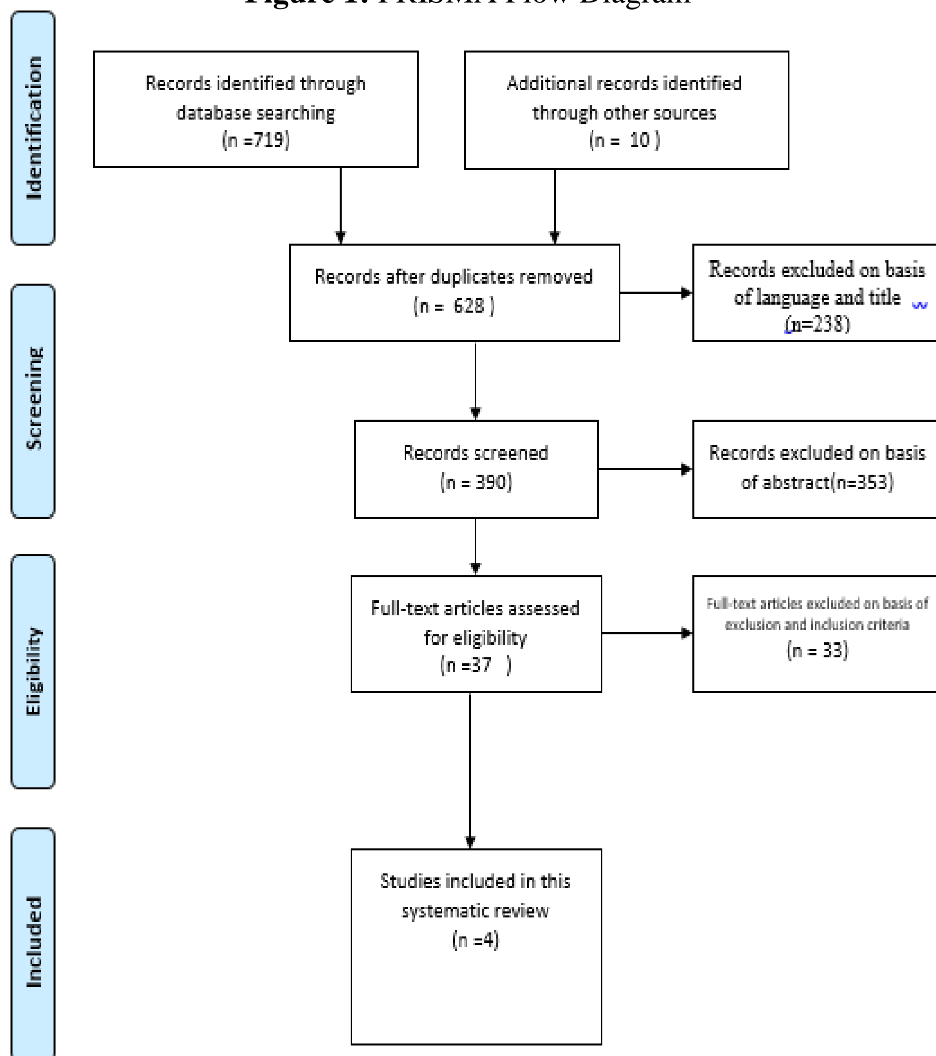
Data were then extracted from all studies. Extracted data included the study design, sample size, type of intervention, type of control/comparison, treatment duration, follow-up, and outcome data, i.e. type of outcome, outcome measure, type of data obtained, and main finding observed. Using ROB 2, the Cochrane Risk of Bias Tool's questions were used to assess the risk of bias in included studies. The assessed criteria were 1) Randomization process, 2) Deviations from the intended interventions, 3) Missing outcome data, 4) Measurement of the outcome, 5) Selection of the reported result.

3. Results:

3.1 Literature search results

PRISMA flow diagram provides a summary of the search results (Figure 1). The original search yielded 729 studies, of which four were included: Bohus 2013(16), Harned 2014(7), Kleindeinst 2021(17), and Steuwe 2021(18). All included studies were RCTs according to our inclusion criteria, except for Kleindeinst 2021, which is a subgroup analysis of a large previously conducted RCT, Bohus 2020 (19), focusing on the population relevant to our review, that is, patients with a dual diagnosis of BPD and PTSD.

