FIRST SUBMITTED VERSION

Treatment Efficacy and Effectiveness in Adults with Major Depressive Disorder and Childhood Trauma History: A Comprehensive Meta-Analysis

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Abstract

Background: Childhood trauma (CT) is a common and potent risk factor for developing major depressive disorder (MDD) in adulthood, characterized by earlier onset, more chronic/recurrent symptoms, and higher levels of comorbidity. Some studies indicate that evidence-based pharmacotherapies and psychotherapies for adult depression may be less efficacious in patients with a history of CT than patients without CT, but a comprehensive meta-analysis of treatment effects is lacking. Therefore, we examined whether individuals with MDD, including chronic forms of depression, and a reported history of CT (emotional/physical neglect or emotional/physical/sexual abuse before the age of 18), compared to depressed individuals without CT: (1) are more severely depressed prior to treatment, (2) have more unfavorable treatment outcomes with active treatments, and (3) are less likely to benefit from active treatments relative to a control condition (placebo, waitlist, or care-as-usual).

Methods: We conducted a comprehensive meta-analysis (PROSPERO CRD42020220139). Study selection combined the search of bibliographical databases (PubMed, PsycINFO, and Embase; November 21st, 2013 to March 16th, 2020) and full-text randomized clinical trials (RCTs) databases (1966 up to 2016-2019). RCTs and open trials comparing the efficacy or effectiveness of evidence-based pharmacotherapy, psychotherapy, or combination intervention for adult patients with depressive disorders and the presence or absence of CT were included. Two independent researchers extracted study characteristics. Group data for effect size calculations were requested from study authors. The primary outcome was depression severity change from baseline to the end of the acute treatment phase, expressed as standardized effect size (Hedges' g). Meta-analyses were performed using random-effects models.

Findings: From 10,505 publications, 54 trials met inclusion criteria, of which 29 (20 RCTs, nine open trials) contributed data of a maximum of 6,830 participants. Over half (62.5%) of MDD patients reported a history of CT. Despite being more severely depressed at baseline (g = 0.20, 95% CI = 0.15 to 0.26, I^2 = 0%), patients with CT benefited from active treatment similarly to patients without CT history (treatment effect difference between the groups: g = 0.02, 95% CI = -0.09 to 0.13, I^2 = 44.3%), with even slightly larger treatment (relative to control condition) effects for individuals with CT (CT: g = 0.61, 95% CI = 0.29 to 0.92, I^2 = 58%; no CT: g = 0.18, 95% CI = -0.20 to 0.55, I^2 = 67.5%; between-group p = 0.05) and similar dropout rates (RR = 1.06, 95% CI = 0.95 to 1.20, I^2 = 0%). Findings did not significantly differ by CT type, study design, depression diagnosis, assessment method of

CT, study quality, year, treatment type or length, but differed by country (North American studies showed larger treatment effects for patients with CT, $p_{FDR} = 0.01$). Most studies had a moderate to high risk of bias (72.4%), but sensitivity analysis in low-bias studies yielded comparable findings.

Interpretation: Contrary to what is currently theorized, MDD patients with CT improve well after pharmacological and psychotherapeutic treatments, notwithstanding their higher severity of depressive symptoms. Evidence-based psychotherapy and pharmacotherapy should be offered to MDD patients regardless of CT status.

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Keywords: childhood trauma; childhood maltreatment; depression; major depressive disorder; MDD; chronic depression; treatment-resistant depression; persistent depressive disorder; psychotherapy; pharmacotherapy; meta-analysis

