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Psychotherapies for adults with complex presentations of PTSD: a clinical guideline and five systematic reviews with meta-analyses

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ABSTRACT

Objective To develop a clinician-guided, research-based guideline for adult outpatient psychotherapy for complex presentations of post-traumatic stress disorder (PTSD).

Methods We used state-of-the-art methods to develop clinical guideline recommendations and conduct systematic reviews with meta-analyses for five research questions: (Q1) When treating adults with PTSD, should trauma-focused psychotherapy include exposure? Which psychotherapies are effective for PTSD with co-occurring: (Q2) personality disorder; (Q3) depression; and (Q4) dissociative disorder? (Q5) for complex PTSD (C-PTSD)?

Results (Q1) We found no evidence of a difference between trauma-focused psychotherapies with or without exposure on PTSD symptoms (standardised mean difference (SMD) 0.02, 95% CI −0.11 to 0.15, p=0.75, I^2=64%). (Q2) Dialectical behaviour therapy (DBT-for-PTSD) showed beneficial effects over cognitive processing therapy (CPT) on co-occurring borderline personality disorder (BPD) symptoms (mean difference (MD) −0.58, 95% CI −0.94 to −0.22, p=0.003). (Q3) Mindfulness and body-focused psychotherapies, prolonged exposure (PE), narrative exposure therapy (NET) and CPT showed beneficial effects on symptoms of PTSD and co-occurring depression. Results for present-centred therapy (PCT) were uncertain. (Q4) No statistically significant differences were found among psychotherapies for PTSD with co-occurring dissociation. (Q5) Skills training appeared promising for C-PTSD.

Conclusion Weak clinical recommendations were reached for trauma-focused therapies with or without exposure for PTSD; DBT-for-PTSD for PTSD with co-occurring BPD; CPT, NET, PE and Mindfulness and body-focused psychotherapies for PTSD with co-occurring depression; and Skills training for C-PTSD. A weak recommendation was reached against PCT for PTSD with co-occurring depression. It is good practice to include interventions targeting dissociation for PTSD with co-occurring dissociation. Overall, the certainty of evidence was low; high-quality trials are needed to strengthen the recommendations.

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INTRODUCTION

Post-traumatic stress disorder (PTSD)[1 2] is a prevalent mental disorder which profoundly impacts well-being and functioning[3–5] and is associated with a higher risk of cardiovascular disorders[6] and suicide.[7] The lifetime prevalence of PTSD is estimated at 4%,[8] and roughly 12.5% of patients in primary care settings meet the criteria for PTSD.[9] PTSD is associated with high rates of psychiatric comorbidity,[8] with up to 78% of patients meeting the criteria for a comorbid mental disorder[10]—for example, 30–50% meet the criteria for comorbid major depressive disorder[11] and 6–24% meet the criteria for borderline personality disorder (BPD).[12] The Diagnostic and Statistical Manual of Mental Disorders (DSM-5/DSM-5-TR) also recognises a dissociative subtype of PTSD (PTSD with dissociative symptoms),[1] which affects 14–45% of those diagnosed with PTSD.[13 14] Additionally, the 11th revision of the International Classification of Diseases (ICD-11) implemented Complex PTSD (C-PTSD) as a new diagnosis. C-PTSD is characterised by symptoms of PTSD and 'Disturbances in Self-Organisation'[15 16] and affects 1–8% of the general population.[15] Taken together, PTSD with comorbidity and C-PTSD (hereafter referred to under the umbrella term 'complex presentations of PTSD')[17 18] are highly prevalent in the mental health services[16] and are associated with increased distress and impairment.

National clinical guidelines recommend trauma-focused psychotherapies as first-line treatment of PTSD, on par with or even over pharmacological treatment.[19 20] Notably, most patients also prefer psychotherapy over pharmacological treatment.[21] In particular, guidelines have recommended trauma-focused approaches based on cognitive behavioural therapy (CBT).[22 23] These approaches typically involve structured techniques aimed at processing trauma and trauma exposure exercises to facilitate therapeutic progress.[24 25] While trauma exposure has been found effective at treating PTSD,[23] several authors highlight potential risks of adverse effects/events (AEs) (eg, symptom exacerbation

and dropout), especially in treating complex presentations of PTSD.[19 20 26–28]

Despite the prevalence of complex presentations of PTSD in mental health services, existing clinical guidelines offer few to no recommendations on psychotherapy for these populations.[29–32] Nor do they offer explicit guidance for including exposure and at what level.[20 33] Furthermore, the 20% dropout rate among patients receiving guideline-recommended psychotherapy for PTSD[34] calls into question whether the absence of tailored recommendations for complex presentations of PTSD is the reason clinical guidelines are not sufficiently bridging the gap between empirical research and clinical practice. Addressing this gap requires a concerted effort to consolidate existing evidence and develop tailored treatment recommendations. Systematic reviews play a pivotal role in synthesising current evidence and informing such tailored recommendations for the rapidly evolving research landscape of PTSD and C-PTSD.