Figure 1: PRISMA Flow Diagram



3.2 Study Characteristics and Quality Assessment

Table 1 summarizes the characteristics of the four studies that included individuals with BPD and PTSD. The combined sample size from these RCTs was 210, of which 72% (151) belonged to two major RCTs conducted by Kleindienst and Steuwe. All studies were restricted to middle-aged women between the ages of 17-65 years old. These findings are limited to this specific population and care must be taken when generalizing beyond this group. Despite definite variations, similarities in socio-demographic and clinical traits have been observed in different studies.

Table 1: Study Characteristics of all included studies

Study (Year)	**Bohus (2013)**	**Harned (2014)**	**Kleindienst (2021)**	**Steuwe (2021)**
Sample Size (n=)	33 I=17 C=16	26 I=7 C=19	93 I=43 C50	58 I= 29 C=29
Treatment	I= DBT-PTSD/ C= TAU-WL	I= standard DBT/ C= DBT PE	I= Disorder DBT-PTSD / C= CPT	I= DBT-bt / C= NET
Duration (months)	4	12	12	3.5
Follow up (months)	6	15	15	12

Inclusion Criteria	(1) be female, (2) be between the ages of 17 and 65, (3) have a DSM-IV-defined diagnosis of post-traumatic stress disorder (PTSD) related to child sexual abuse (CSA), (4) have experienced CSA as the index trauma that led to PTSD, and (5) have experienced sexual assault before the age of 18 that fulfills the PTSD A criterion. (6) must meet at least one of the following conditions: current eating disorder, current major depressive disorder, current substance abuse, or meeting ≥ 4 DSM-IV criteria for BPD.	(1) female, (2) age 18-60, (3) meets criteria for BPD, (4) meets criteria for PTSD, (5) can remember at least some part of the index trauma, (6) recent and recurrent intentional self-injury (defined as at least two suicide attempts or NSSI episodes in the last 5 years, with at least one episode in the past 8 weeks), and (7) lives within commuting distance of the clinic.	female sex and gender identity; an age 18 - 65 years; a diagnosis of PTSD (according to the DSM-5) following sexual or physical abuse before age 18 years; meeting 3 or more BPD criteria, including criterion 6 (affective instability); and availability for 1 year of outpatient treatment.	female gender, being aged 18–65 years as well as meeting a DSM-IV-TR-defined diagnosis of BPD and PTSD
Exclusion Criteria	(1) Lifetime diagnosis of schizophrenia. (2) Current substance dependence. (3) Body mass index (BMI) less than 16.5. (4) Intellectual disability. (5) Medical conditions that would prevent participation in exposure protocol (e.g. severe cardiovascular disorders) (6) Individuals who had demonstrated life-threatening behavior within the past 4 months (as assessed by the Severe Behavior Dyscontrol Interview) were also excluded and referred to standard DBT treatment.	(1) met criteria for a psychotic disorder, bipolar disorder, or mental retardation, (2) were legally mandated to treatment, or (3) required primary treatment for another debilitating condition (e.g., life-threatening anorexia nervosa).	(a) diagnosis of schizophrenia, bipolar I disorder, or mental retardation, (b) severe psychopathology necessitating immediate treatment in a different setting (e.g., body mass index < 16.5), (c) current substance dependence, (d) medical conditions contradicting exposure (e.g., pregnancy), (e) a highly unstable life situation (e.g., homelessness), (f) scheduled residential treatment, and (g) receipt of either CPT or DBT-PTSD during the last year.	doubts about the capacity to consent and to contract, pregnancy, or breastfeeding, a lifetime diagnosis of schizophrenia, body mass index <16.5, current substance use, a suicide attempt 2 months before admission, ongoing victimizing perpetrator contact, and undergoing a DBT- or exposure-based therapy within the last 12 months.
Age, years Mean (SD)	I=31.76 (9.51) C= 33.06 (6.98)	32.6 (12.0)	33.5 (10.6)	I= 31.88 (9.11) C= 31.50 (7.76)
Primary Outcome Measures	Reduction of PTSD symptoms assessed by the CAPS and by PDS	PSS-I was used to assess PTSD presence and severity	CAPS-5 score at 15 months	Change in PTSD severity as assessed by CAPS
No. of BPD criteria Mean (SD)	4.18 (1.66) I= 5.56 (0.84) C= 6.07 (1.07)	NA	6.23 (1.16) I= 6.2 (1.2) C= 6.2 (1.1)	I= 6.75 (1.24) C= 6.96 (1.23)
Drop Outs N (%)	I= 2 (11.8%) C= 3 (18.8%)	I= 4 (57.1%) C= 7 (36.8%)	I= 15 (32.6%) C= 15 (32.6%)	I= 13 (44.8%) C= 5 (17.2%)