Research in Context

Evidence before this study

Childhood trauma (CT) has been increasingly recognized as a common and major risk factor for the development and poorer course of major depressive disorder (MDD) in adulthood. A number of individual and meta-analytic studies indicate that a history of CT predicts poorer response to first-line depression treatments, suggesting the need for new personalized treatments for patients with MDD and CT. However, the evidence on poorer treatment outcomes in depressed adults with a history of CT has not been definitive: meta-analytic studies show high between-study heterogeneity, and some primary studies reveal similar or even better improvement for patients with CT following evidence-based psychotherapy or pharmacotherapy. It also remains unknown whether adults with MDD and CT benefit less from active treatment relative to control condition (e.g., placebo, waitlist, or care-as-usual) than adults with MDD but without CT history, or what is the relative contribution of different CT types. To comprehensively update and extend previous meta-analytic findings, we searched for eligible clinical trials in three bibliographical databases (PubMed, PsycINFO, and Embase; November 21st, 2013 to March 16th, 2020) and three full-text randomized clinical trials (RCTs) databases (1966 up to 2016-2019). RCTs and open trials comparing acute efficacy or effectiveness of evidence-based pharmacotherapy, psychotherapy, or combination treatment for adult patients with depressive disorders and the presence or absence of CT were included.

Added value of this study

Our meta-analysis is the largest and most comprehensive study of available evidence examining the impact of CT on the efficacy and effectiveness of first-line treatments for adults with MDD. Our findings suggest that despite being more severely depressed at the start and end of treatment, patients with MDD and CT benefit from acute treatment similarly to patients with MDD but without CT history, showing similar dropout rates. Findings seem consistent across CT types and treatment approaches (psychotherapy or pharmacotherapy).

Implications of all the available evidence

Contrary to previous evidence, patients with MDD and CT history experience similar improvement after acute pharmacological and psychotherapeutic treatments compared to patients without CT history. Thus, evidence-based psychotherapy and pharmacotherapy should be offered to MDD patients regardless of CT status. To provide further progress and

improve outcomes for individuals with CT, future comprehensive (collaborative) research is necessary to examine long-term treatment outcomes and mechanisms through which CT exerts its long-lasting effects.

Introduction

Childhood trauma (CT), often operationalized as emotional/physical neglect or emotional/physical/sexual abuse before the age of 18, is a common and major risk factor for the development and more severe course of depression in adulthood [1-4]. A high prevalence of CT (~46%) in adults with depression has been found, with even higher rates in chronic depression [3,5,6]. Patients with depressive disorders, including major depressive disorder (MDD), and the presence of CT, are more often characterized by an earlier onset and more severe course of illness, greater disease recurrence, increased comorbidity, and worse outcomes to psychotherapy or pharmacotherapy treatments [2-4,7]. Several neurobiological and psychological pathways such as dysregulated bodily stress systems or maladaptive personality characteristics may explain how CT contributes to the persistently increased risk for and greater severity of MDD across the life span, possibly contributing to poorer response to first-line depression treatments [8-11].

Being a common and potent risk factor for depression, CT presents an opportunity to better understand for whom one treatment may be less beneficial than the other and to provide insights into personalized treatment planning, essential to reduce personal and societal burden [12,13]. Indeed, previous meta-analytic findings of studies published before 2010 revealed that adults and adolescents with depression and a history of CT were around 1.5 times more likely to not respond or remit after pharmacotherapy, psychotherapy, or combination treatment (10 trials, n = 3,098) [4]. These findings were further extended by a meta-analysis of studies published by 2013, suggesting that depressed adults with CT were twice as likely to not respond to psychotherapy or pharmacotherapy (5 trials, n = 1,229) [3]. However, evidence on poorer treatment outcomes in patients with CT has not been definitive, with meta-analytic findings synthesizing various treatment outcomes and, thus, showing large between-study heterogeneity. In fact, some primary studies showed that CT history predicted better improvement following solution-focused or psychodynamic psychotherapies in comparison to the absence of CT in adults with mood or anxiety disorders [14] and better response to Cognitive Behavioral Analysis System of Psychotherapy (CBASP) in comparison to antidepressant medication (nefazodone) or supportive psychotherapy in adults with chronic depression [15,16]. Similar effects of antidepressant medication (vortioxetine) in adults with and without trauma (childhood or recent) were also found by synthesizing data from four clinical trials on MDD [17]. Moreover, previous meta-analyses did not examine whether adults with depression and CT benefit less from active treatment relative to a control condition (e.g., placebo, waitlist, or care-as-usual) than adults with depression but without

CT history. For instance, some findings suggested that vortioxetine was more beneficial than pill placebo for adults with MDD and CT [17]; however, neither fluoxetine, cognitive-behavioral therapy (CBT), nor their combination, was more efficacious than pill placebo for adolescents with MDD and CT (physical abuse) [18]. In fact, exposure to sexual abuse predicted lower depressive symptoms following a placebo than CBT in the latter study. Nevertheless, active treatment effects relative to a control group have been lacking and have not been meta-analytically examined to provide meaningful conclusions.