In this project, systematic reviews formed the basis for developing a Danish clinical guideline for psychotherapy for patients with complex presentations of PTSD, to ensure that these individuals receive the highest standard of care. A multidisciplinary clinical guideline panel defined the five research questions to be answered (see online supplemental A and B for details):

Q1) When treating adults with PTSD, should trauma-focused psychotherapy include exposure?

(Q2) Which psychotherapies are effective in treating PTSD and comorbid personality disorder?

(Q3) Which psychotherapies are effective in treating PTSD and comorbid depression (or moderate-to-severe depressive symptoms)?

(Q4) Which psychotherapies are effective in treating PTSD and comorbid dissociative disorder, or PTSD with dissociative symptoms?

(Q5) Which psychotherapies are effective in treating C-PTSD?

METHODS

Systematic reviews with meta-analyses

The systematic reviews were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions,[35] the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[36] and the Population, Interventions, Comparators and Outcomes (PICO) framework.[35] The research protocol was registered with the PROSPERO database (CRD42022376117) before literature searches began. No ethics approval was required for this project.

Study eligibility criteria

Eligibility criteria for inclusion of trials were specified using the PICO framework (table 1). For details, see online supplemental C.

Literature search and study selection

We used the Danish health authority's model of literature selection[37]; that is, evidence was chosen and evaluated stepwise, starting with a search for existing international clinical guidelines, followed by a search for existing systematic reviews and a search for randomised clinical trials (RCTs). For the full search strategy, see online supplemental A.

Study selection and quality assessment

Quality assessments of existing guidelines were made with the Appraisal of Guidelines for Research and Evaluation-II tool.[38] Systematic reviews were assessed with A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2).[39] RCTs were assessed using Cochrane's Risk of Bias tool (RoB 2).[40] For details, see online supplemental C.

Meta-analysis

Procedures for the meta-analyses followed the Cochrane Handbook for Systematic Reviews of Interventions.[35] For details, see online supplemental C.

Certainty of the evidence and clinical guideline recommendations

We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[41] to summarise and evaluate the certainty of the evidence. We adhered to the Danish health authority's model of clinical guideline development[37] and GRADE's evidence-to-decision framework (EtD),[42] that is, clinical guideline recommendations were based on triaged information: (1) results of the systematic reviews for each research question, (2) patient preferences and (3) clinical expertise. Patient preferences were gathered via a survey (n=126 people with PTSD) which investigated experiences and opinions about various psychotherapies. See online supplemental C and D for details.

RESULTS

In the following, we present the main findings for the interventions which received a clinical recommendation. Results for other interventions, analyses of secondary outcomes and subgroups, and full information on the GRADE EtD for each clinical question is presented in online supplemental B and D.

Q1: when treating adults with PTSD, should trauma-focused psychotherapy include exposure?

Description of studies

The literature search for clinical guidelines and systematic reviews was conducted on 7 October 2021, and one[43] was selected to form the basis of our review. As the literature search of this review was conducted on 7 October 2021, and the search strategy was evaluated to be adequate by means of the AMSTAR 2,[39] our searches for additional RCTs were set from this date and conducted on 19 April 2023. PRISMA flowcharts for clinical guidelines, systematic reviews and RCTs are provided in online supplemental E, figure S1, S2.1 and S2.2, respectively. A total of 31 RCTs (n=3837 participants) were included in the Q1 meta-analyses across primary and secondary outcomes. All RCTs included a PTSD population. Across the included studies, 16 trauma-focused psychotherapies with exposure were compared with 10 trauma-focused psychotherapies without exposure (see online supplemental F, table S1 for study details).

Risk of bias assessment

29 of the included RCTs reported the primary outcome of PTSD symptoms; 4 were considered low risk of bias, 9 to raise some concerns and the remaining 16 to be at a high risk of bias. All 31 included trials reported the primary outcome of attrition; 2 were considered to raise some concerns and the remaining 29 to be at a high risk of bias. Funnel plots were constructed for PTSD symptoms and attrition rates and indicated no publication bias. See online supplemental E, figure S3 for RoB 2 evaluations and online supplemental figures S4.1–S4.5 for funnel plots.