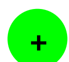
I= intervention, C= control, DBT PTSD= dialectical behavioral therapy adapted for PTSD, TAU-WL= = treatment-as-usual wait-list, DBT-PE= DBT with Prolonged Exposure protocol, CPT= Cognitive Processing Therapy, DBT-bt= = DBT-based treatment, NET= Narrative Exposure Therapy
Three out of the four studies included subjects for a year, either as primary treatment duration (e.g., Harned 2014 and Kleindeinst 2021) or as follow-up care (e.g., Steuwe 2021); only one study, Bohus 2013, had a shorter duration of six months. Three out of four trials reported attrition rates exceeding 20% in both control and treatment groups. The control groups across all four trials used various methods, such as TAU (Treatment as Usual), NET (Narrative Exposure Therapy), DBT-PE (DBT - prolonged exposure) and CPT (Cognitive Processing Therapy), while outcomes were evaluated using standardized psychological measures. In three of the studies, the symptoms of PTSD were reported to be lessened more effectively using DBT.

Furthermore, each study underwent a risk of bias assessment to evaluate the quality and potential sources of bias using RoB 2(20), the results of which are presented in Table 2 and the summary in Figure 2.

Table 2: Risk of Bias Assessment using the Cochrane RoB 2 tool

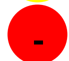
Unique ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Bohus 2013	DBT-PTSD	TAU-WL	Reduction of PTSD symptoms as assessed by Clinician Administered PTSD scale (CAPS) and Posttraumatic Stress Diagnostic Scale (PDS) by BPD therapy is superior to TAU-WL in patients with CSA-related PTSD with and without BPD	74	+	+	+	+	+	+
Harned 2014	DBT+DBT PE	DBT	(1) to evaluate the feasibility and acceptability of DBT+DBT PE relative to DBT alone. (2) To evaluate the safety of DBT+DBT PE relative to DBT (3) Estimation of the degree of change in DBT+DBT PE relative to DBT on primary outcomes of intentional self-injury and PTSD as well as other secondary outcomes.	26	+	!	+	+	!	!
Kleindienst 2021	DBT-PTSD	CPT	Evaluating comparative efficacy of DBT-PTSD and CPT on patients with dual diagnosis of BPD plus CA-related PTSD	93	+	+	+	+	+	+
Steuwe 2021	NET	DBT-bt	The efficacy of NET compared to DBT-bt with reference to change in PTSD severity	60	!	!	+	-	+	-

Key:



Low risk

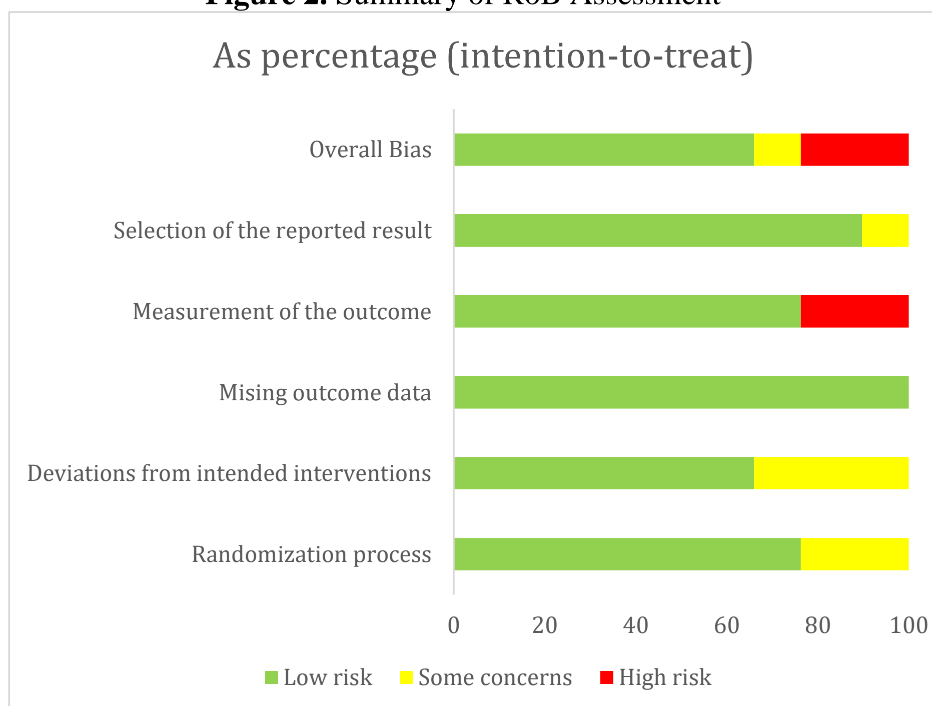
Some concerns



High risk

D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure 2. Summary of RoB Assessment



Harned' s study raised some concerns due to the minimization randomization procedure being used. Independent clinical assessors who were blind to the treatment condition carried out each assessment. Consequently, there was no data indicating that the two intervention groups' baseline characteristics were different. Steuwe's study demonstrated a high risk because pretreatment assessments were conducted by independent clinical assessors who were blind to the treatment condition. We were unable to reliably guarantee that clinical raters were blinded after randomization.

3.3 Outcome analysis

3.3.1 Efficacy of DBT in Treating PTSD symptoms:

TabbCompared to those who received other interventions, the findings showed a significant improvement in PTSD and BPD symptoms in those who received DBT intervention. However, Harned's 2014 study showed that the DBT prolonged exposure protocol yielded better results than the regular DBT protocol.

All studies performed separate analyses for PTSD assessments using psychological scales, such as CAPS in three studies done by Bohus, Kiendienst, and Steuwe and PSS1 in Harned (2014), before combining them using Hedges' g in Bohus, Harned and Steuwe studies or Cohen's d in Kleindienst study to measure between-group effect sizes. The reported data from all trials are presented in Table 2. Notably, although Steuwe et al.'s pre-post analysis after 3.5 months favored DBT therapy over others, their follow-up analysis after 12 months showed that NET was slightly more effective.

Table 3: Results Extracted regarding PTSD Symptoms

Author (Year)	*Bohus (2013)*	*Harned (2014)*	*Steuwe (2021)*	*Kleindienst (2021)*
Treatment vs Control	DPT-PTSD vs TAU-WL	DBT vs DBT PE	DBT vs NET	DBT PTSD vs CPT
Duration	4 months	12 months	3.5 months	12 months
Outcome: PTSD Symptoms	CAPS score	PSS-I score	CAPS score	CAPS score
Type of data	Hedges' g	Hedge's g	Hedge's g	Cohen's d
Data	between groups=1.34	between group= 0.7 DBT= 1.5 DBT PE=2.9	NET=1.2 DBT-bt=1.4	between groups= 0.337 DBT=1.447 CPT=1.171
Main Finding	Greater improvement in DBT group	DBT PE group showed greater improvement	Greater improvement in DBT group	Greater improvement in DBT PTSD group
Outcome: BPD	BSL score	NA	BSL score	BSL score
Type of data	Hedges' g	NA	Hedge's g	Cohen's d
Data	between groups=0.28	NA	DBT-bt= 1.6 NET= 0.6	DBT-PTSD d=1.653 CPT d=0.813 between d=0.238
Main Finding	Greater improvement in DBT group	NA	Greater improvement in DBT group	Greater improvement in DBT group