Further findings on treatment type suggest that psychotherapy alone (i.e., CBASP) could be more beneficial than pharmacotherapy alone and slightly less efficacious than combination treatment for chronically depressed individuals with CT [15]. However, the evidence has not been consistent, with meta-analytic findings showing no significant differences between psychotherapy and pharmacotherapy treatment approaches [3,4]. Although understudied, addressing CT type is essential to understand better whether depression persistence stems from a particular type of CT (such as emotional maltreatment) or severity and comorbidity of CT (frequency and combination of different types of CT) [6,16,19]. Yet, there are currently no meta-analytic findings on specific CT types concerning depression treatment outcomes. Therefore, the current meta-analysis aimed to comprehensively update and extend previous meta-analytic findings by examining whether adults with MDD, including chronic depression, and self-reported CT history: (1) are more severely depressed prior to treatment, (2) have more unfavorable baseline to post-treatment outcomes with active treatments, and (3) are less likely to benefit from active treatments relative to a control condition (placebo, waitlist, or care-as-usual). We also examined the influence of CT on dropout rates (for any reason), the relative contribution of CT types (emotional/physical neglect or emotional/physical/sexual abuse), and the impact of potential effect modifiers such as treatment type or study quality was examined.

Methods

Search strategy and selection criteria

For the present meta-analysis, we employed a comprehensive study-selection approach searching three bibliographical databases (PubMed, PsycINFO, and Embase - from November 21st, 2013 [search date of the latest meta-analysis; [3]] to March 16th, 2020) and the full-text screening of studies in three existing randomized clinical trials (RCTs) databases on psychological depression treatment (from 1966 to 2019) (also see www.metapsy.org) [20], pharmacological depression treatment (from 1966 to 2016) [21], and a landscape of clinical

trials (from 1966 to 2018) [22], to identify journal articles in English on CT and adult depression treatment outcome. We also screened the studies included in earlier meta-analyses [3,4,17] and considered available trials that assessed CT, but had not yet published their findings and were not identified via search and screening. Studies in bibliographical databases were identified by the search string combining index and free terms (see supplement for the search string in PubMed). Both RCTs and open trials (non-randomized/non-controlled studies of interventions) comparing the efficacy or effectiveness of evidence-based psychotherapy, pharmacotherapy, or a combination intervention for acute treatment of adult depression for patients with and without CT were considered for inclusion.

Studies were included if they focused on (1) adults (age ≥ 18 years old), (2) depression as a primary diagnosis operationalized as diagnosis or elevated depressive symptoms, (3) available CT assessment (presence or absence of emotional/physical neglect or emotional/physical/sexual abuse before the age of 18), (4) intervention for depression, defined as psychotherapy or pharmacotherapy, alone or in combination with another treatment (non-evidence-based interventions such as yoga or ketamine therapy were excluded), (5) comparator group (when applicable), including control condition (no treatment, waitlist, care-as-usual, or therapy/pill placebo) or another active treatment, and (6) reported either clinician or self-reported depression severity using validated measures before and after the acute treatment phase. Study results that were not published as a formal research article in journal, articles in a language other than English, literature reviews or meta-analyses, studies in children, adolescents, or animals, and studies using routine outcome monitoring (ROM) data (regular measurements of patients' progress in clinical practice) were excluded. If the number of participants (with and without CT) per treatment group, pre-post treatment mean depression severity with corresponding standard deviations (SDs), and the correlation coefficient between pre-post treatment depression severity were not reported, we contacted study's corresponding author or principal investigator, asking them to contribute their group's data to this meta-analysis. The presence of CT was based on the study's definition (see Table 1 for the list of CT measures); however, when available, we asked authors to dichotomize CT as *no/low* vs. *moderate/severe* (see supplement with applied cut-offs of CT measures that had such division) to account for low levels of CT in the general population and, thus, provide higher sensitivity in a clinical population [23]. If possible, we also asked for data for different CT types. Studies not providing the needed data were excluded. Two independent researchers screened all studies, and the decision to include a study in the

meta-analysis was mutual. Disagreements were resolved by discussion or involvement of another independent researcher.