Table 1 PICO eligibility criteria per research question

	Q1	Q2	Q3	Q4	Q5
Types of Participants	**Main criteria**				
	Adults (aged >18), in outpatient settings, with a diagnosis of PTSD according to DSM-III to DSM-5-TR or ICD-10/11 criteria, by means of a structured interview or previous clinician-administered diagnosis.				
	Additional question specific-criteria				
	N/A	Diagnosed with a personality disorder according to DSM-III to DSM-5-TR or ICD-10/11 criteria, by means of a structured interview or clinician-administered diagnosis, or considered to have clinically significant symptoms* of a personality disorder.	Diagnosed with a depressive disorder according to DSM-III to DSM-5-TR or ICD-10/11 criteria, or considered to have clinically significant depressive symptoms.*	Diagnosed with a dissociative disorder according to DSM-III to DSM-5-TR or ICD-10/11 criteria, or considered to have clinically significant dissociative symptoms.*	Clinically significant symptoms of the C-PTSD domain 'Disturbances in Self-Organisation' (DSO), namely emotion dysregulation, negative self-concept and interpersonal disturbance.
				Alternative question-specific criteria†	
				Diagnosed with PTSD with dissociative symptoms according to DSM-5/5-TR, by means of a structured interview or clinician-administered diagnosis.	Diagnosed with complex PTSD (C-PTSD) according to ICD-11 criteria, by means of a structured interview or a clinician-administered diagnosis.
Types of Interventions	Any trauma-focused psychological intervention including exposure, delivered by any mode, including to individuals, groups or couples. Body-oriented interventions are also considered eligible, as long as they include exposure and a talk-based modality delivered by a trained therapist.	Any psychological intervention delivered by any mode, including given to individuals, groups or couples, in an outpatient setting. Body-oriented interventions are also considered eligible, as long as they include a talk-based modality delivered by a trained therapist. Furthermore, two of the following four criteria should be met[66]: 1. There should be a citation to an established school/approach to psychotherapy. 2. There should be a description of the therapy, which contains a reference to a psychological process. 3. A treatment manual should be referenced, which was used to guide treatment delivery. 4. Active ingredients of the treatment should have been identified and cited.			
Types of Comparators	Any psychological intervention which does not include trauma-focused exposure, delivered by any mode, including to individuals, groups or couples. Body-oriented interventions are also considered eligible, so long as they include a talk-based modality delivered by a trained therapist.	Eligible comparators include any psychological intervention as defined above, unspecific control interventions such as standard care or treatment-as-usual (TAU), any specific active non-psychological intervention (eg, relaxation techniques, patient education programmes or community treatments) or any passive comparators such as waitlist or no treatment.			
Types of Outcomes	Outcomes can be either self-rated by patients or observer-rated by clinicians. Only adequately validated assessment instruments will be included, in addition to spontaneous reporting of adverse effects. Outcomes are categorised as either primary or secondary.				
	Outcomes for all questions				
	Primary: ► PTSD symptoms (ICD-10/11, DSM-III to DSM-5-TR criteria) Secondary: ► Psychosocial/occupational functioning ► Quality of life ► Adverse effects‡§				
	Question-specific outcomes				
	Primary: ► Attrition Secondary: ► Treatment satisfaction	Secondary: ► Self-harm, assessed on a validated scale or by the proportion of participants with self-harming behaviour. ► Suicidal behaviour, assessed by a validated scale or by the proportion of participants with suicidal acts. ► Attrition, in terms of participants lost after randomisation in each treatment group.			
		Primary: ► Personality disorder symptoms Important: ► Violent/aggressive behaviour	Primary: ► Depressive symptoms	Primary: ► Dissociative symptoms	Primary: ► DSO symptoms Important: ► Violent/aggressive behaviour
Time frame	End of treatment and longest follow-up.				

*In the absence of a diagnosis, a participant can be considered to have clinically significant symptoms of a specific disorder, should the symptoms be measured on a scale with a validated cut-off score and their score be above said cut-off. The cut-off should be from either (1) a published article on the clinical validity of the cut-off or (2) a validation article of the scale in question, in which a clinical cut-off is established.
†Considered an eligible alternative to the main and additional question-specific criteria, that is, participants solely fulfilling this criterion are considered eligible.
‡We define adverse effects as unfavourable outcomes that occur during or after the intervention. No limitations will be made on the type of adverse effects. Potential examples may include events that lead to death, require inpatient hospitalisation or prolongation of existing hospitalisation, are life-threatening, result in significant or persistent disability, or an increase in unfavourable psychopathological outcomes, for example, significant clinical increase of anxiety or depression. Adverse effects can be assessed by the use of standardised psychometric rating scales or through spontaneous reports.
§Since self-harm and suicide-related outcomes are not included as individual outcomes in Q1, these will be considered as adverse effects/events, should they be reported.
DSM, the Diagnostic and Statistical Manual of Mental Disorders; ICD, the International Classification of Diseases; PTSD, post-traumatic stress disorder.