4. Discussion

4.1. Summary of findings.

This systematic review conducted a comprehensive analysis of four randomized controlled trials that investigated the efficacy of dialectical behavioral therapy (DBT) in patients with post-traumatic stress disorder (PTSD) and borderline personality disorder (BPD). The results indicated significant improvements in PTSD and BPD symptoms among those who underwent DBT intervention compared to those who underwent other interventions. However, it is important to note that Harned's 2014 study demonstrated better outcomes with the DBT prolonged exposure protocol than with the standard DBT protocol. Moreover, studies by Bohus (2013) and Kleindienst (2021) primarily focused on analyzing the impact of the specific DBT-PTSD protocol.

4.2. Comparison with previously conducted studies.

The outcomes of our comprehensive analysis of BPD management are consistent with those of earlier reviews undertaken by Jones et al.(21). and Stoffers-Winterling et al(9). Stoffer-Winterling et al. scrutinized a combined total of 31 RCTs, including more than 1870 participants, and revealed that DBT was an efficacious intervention, both as monotherapy and in combination with other treatments. However, these investigations were restricted to examining only BPD, without addressing the comorbidity between BPD and PTSD.

Concerning the simultaneous occurrence of BPD and PTSD, research conducted by Zeifman et al.(22) and Choi Kain et al.(23) revealed that DBT remains effective in treating individuals with comorbid PTSD despite its presence not obstructing progress. As stated by Zeifman et al., protocols for DBT are altered when addressing co-occurring PTSD; specifically, treatments such as DBT PE and DBT PTSD may serve as more efficacious interventions, a conclusion supported by Harned et al.'s investigation included in our review. Moreover, Kleindienst et al.'s (24) study on the efficacy of the DBT-PTSD protocol reinforces this notion because it demonstrates improved outcomes for persons with concurrent BPD and PTSD by incorporating specific interventions targeted toward managing symptoms unique to those experiencing both disorders within standard practice. Similarly, Gratz et al.(25) reported comparable findings, indicating that an association exists between positive outcomes related to BPD treatment under a regime using DBT, where concomitant PTSD is present. These results are also corroborated by Fitzpatrick et al.(26) who state that many comorbid symptoms of BPD, such as PTSD and anxiety, show improvement when treated with DBT.

Taken together, the findings of our systematic review and comparisons with previous studies suggest that DBT is a highly effective treatment for individuals with co-occurring BPD and PTSD.

4.3. Pathophysiology and mechanism of action of DBT.

DBT is the most researched and widely available evidence-based treatment for BPD. DBT has a multifaceted approach and is based on the bio-social theory of personality disorders. Standard DBT protocol consists of 4 components, each aiming to teach coping skills and help patients apply them to their individual situations. These components include skills training, where patients are taught useful skills for coping with painful experiences; individual sessions focusing on the application of these skills; skill coaching and consultations through telephone; and a consultation team with a therapist. Skills include mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance(27). DBT has also been adapted to account for the various comorbidities of BPD. Distinguishing modifications aimed at post-traumatic stress disorder (PTSD) comprise the DBT-PTSD by Bohus (2013), which merges dialectical behavior therapy with cognitive therapy grounded in exposure and trauma. Likewise, Harned (2013)(28), developed an adapted version referred to as DBT-PE, which fuses prolonged exposure psychotherapy, a form of cognitive-behavioral treatment for PTSD, where individuals revisit traumatic experiences within a secure environment to alleviate the adverse influence of such memories on their emotional and behavioral reactions(22)(29).
In general, there is limited understanding of the pathophysiology underlying DBT's efficacy of DBT in treating BPD. Nonetheless, research has indicated that emotional regulation plays a critical role in this process(30). Specifically, it appears that mindfulness techniques taught in DBT are key to achieving emotional regulation(31). In particular, Perroud et al.(32) identified acceptance without judgment as a particularly significant skill for achieving these goals. Other studies by Mochrei et al.(33) and Krantz et al(34). suggested reductions in depression scores and NSSI episodes, respectively, following treatment with DBT. However, despite these promising findings, the precise mechanisms through which DBT reduces BPD symptoms remain largely unclear and warrant further investigation through rigorous scientific inquiry into its effects on individuals diagnosed with the disorder as well as the long-term effectiveness of the treatment.