Data analysis

The protocol for this meta-analysis was registered at PROSPERO (CRD42020220139). The main extracted characteristics of the study included the number of participants, study year, country, design, depression diagnosis, depression severity measure, CT type, CT measure, treatment type, treatment length, and (if applicable) control group type. The primary outcome was a clinician or self-reported difference in mean depression severity change from baseline to the end of the acute treatment phase, expressed as the standardized mean difference - Hedges' g with corresponding 95% confidence intervals (CIs). If both clinician and self-reported measures were available, a clinician-rated measure was preferred from study authors to avoid high heterogeneity of used self-reported assessment tools (comparison of clinician and self-reported tool showed no significant outcome difference in our study). The secondary outcome was a study's dropout rate (for any reason) from baseline to post-treatment, expressed as a risk ratio (RR) with a corresponding 95% CI.

The quality of the included studies was assessed by the Cochrane Collaboration Risk of Bias (RoB 2.0) Tool for RCTs [24] and the modified Non-randomized Studies of Interventions (ROBINS-I) Tool for open trials [25]. The RoB 2.0 assesses five sources of bias: (1) bias arising from the randomization process, (2) bias due to deviations from the intended interventions, (3) bias due to the treatment of missing data, (4) bias in the measurement of the outcome (regardless of blinding status, if only self-report was available, it was rated as low risk in the current study), and (5) bias in the selection of reported results. The ROBINS-I assesses seven sources of bias: (1) bias due to confounding, (2) bias in the selection of participants into the study, (3) bias in classification of interventions (not used in the current study), (4) bias due to deviations from the intended interventions, (5) bias due to the treatment of missing data, (6) bias in the measurement of the outcome, and (7) bias in the selection of reported results. The overall study quality was coded as "low", "some concerns" (equivalent to ROBINS-I "moderate"), or "high" RoB (equivalent to ROBINS-I "serious" or "critical"). Two independent researchers performed study quality assessments (weighted kappa for inter-rater reliability was 0.532 ($p = 0.003$), indicating moderate and statistically significant agreement (69.0%) [26,27]). A consensus or a third-person involvement resolved inconsistencies.

Data were synthesized by the *meta* [28,29] R software package (R 4.0.2 and R Studio 1.3.959) [30,31]. The number of participants (with and without CT) within the treatment and, if applicable, control group, mean pre-post treatment depression severity with corresponding SDs, and the pre-post treatment depression severity correlation, essential for the calculation of pre-post treatment effects [32], was used to calculate effect sizes (Hedges' g, 0.2 - small, 0.5 - moderate, 0.8 - large effect) [33,34]. Syntheses were performed using the random-effects models with Sidik-Jonkman (SJ) estimator and the Hartung-Knapp-Sidik-Jonkman method (HKSJ) due to anticipated heterogeneity among the studies [35-37].

First, we determined whether individuals with CT were more severely depressed than those without CT prior to depression treatment using all eligible studies. This was performed by pooling effect sizes, indicating the difference at baseline between individuals with CT and those without CT. Second, we determined whether individuals with CT showed more unfavorable depression treatment outcome than those without CT. This was performed by pooling the effect sizes indicating the difference within each active treatment condition between the change from baseline to post-treatment separately in individuals with and without CT. Last, we determined whether individuals with CT were less likely to benefit from active depression treatment than a control condition (placebo, waitlist, care-as-usual). This was achieved by pooling effect sizes, indicating the difference between the baseline to post-treatment change in individuals with CT in the treatment condition compared to the baseline to post-treatment change in individuals with CT in the control condition (examined in the context of RCTs). The latter analysis was also performed for patients without CT, and pooled effects were statistically compared between CT and no CT groups. Additionally, we examined the influence of CT on dropout rates from the baseline to post-treatment (examined in studies with dropout and without imputed data). All meta-analyses were also performed separately for different CT types (relative to no CT group).