Primary outcomes

The meta-analyses found no significant difference between trauma-focused psychotherapies with versus without exposure, neither on the severity of PTSD symptoms at the end of treatment (standardised mean difference (SMD) 0.02, 95% CI −0.11 to 0.15, p=0.75, I^2=64%; 29 trials, n=3507, low certainty), nor on the rate of attrition throughout treatment (risk ratio (RR) 1.18, 95% CI 0.99 to 1.41, p=0.06, I^2=56%; 31 trials, n=3837, low certainty). See online supplemental B for results on other outcomes, and sensitivity and subgroup analyses. All analyses with significant outcomes are reported in online supplemental G, table S1.

Certainty of evidence

The overall certainty of evidence for Q1 was considered low due to a high risk of bias and inconsistency. See online supplemental G, table S1 for GRADE assessments per outcome.

Evidence-based recommendations

Though the certainty of the evidence was low, it indicated no statistically or clinically significant differences between trauma-focused psychotherapies with versus without exposure on beneficial outcomes (symptoms) or harmful outcomes (attrition). Based on these results and patients' mixed preferences for exposure, the clinical guideline panel provided a weak recommendation for offering trauma-focused psychotherapy with as well as without exposure to patients with PTSD. Based on patient preferences and clinical experts' experiences, the guideline panel stressed that including exposure in treatment should be a shared decision. Further, therapy should be manualised, and training and regular supervision a prerequisite for using a specific method.

Q2: which psychotherapies are effective in treating PTSD and comorbid personality disorder?

Description of studies

The literature search for clinical guidelines and systematic reviews was conducted in February 2023, and one[44] was selected to form the basis of our review. As the literature search of this review was conducted in June 2020, and the search strategy was evaluated to be adequate by means of the AMSTAR 2,[39] our search for additional RCTs was set from this date and conducted on 3 May 2023. PRISMA flowcharts for clinical guidelines, systematic reviews and RCTs are provided in online supplemental E, figure S1, S5.1 and S5.2, respectively.

A total of seven RCTs reported in six publications were included in the Q2 meta-analysis across the primary and secondary outcomes.

All six trials included a population with PTSD and comorbid BPD. Four different groups of psychotherapies were investigated: dialectical behaviour therapy (DBT-for-PTSD) (2 trials), stabilising group treatment+treatment-as-usual (TAU) (1 trial), narrative exposure therapy (NET, 2 trials) and CBT (2 trials). See online supplemental F, table S2 for study details.

Risk of bias assessment

All included RCTs were estimated to have a high risk of bias across all outcomes (online supplemental E, figure S6). Funnel plots were not constructed due to the low number of trials.

Primary outcomes

No significant differences in treatment effects were found between any of the interventions on PTSD symptoms at the end of treatment. A single trial found a clinically significant difference (SD=0.78) between interventions on BPD symptoms at the end of treatment (mean difference (MD) −0.54, 95% CI −0.89 to −0.19, p=0.003, 1 study, n=93; low certainty), favouring DBT-for-PTSD over cognitive processing therapy (CPT). See online supplemental B for results on other outcomes and sensitivity and subgroup analyses. All analyses with significant results are reported in online supplemental G, table S2.

Certainty of evidence

The overall certainty of evidence for stabilising group therapy and TAU was considered very low due to risk of bias, indirectness and imprecision. The overall certainty of evidence for DBT-for-PTSD was considered low due to risk of bias and imprecision. See online supplemental B for a complete report. For GRADE assessments per outcome, see online supplemental G, table S2.

Evidence-based recommendations

An equally large improvement on PTSD symptoms was found for the interventions CPT and DBT-for-PTSD. However, compared with CPT, DBT-for-PTSD had a clinically significant larger beneficial effect on BPD symptoms and demonstrated a larger decline in self-harming behaviour (including suicidality). Despite the limited evidence and the fact that patient preferences regarding DBT-for-PTSD were unknown, the clinical guideline panel stressed the need for guiding treatment for this prevalent mental health service population. Thus, the guideline panel reached a weak recommendation for the use of DBT-for-PTSD to treat adults with PTSD and comorbid BPD. For complete research recommendations, see online supplemental B.

Q3: which psychotherapies are effective in treating PTSD and comorbid depression or moderate-to-severe depressive symptoms?

Description of studies

The literature search for clinical guidelines and systematic reviews was conducted in February 2023, and one[45] was selected to form the basis of our review. As the literature search of that review was conducted on 1 July 2013, and the search strategy was evaluated to be adequate by means of the AMSTAR 2,[39] our search for additional RCTs was set from this date and conducted on 5 May 2023. PRISMA flowcharts for clinical guidelines, systematic reviews and RCTs are provided in online supplemental E, figure S1, S7.1 and S7.2, respectively.

A total of 55 RCTs were included in the Q3 meta-analysis across the primary and secondary outcomes, reporting on 41 different psychotherapies. For meta-analysis, interventions were grouped in the following 11 intervention groups: (1) mindfulness and body-focused psychotherapies, (2) present-centred therapy (PCT), (3) cognitive therapy (CT), (4) interpersonal psychotherapy (IPT), (5) prolonged exposure (PE), (6) CPT, (7) virtual reality exposure, (8) CBT, (9) imagery, (10) NET and (11) eye movement desensitisation and reprocessing (EMDR). For study details, see online supplemental F, table S3.