4.4. Heterogeneity.

Due to the low number of studies and the amount of observed heterogeneity, a meta-analysis was deemed inappropriate. Additionally, differences in DBT variations and control arms between studies, as indicated in Table 1, contributed significantly to such heterogeneity. The types of randomization used in the research varied, with the more recent ones using more complex computerized adaptive minimization randomization techniques. Differences in attrition rates between the control and treatment arms of more than 20% in three of the four trials suggest the possibility of risks to internal validity in the research due to variations in study group equivalence. As for PTSD symptom reduction outcomes, three out of four included studies utilized either the CAPS-5 or Clinician-Administered PTSD Scale to assess changes, whereas Harned (2014) relied on the PSS-I scale. Similarly, BPD symptoms were assessed using BSL in three out of four studies, with no relevant information provided by Harned (2014). Notably, Hedge's g was employed as a data presentation format in most studies except Kleindienst's study (2021), which presented Cohen's d instead. Nonetheless, it should be noted that all investigations employed some variants of DBT interventions and exclusively evaluated female individuals. Additionally, the average age of patients was comparable across studies, while the mean number of BPD criteria exceeded five for each study, with the exception of Harned (2014), who did not disclose this information. In conclusion, while studies have highlighted the potential effectiveness of DBT in reducing the symptoms associated with BPD and PTSD, further investigations are needed.

4.5. Clinical and Research Implications.

The findings have significant implications for clinical practice and future research. In clinical practice, the findings indicate that DBT protocols could be a useful therapy option for people suffering from

borderline personality disorder and post-traumatic stress disorder. Incorporating DBT into clinical practice may provide relief to individuals struggling with BPD and PTSD symptoms. This is particularly important, as comorbid PTSD is thought to lead to increased intensity of BPD symptoms, increased suicidal events, self-harm, and lower remission rates (22). However, the demanding nature of DBT as a therapy must be considered before its clinical integration. DBT requires patients to attend multiple sessions of therapy over the course of at least a year. In fact, three of the four studies in our review also reported outcomes after 1 year of DBT therapy. Although this can lead to an increased financial burden on patients (35), recent studies have shown due to high effectiveness DBT integration may actually be cost-effective in the long term (36). Furthermore, DBT also requires highly trained therapists and resources, which may be a burden on the healthcare system (37) (38). but has been successfully implemented on a national scale before (39). Current studies on DBT for BPD and PTSD show promising results, but are usually low-powered and do not assess long-term effects; thus, further high-quality research is still required.

4.6. Limitations.

This review only analyzed the results of a few low-powered studies with considerable heterogeneity, as discussed above. Although our inclusion of only RCTs ensured a relatively high quality of results and a lower chance of bias, the chance of bias cannot be written off completely. Furthermore, all studies solely studied females between the ages of 18 and 65 and no risk factors such as a low BMI or a schizophrenia diagnosis, as stated in our exclusion criteria above; thus, the results cannot be generalized to males, children, senior citizens, or individuals with risk factors.

Conclusion:

In summary, this study demonstrates that dialectical behavioral therapy (DBT) effectively treats post-traumatic stress disorder (PTSD) symptoms in individuals with borderline personality disorder (BPD). Compared to alternative interventions, those who received DBT experienced significant improvement in both PTSD and BPD symptoms. However, the effectiveness of DBT prolonged exposure may surpass standard DBT treatment. More research is required to assess the long-term efficacy of different therapies in this population. Although limited by small sample size and study heterogeneity, these findings offer valuable insights into treating co-occurring PTSD and BPD.

Data Availability:

The manuscript contains all the necessary data. Data that are not available can be obtained from the corresponding author.

Conflicts of Interest:

The authors declare that they have no conflicts of interest.

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Supplementary Materials:

Detailed search string available in supplementary file S1.

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