For sensitivity analysis, we reran all analyses, including only studies with a low RoB. Further, we assessed the impact of the study's quality (low, some concerns, high), year, and treatment length (weeks) using meta-regression analyses. We determined whether results differed by study design (RCT vs. open trial), country (North America vs. Europe vs. other), depression diagnosis (chronic/treatment-resistant depression vs. other), CT measure (CTQ vs. other), and treatment type (pharmacotherapy vs. psychotherapy) for the subgroup analyses. The Benjamini-Hochberg False Discovery Rate (FDR p-value < 0.05) was used to correct for multiple meta-regression and subgroup analyses [38].

Potential outlier studies were identified by 95% CI of the effect size not overlapping with the 95% CI of the pooled effect size and observed in the Baujat plot for heterogeneity of individual studies [37]. The extent of heterogeneity among the studies in all analyses was assessed by Higgin's I^2 statistic with corresponding 95% CI, indicating low (25%), moderate (50%), or high (75%) heterogeneity [39]. Publication bias was investigated by performing the Egger's test for the asymmetry of the funnel plot [40] and Duval & Tweedie's trim-and-fill procedure to estimate the true effect size [37,41].

Results

Study inclusion and characteristics

A total of 10,505 publications were examined. After screening 8,310 abstracts (k = 5,218 after removal of duplicates) from three bibliographical databases, 65 full-text articles were retrieved (Figure 1). Of these, 41 were excluded, leaving 24 studies for inclusion. After the full-text screening of psychotherapy for depression database (k = 501) [20], the pharmacotherapy for depression database (k = 522) [21], and the landscape of clinical trials database (k = 1,149 focused on CT) [22], 12, zero, and 19 studies, respectively were identified as fitting our inclusion criteria (21 after removal of duplicates). Twelve studies were identified from the full-text screening of records in earlier meta-analyses (k = 19). Four additional studies were included that were available but had not yet published their findings and, thus, were not identified via search and screening. Overall, 61 studies met inclusion criteria (54 unique studies after removal of duplicates), of which 29 (53.7%) agreed to contribute their data and, therefore, were included in the meta-analysis (see supplement with the reference list). As compared to studies, which did not provide data (k = 25), examined studies were more recent (median = 2017, IQR = 4 vs. median = 2014, IQR = 6, p = 0.012) and more often conducted in Europe (X^2 = 18.791, df = 2, p < 0.001).

A maximum of 29 studies (20 RCTs, nine open trials) were available for analysis, with 57 CT vs. no CT group comparisons (48 in RCTs, nine in open trials) and 6,830 participants (5,609 in RCTs, 1,221 in open trials). Characteristics of included studies are presented in Table 1 (see supplement with summary descriptives). Briefly, the majority of the clinical trials (k = 15, 51.7%) were conducted in Europe, followed by North America (k = 9, 31.0%). Most of the studies focused on MDD (k = 16, 55.2%) and eleven trials solely focused on patients with chronic/treatment-resistant depression (37.9%). Clinician-rated depression severity measures were most common (k = 21, 72.4%) and CT was mostly assessed by the self-reported CTQ (k = 18, 62.1%). The majority of studies were characterized by a moderate

to high RoB (*k* = 21, 72.4%), with eight studies scoring at low risk (27.6%) (see supplement for RoB plots). Out of 57 available trial arms, 27 focused on psychotherapy (47.4%), 21 on pharmacotherapy (36.8%), one on combination treatment (1.8%), and eight on control conditions (14.0%). CBT and SSRIs were the most commonly used psychotherapy and pharmacotherapy types (10 clinical trial arms each, 37.0% and 47.6%, respectively), while care-as-usual was the most frequent control condition (four arms, 50.0%). The median time from pre- to post-treatment was 12 weeks (5 to 144 weeks).

More than half (*n* = 4268, 62.5%) of the participants from the included studies reported the experience of CT. The most common CT types were emotional neglect (57.9%) and emotional abuse (52.1%), followed by physical abuse (42.5%), physical neglect (39.6%), and sexual abuse (34.8%).