Risk of bias assessment

Of the 48 RCTs reporting on the primary outcome of PTSD symptoms, 6 were considered to raise some concerns and the remaining to be at a high risk of bias. All 51 RCTs reporting on the primary outcome of depressive symptoms were deemed at a high risk of bias. See online supplemental E, figure S8.1–S8.6 for RoB 2 assessments, and online supplemental figures S9.1–S9.9 for funnel plots.

Primary outcomes

We found a clinically significant difference in treatment effect on PTSD symptoms at the end of treatment, favouring the following psychotherapies over their respective comparators. Mindfulness and body-focused psychotherapies were favoured over mind–body intervention, TAU and waitlist (SMD −0.81, 95% CI −1.28 to −0.34, p=0.0008, I^2=41%; 3 trials, n=137, moderate certainty). NET was favoured over trauma-focused psychotherapy, TAU and waitlist (SMD −0.66, 95% CI −1.22 to −0.10, p=0.02, I^2=65%; 5 trials, n=175, low certainty) and when removing the active comparators, NET showed an SMD of −1.07 (95% CI −1.22 to −0.10, p<0.00001, I^2=0%; 3 trials, n=175). CPT was favoured over trauma-focused psychotherapy, psychotherapy, TAU, sertraline placebo and alternative intervention (SMD −0.76, 95% CI −1.36 to −0.17, p=0.01, I^2=95%; 8 trials, n=1564, low certainty) and when removing

the outlier sertraline placebo, CPT showed an SMD of −0.32 (95% CI −0.68 to 0.03, p=0.07, I^2=86%; 7 trials, n=1475). A statistically significant difference favoured PE over trauma-focused therapy, non-trauma-focused therapy, TAU, waitlist and alternate intervention (SMD −0.35, 95% CI −0.64 to −0.05, p=0.02, I^2=78%; 11 trials, n=1567, low certainty) and when removing the outlier waitlist, PE showed an SMD of −0.16 (95% CI −0.32 to 0.01, p=0.06, I^2=33%, 10 trials, n=1520, low certainty).

We found a clinically significant difference in treatment effect on depressive symptoms at the end of treatment, favouring the following psychotherapies over their respective comparators. Mindfulness and body-focused psychotherapies were favoured over mind-body intervention, TAU and waitlist (SMD −0.81, 95% CI −1.36 to −0.26, p=0.004, I^2=76%; 5 trials, n=247, low certainty). NET was favoured over trauma-focused psychotherapy, TAU and waitlist (SMD −0.77, 95% CI -1.38 to −0.15, p=0.01, I^2=69%; 5 trials, n=174, low certainty). When removing the outlier waitlist, NET showed an SMD of −0.45 (95% CI −0.77 to −0.13, p=0.006, I^2=0%, 4 trials, n=155). CPT was favoured over trauma-focused psychotherapy, psychotherapy, TAU, sertraline placebo, alternative intervention (SMD −1.21, 95% CI −2.01 to −0.42, p=0.003, I^2=97%; 8 trials, n=1663, low certainty). When removing the outlier sertraline placebo, CPT showed an SMD of −0.58 (95% CI −1.18 to 0.01, p=0.05, I^2=95%; 7 trials, n=1574). PE was favoured over trauma-focused therapy, non-trauma-focused therapy, TAU, waitlist and alternate intervention (SMD −0.29, 95% CI −0.58 to 0.00, p=0.05, I^2=62%; 8 trials, n=1261, very low certainty). When removing the four active comparators, PE showed an SMD of −0.68 (95% CI −1.06 to −0.30, p=0.005, I^2=21%; 4 trials, n=165). CBT compared to trauma-focused psychotherapy, psychotherapy, TAU, waitlist, and an online intervention (SMD -0.30, CI 95% -0.58 to -0.02, p = .03, I^2=68%, 10 trials, n = 715, very low certainty)

We found a difference in treatment effect on depressive symptoms, favouring trauma-focused therapy and non-trauma-focused therapy over PCT (SMD −1.33, CI 95% −2.61 to −0.04, p=0.04, I^2=93%; 5 trials, n=225, low certainty). No significant difference in effect was found on PTSD symptoms at the end of treatment between PCT and trauma-focused psychotherapy.

After removing the outliers described above, there were no significant subgroup differences in any of the therapies for PTSD nor depression outcomes, except for CPT, where significant subgroup differences remained. However, these differences appear to be driven by the active comparators. See online supplemental H for subgroup analyses. All analyses with significant results are reported in online supplemental G, table S3.