[Figure 1 around here]

[Table 1 around here]

Main findings

The difference in baseline depression severity between individuals with CT and those without CT was analyzed using 29 studies with 56 comparisons and a total of 6,805 participants (Table 2). Individuals with CT were significantly more depressed at baseline (g = 0.202, 95% CI = 0.145 to .258, $p < 0.001$) with low between-study heterogeneity ($I^2 = 0\%$). Exclusion of two potential outlier studies resulted in comparable outcomes (g = 0.200, 95% CI = 0.148 to 0.253) (see supplement for Baujat plots). No significant publication bias was observed (Egger: t = -1.48, p = 0.144), but a trim-and-fill procedure added nine studies and increased the effect size to g = 0.235 (95% CI = 0.172 to 0.298) (see supplement for funnel plots).

Treatment was efficacious in reducing depression severity from baseline to post-treatment for both individuals with CT (g = 1.272, 95% CI = 1.062 to 1.482, $p < 0.001$; 29 studies with 49 comparisons with 3892 participants) and those without CT (g = 1.400, 95% CI = 1.114 to 1.685, $p < 0.001$; 29 studies with 48 comparisons with 2382 participants). In both meta-analyses, the heterogeneity was very high (CT: $I^2 = 88.6\%$; no CT: $I^2 = 86.5\%$). Direct comparison of depression severity changes from baseline to post-treatment between individuals with CT and without CT was meta-analyzed using 29 studies with 48 comparisons and 6,250 participants (Figure 2). Results showed no difference between the groups (g = 0.016, 95% CI = -0.094 to 0.125, p = 0.774) with moderate heterogeneity (I^2 =

44.3%). Exclusion of four potential outlier studies resulted in comparable outcomes (g = 0.030, 95% CI = -0.061 to 0.121). No significant publication bias was observed (Egger: t = -1.52, p = 0.134), but a trim-and-fill procedure added five studies and increased effect size to g = 0.070 (95% CI = -0.032 to 0.172). Figure 3 shows a visual representation of mean depression severity changes from baseline to post-treatment, highlighting patients with CT being more severely depressed at the start and end of the treatment but experiencing similar treatment gains to patients without CT history.

Synthesis of 8 studies with 11 comparisons and 902 participants showed that individuals with CT who received active treatment experienced greater reductions in symptoms than individuals with CT placed in control conditions (g = 0.605, 95% CI = 0.294 to 0.916, p = 0.002; I^2 = 58%). Exclusion of two potential outlier studies resulted in comparable outcomes (g = 0.614, 95% CI = 0.307 to 0.922). Publication bias was not significant (Egger: t = 1.88, p = 0.093), but a trim-and-fill procedure added three studies and reduced the effect size to g = 0.456 (96% CI = 0.126 to 0.787). Similarly, individuals without CT benefited from active treatment more than being placed in control groups (8 studies with 11 comparisons and 450 participants), although treatment effect was smaller and not significant (g = 0.178, 95% CI = -0.195 to 0.552, p = 0.312; I^2 = 67.5%). Comparison of pooled baseline to post-treatment effects (active treatment vs. control condition) between patients with and without CT showed no significant difference (p = 0.051). Exclusion of two potential outlier studies resulted in comparable outcomes (g = 0.173, 95% CI = -0.084 to 0.429). The effect for publication bias was not significant (Egger: t = 2.27, p = 0.050) with a trim-and-fill procedure adding four studies and reducing effect size to g = 0.026 (95% CI = -0.252 to 0.304).

The difference in dropout rate for any reason was synthesized using 17 studies with 29 comparisons and 3,501 participants. Individuals with CT were more likely to dropout, but the difference was not significant (RR = 1.063, 95% CI = 0.945 to 1.195, p = 0.297; I^2 = 0%). Exclusion of two potential outlier studies resulted in comparable outcomes (g = 1.055, 95% CI = 0.946 to 1.176). Publication bias was not significant (Egger: t = -2.04, p = 0.051); a trim-and-fill procedure added five studies and increased effect size to RR = 1.108 (95% CI = 0.968 to 1.269).

[Table 2 around here]

[Figure 2 and 3 around here]

Meta-regression and subgroup analyses

Findings did not significantly differ by CT type, study design, depression diagnosis, CT assessment tool, study quality, year, treatment type or length (Table S2 and S3). Subgroup analyses on country showed significant difference (p_{FDR} = 0.024) with larger CT vs. no CT treatment effect in studies conducted in North America (g = 0.150, 95% CI = 0.030 to 0.269) than those conducted in other Asia-Pacific countries (g = -0.255, 95% CI = -0.508 to -0.002; subgroup p_{FDR} = 0.008), with no significant difference compared to studies conducted in Europe (g = 0.010, 95% CI = -0.182 to 0.202). However, due to limited power and many analyses conducted, these findings should be interpreted with caution [42].

Sensitivity analysis

Sensitivity analysis using data from the low RoB studies (n = 8) yielded smaller effects, but results were similar to the primary findings. Individuals with a history of CT were more severely depressed at baseline (g = 0.137, 95% CI = 0.029 to 0.246, p = 0.016; k = 20), benefited from depression treatment comparably to patients without CT (g = -0.077, 95% CI = -0.280 to 0.125, p = 0.426, k = 15) and dropped out as much as those without CT (RR = 0.964, 95% CI = 0.726 to 1.282, p = 0.782, k = 11), with treatment being more efficacious relative to a control condition (g = 0.546, 95% CI = 0.109 to 0.983, p = 0.021; k = 8).

Discussion

The current meta-analysis comprehensively examined the impact of CT on the efficacy and effectiveness of pharmacotherapy and psychotherapy for adults with depression using data from 29 interventional studies and 6,830 patients with MDD, including chronic depression. The presence of CT was relatively high (63%), with emotional neglect (58%) and emotional abuse (52%) showing the highest rates. Despite being more severely depressed at the start and end of treatment, patients with CT benefited from treatment similarly to patients without CT history, with even slightly larger treatment (relative to the control condition) effects for individuals with CT and similar dropout rates. Findings did not differ by CT type, study design, depression diagnosis, assessment method of depression and CT, study quality, year, treatment type or length.

The prevalence rates of CT were slightly higher but rather comparable to previous meta-analyses, suggesting that around 46% of depressed adults report a history of CT, with emotional neglect/abuse being the most common [3]. Relatively higher CT rates in our study could be explained by the high number of studies focused on chronic/treatment-resistant

depression, as this sample often reports even higher CT rates (~75%) [5,6]. Our results on CT predicting similar or slightly better (relative to placebo, waitlist, or care-as-usual) treatment outcome contrasts with previous meta-analytic findings highlighting poorer treatment response in depressed individuals with CT [3,4]. The inconsistencies with earlier meta-analytic findings could be explained by differences in treatment outcome definition or publication and selection bias. Previous meta-analyses conceptualized outcome as a response or remission rate, with primary studies inconsistently controlling for baseline depression severity, likely allowing for stronger contrast between CT and no CT groups. Subsequently, more improvement could be required for patients with CT to meet the definition of remission. In contrast, in our meta-analysis, we examined baseline to post-treatment mean depression severity change consistently taking baseline symptoms into account and using pre-post treatment depression severity correlations in effect size calculations [32]. Publication bias could also play a role. Earlier meta-analyses included studies only from bibliographical databases searching for combinations of terms such as *childhood maltreatment*, *depression*, and *treatment* in study titles or abstracts. There is a high chance that mostly studies with significant CT findings were identified. In contrast, we additionally included many trials from a full-text screening of existing databases, likely providing a broader overview and a more realistic picture of CT's impact on depression treatment outcome. Selection bias is also noteworthy, because not all identified studies contributed their data, leading to significant study differences in year and country, making a comparison of findings with previous meta-analyses more difficult. Nevertheless, our findings align with studies showing similar or even better treatment efficacy in depressed patients with CT than without CT following solution-focused or psychodynamic psychotherapies, CBASP, and vortioxetine treatment [14,15,17]. Our findings also support the evidence that important clinical factors in depression, such as comorbid personality disorders, considered to lead to worse treatment outcomes, actually do not significantly impact the effectiveness of acute depression treatment [43].