Certainty of evidence

We considered the overall certainty of evidence to be moderate for mindfulness and body-focused psychotherapies (due to risk of bias). The overall certainty of evidence was considered to be low for PCT, PE and CPT (due to risk of bias, inconsistency and/or imprecision) as well as for NET (due to risk of bias and imprecision). See online supplemental B for a complete report and online supplemental G, table S3 for GRADE assessments per outcome.

Evidence-based recommendations

The evidence showed a statistically ($p<0.05$) and clinically (SMD>0.5) significant beneficial effect over comparators most evident for NET, and mindfulness and body-focused psychotherapies, but was also significant for CPT and PE on both PTSD and depressive symptoms. This statistical significance of PE over comparators disappeared when removing the waitlist group. There was minimal indication that any of these treatments led to more harmful effects in the form of AEs. Based on these results, clinician preference for PE, and considering patients were expected to prefer mindfulness and body-focused psychotherapies, the guideline panel reached a weak recommendation for using NET, mindfulness and body-focused psychotherapies, PE and CPT, when treating adults with PTSD and co-occurring depression. Due to the low to very low certainty of evidence and considering that the relative effects of PCT over other trauma-focused interventions were uncertain, the guideline panel reached a recommendation against routinely using PCT for PTSD and co-occurring depression. For complete research recommendations, see online supplemental B.

Q4: which psychotherapies are effective in treating PTSD and comorbid dissociative disorders or PTSD with dissociative symptoms?

Description of studies

The literature search for clinical guidelines and systematic reviews was conducted on 9 March 2023, and a search for additional RCTs was set from this date and conducted on 22 March 2023. PRISMA flowcharts for clinical guidelines, systematic reviews and RCTs are provided in online supplemental E, figure S1, S10.1 and S10.2, respectively.

In total, three RCTs were included in the Q4 meta-analysis across the primary and secondary outcomes. The trials evaluated (1) the effect of DBT+PE versus DBT in a population with PTSD and co-occurring BPD with moderate-to-severe dissociative symptoms, (2) CPT versus CPT-cognitive-protocol versus written account in a population with PTSD with dissociative symptoms and (3) PE versus PCT for PTSD with dissociative symptoms. See online supplemental F, table S4 for study details.

Risk of bias assessment

All trials were considered at a high risk of bias for both primary outcomes. The full risk of bias assessments for all outcomes can be observed in online supplemental figure E, figure S11. It was not possible to construct funnel plots due to the low number of trials.

Primary outcomes

We found no significant difference in treatment effect between any of the psychotherapies on PTSD or dissociative symptoms at the end of treatment. Results are reported in online supplemental G, table S4. See online supplemental B for results on other outcomes, and for sensitivity and subgroup analyses.

Certainty of evidence

The overall certainty of evidence was considered very low for all trials due to risk of bias, very serious imprecision and, in the case of one study (DBT+PE vs DBT), indirectness too. See online supplemental G, table S4 for GRADE assessments per outcome.

Evidence-based recommendations

Due to insufficient evidence to empirically address the research question, the guideline panel issued a 'good practice' recommendation. This recommendation was based on professional consensus among panel members to provide clinicians with some guidance on treating this prevalent mental health service

population. However, the guideline panel stressed that further research is needed to establish a solid evidence base.

Q5: which psychotherapies are effective in treating C-PTSD?

Description of studies

The literature search for clinical guidelines and systematic reviews was conducted in March 2023, resulting in one systematic review[46] being considered relevant for quality assessment, and as the basis for our review. The search strategy was evaluated to be adequate by means of the AMSTAR 2.[39] The literature search of the included systematic review was conducted in January 2018, and our search for additional RCTs was set from this date and conducted on 8 May 2023. PRISMA flowcharts for clinical guidelines, systematic reviews and RCTs are provided in online supplemental E, figure S1, S12.1 and S12.2, respectively.

In total, five RCTs were included in the Q5 meta-analysis across primary and secondary outcomes. Participants had either C-PTSD (ICD-11) or PTSD and a clinically significant level of the three Disturbances in Self-Organisation symptom domains. For meta-analysis, seven psychotherapies were grouped into: (1) imagery psychotherapy, (2) group psychotherapy and (3) skills training as an add-on to treatment. See online supplemental F, table S5 for study details.

Risk of bias assessment

Four trials reporting the primary outcome of PTSD symptoms were considered at a high risk of bias, while one was considered to pose some concerns (see online supplemental E, figure S13). Due to the low number of trials, it was not possible to construct funnel plots.

Primary outcomes

We found no significant difference in treatment effect between skills training as an add-on to treatment and waitlist or no-intervention control group comparators, neither for end-of-treatment symptoms of PTSD (three trials, low certainty) or Disturbances in Self-Organisation (three trials, low certainty). All results can be found in online supplemental G, table S5.

Certainty of evidence

The overall certainty of evidence was considered low for skills training as an add-on to treatment, due to risk of bias, imprecision and/or indirectness. See online supplemental G, table S5.

Evidence-based recommendations

No significant differences in beneficial or harmful effects were found between skills training as an add-on to treatment and the treatment alone (PE, imagery rescripting, and TAU). Patient preferences were unknown. Though evidence was limited, clinical experts stressed the need for treatment guidance for this prevalent mental health service population. The guideline panel provided a weak recommendation for offering psychotherapy with or without skills training as an add-on intervention for C-PTSD. For complete research recommendations, see online supplemental B.

DISCUSSION

Summary of findings and recommendations

Q1: The review identified 31 RCTs addressing trauma-focused psychotherapy for patients with adult PTSD and found no significant differences in symptom reduction or attrition rates between trauma-focused psychotherapy with or without exposure. As both approaches showed comparable effectiveness, a weak recommendation advises clinicians to offer either option while emphasising patient involvement in treatment decisions (cf. the potentially overwhelming effects of exposure therapy).

Q2: Seven RCTs examining psychotherapies for PTSD with comorbid BPD were identified, supporting DBT-for-PTSD as a promising treatment, comparable to CPT in reducing PTSD symptoms and superior in addressing BPD symptoms and self-harming behaviours. Despite low certainty of the evidence, DBT-for-PTSD received a weak recommendation, with the guideline panel stressing the need for further research.

Q3: The review identified 55 RCTs investigating PTSD with comorbid depression. Mindfulness and body-focused psychotherapies, PE, NET and CPT were found to be the most promising treatments for this population, improving both PTSD and depressive symptoms. However, since the certainty of evidence was considered low, only a weak recommendation was provided for their use. Due to uncertainty about its effectiveness, the guideline panel recommended against PCT for PTSD with depression.

Q4: Only three RCTs were identified for PTSD with dissociative symptoms and demonstrated no significant differences between treatments and comparators across outcomes. With very low certainty of the evidence, further rigorous studies are recommended to guide optimal treatment strategies, including integrating interventions targeting dissociative symptoms alongside PTSD treatment. To guide treatment for this prevalent mental health service population, the guideline panel issued a consensus-based 'good practice' recommendation for integrating interventions targeting dissociative symptoms alongside PTSD treatment.

Q5: Five RCTs examining psychotherapies for C-PTSD (ICD-11) were identified. The results suggested no significant benefits of skills training as an add-on over active interventions without the add-on. To guide treatment for this prevalent mental health service population, the guideline panel reached a weak recommendation for using Skills Training as an add-on to treatment was provided; however, they emphasised the need for more robust studies to guide clinical practice.

The results in context

Q1: A previous systematic review[43] supports our findings that trauma-focused psychotherapies with or without exposure are equally effective, and that treatment should be tailored to the patients' preferences. We reached this result by dichotomising trauma-focused interventions into absence of exposure or low-intensity exposure versus high-intensity exposure. This procedure adds valuable information compared with grouping all trauma-focused therapies as done in previous reviews.[22 47] However, this approach may have failed to capture the full spectrum of exposure strategies and intensities in PTSD treatments,[48] which may also explain why our subgroup analysis did not support superior effects of interventions considered effective for the treatment of PTSD (eg, CPT, EMDR) over trauma-focused psychotherapies with exposure.[47 48] Importantly, our findings address barriers for implementing exposure, demonstrating equal attrition levels across exposure and non-exposure interventions.[22]

Q2: In line with previous research,[44 49 50] DBT emerged as a promising treatment for individuals with PTSD and co-occurring BPD. Our review did not support a previous clinical guideline which endorsed NET for this population.[31] Importantly, the overall scarcity of research and absence of studies for personality disorders other than BPD highlights the need for further research to inform treatment planning.[16 31 50]

Q3: The results indicated beneficial effects in particular of NET and mindfulness and body-focused psychotherapies, but also for PE and CPT for PTSD and co-occurring depression. These interventions are also recommended in existing guidelines for simple PTSD.[29–32] However, these guidelines recommend the same interventions used for patients with and without co-occurring depression,[32 51] for example, CBT and EMDR, or sequential treatment depending on the severity of PTSD versus depression.[30] Our clinical guideline expands these recommendations by being the first to assess how the two diagnoses might most effectively be treated concurrently. Our findings support the efficacy of mindfulness or body-focused interventions, PE, NET and CPT for PTSD and co-occurring depression, whereas the evidence for CBT's and EMDR's effectiveness was inconclusive, highlighting the need for further research on this population.

Q4: Previous research has stressed the need for more robust trials to guide clinical practice for PTSD with comorbid dissociation.[13 52] The scarcity of evidence identified in our review underscores the need for high-quality evidence on psychotherapies for this population. While the consensus-based clinical recommendation in this clinical guideline was not evidence-based, it should provide some guidance for clinicians until further research is conducted.

Q5: This review is the first to require a full ICD-11 C-PTSD diagnosis for study inclusion. Despite the paucity of empirical evidence, the guideline panel reached a clinical recommendation for using trauma-focused psychotherapy with or without skills training. The findings mirror those of previous reviews with less stringent criteria;[53 54] though other reviews[46] have found CBT, exposure alone and EMDR to be effective treatments for C-PTSD. As suggested elsewhere,[55] the scarcity of high-quality studies on C-PTSD was to be expected, due to the recent introduction of the diagnosis. This paucity of evidence might explain the divergent findings and underscores the need for more rigorous trials to inform evidence-based clinical guidelines, tailored to the complex needs of individuals with C-PTSD.

Policy implications and implementation

Our results have significant practical implications for the development of clinical guidelines and the delivery of PTSD treatment. Given the limited evidence and lack of recommendations across clinical guidelines, further research is needed to refine treatment recommendations and improve treatment outcomes. This review underscores the urgent need for policy initiatives to prioritise research funding and foster collaboration among researchers, clinicians and policymakers to address the unique challenges faced by individuals with complex presentations of PTSD. The inclusion of specialised treatments such as DBT-for-PTSD in this guideline may offer promising avenues for improving treatment outcomes for those with comorbid BPD. However, the implementation of such evidence-based interventions will require concerted efforts to ensure accessibility to specialised treatments.

Strengths and limitations

This review adhered rigorously to established methodological frameworks, including the updated Cochrane Handbook for Systematic Reviews of Interventions,[35] the PRISMA guidelines[36] and the updated RoB 2.[40] Another strength is its comprehensive scope, which included a wide range of psychological interventions and rigorous quality assessment criteria. By systematically synthesising evidence, we provided a comprehensive overview of the current research landscape of psychotherapy for complex presentations of PTSD. Focusing on these real-world populations may increase the translatability of the results into clinical practice.

However, this review also has limitations. Despite efforts to minimise publication bias by including trials in multiple languages, our search strategy may not have identified all relevant literature. Additionally, the identified heterogeneity among included trials in terms of participant populations, interventions and comparators posed challenges for direct comparisons and thus the generalisability of the findings. We tested the effect of pooling different control groups by conducting several subgroup analyses and found that this had limited impact on the results. However, we acknowledge the potential limitations of this approach rather than separating the control groups.[56–58] We also acknowledge that the applied definition of psychotherapy may have led to the exclusion of studies on potentially effective interventions, such as guided self-help digital interventions.[59] Grouping interventions by predefined active ingredients, rather than broadly defined categories (eg, CBT), may lessen heterogeneity in future reviews. Furthermore, the scarcity of studies specifically targeting individuals with PTSD and comorbid BPD, dissociative symptoms or C-PTSD is a significant limitation. Moreover, the certainty of evidence for many of the interventions was low or very low, largely due to high risk of bias. Therefore, when evaluating the overall study findings, one should consider that high risk of bias trials tend to overestimate the beneficial effects and underestimate the harmful effects of the experimental interventions.[35] The lack of low risk of bias trials also prevented comparative analysis of low versus high risk of bias trials, as described in the protocol. To increase inclusivity in areas with a scarce evidence base, a study was considered eligible for inclusion if the mean baseline score of, for instance, depression was above a validated clinical cut-off score. This approach may have caused the inclusion of patients not meeting formal diagnostic criteria. However, using scores above cut-off would indicate at least a moderate level of symptoms and excluded many studies in the current review. Finally, the choice of clinical research questions might be biased, since they were chosen by a selected Danish mental health services guideline panel. Recommendations are warranted for other commonly co-occurring psychiatric disorders, such as substance use disorders,[60 61] eating disorders[62] and psychosis spectrum disorders.[63–65]

CONCLUSION

This project used state-of-the-art frameworks to conduct systematic reviews and develop clinical guideline recommendations for five research questions addressing psychotherapy for PTSD and complex presentations of PTSD. Based on the empirical evidence, patients' preferences and clinical expertise, the clinical guideline panel reached weak clinical recommendations for trauma-focused psychotherapies with/without exposure in treating simple PTSD; DBT-for-PTSD for treating PTSD with co-occurring BPD; Mindfulness and body-focused psychotherapies, CPT, NET and PE for treating PTSD with co-occurring depression; and Skills training for treating C-PTSD. A recommendation was also issued against using PCT for PTSD with co-occurring depression. Interventions targeting dissociation should be included in treating co-occurring dissociative symptoms. However, clinicians should apply the recommendations cautiously, since the certainty of the evidence and the number of high-quality studies remain low. This review underscores the urgent need for prioritising research funding and promoting collaboration among researchers, clinicians and policymakers to

meet the unique challenges faced by individuals with complex presentations of PTSD.

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