The finding of CT predicting similar or slightly better (relative to placebo, waitlist, or care-as-usual) treatment outcome could be interpreted in several ways. First, some evidence indicates that patients with CT history are characterized by greater treatment motivation and a more explicit treatment focus than patients without CT [44]. Therefore, although more severely depressed, patients with CT may be more engaged and ready for treatment. In line, the probability of dropout in our meta-analysis was similar among the individuals with and without CT, supporting findings from previous clinical trials [15,45]. Second, because patients with CT history are more severely depressed prior to treatment, they also have more room for

improvement and, thus, could experience similar or even greater treatment gains than patients without CT history. Indeed, a faster symptom decline during treatment in more severely depressed patients has been observed in multiple studies [46,47].

Our findings did not show a difference between psychotherapy and pharmacotherapy treatment approaches, suggesting that psychotherapy and pharmacotherapy effectively reduced depressive symptoms for individuals with and without CT. Although due to power limitations [42], we could not compare specific psychotherapy (e.g., trauma-focused therapy such as CBASP) and pharmacotherapy types or combination treatment to monotherapy, our findings are in line with previous meta-analyses, showing no significant difference between psychotherapy and pharmacotherapy treatment approaches [3,4]. Moreover, no considerable differences between the CT types (relative to no CT group) were observed, contrasting findings by Klein, Erkens [16] on emotional abuse being a significant predictor of CBASP outcome compared to other CT types in chronic depression. Nevertheless, our findings suggest that the impact of CT may stem from the "context of abuse" (frequent recurrence and co-occurrence of multiple CT types) rather than a specific type of CT [48]. In fact, previous evidence showed that depressed patients with CT often report more than one CT type (~19%), and multiple types are even more common in chronic depression (~37%) [3,6]. Hence, future (meta-analytic) studies should further examine the importance of traumatic load on depression treatment outcomes.

Strengths & limitations

To our knowledge, this is the largest and most comprehensive meta-analysis of available studies to date examining the impact of CT on the efficacy and effectiveness of adult depression treatment. The study-selection approach included search in bibliographical databases and the full-text screening in existing RCTs databases to balance the identification of studies with selective publication of significant CT findings. Indeed, most of our analyses showed non-significant publication bias, and funnel plots showed a relatively symmetrical distribution of studies. Moreover, we have extended previous findings by examining active treatment vs. control group effects for individuals with CT and focusing on multiple CT types to determine their relative contribution. A wide selection of potential effect modifiers such as treatment approach or study quality was also considered in meta-regression and subgroup analyses.

However, some limitations have to be acknowledged. First, heterogeneity was moderate to high in most of the analyses, indicating a high variance of the results among the

studies. Although we conducted multiple meta-regression and subgroup analyses to explain this heterogeneity, other potential effect modifiers not examined in the current study could play a role. Second, while consistent with previous meta-analyses in adult depression treatment [21,49], the RoB was moderate to high in most studies, indicating low study quality. However, in line with earlier CT meta-analysis by Nanni, Uher [4], study quality did not significantly impact findings, and sensitivity analysis in low-bias studies showed comparable results. Third, due to methodological design limitations, we did not statistically control for potential confounding factors (demographic or clinical), and although it allowed for a better comparison of effect sizes among the studies, there is a chance of bias. To comprehensively examine this, an individual-patient-data (IPD) meta-analysis is necessary, but previous meta-analytic findings did not show a significant aggregated study-level effect of age or gender in the context of CT and depression treatment outcome [3,4]. Fourth, not all study authors could contribute their data, leading to an increased likelihood of selection bias and a lack of controlled studies and trials from earlier meta-analyses. Subsequently, drawing firm conclusions and directly comparing findings with previous meta-meta-analyses is difficult. Moreover, we could not examine specific subgroups (e.g., trauma-focused therapy vs. other psychotherapies or combination treatment vs. monotherapy). Fifth, our meta-analysis focused on acute treatment outcome, but it may be that depressed patients with CT, who are often characterized by a higher risk of relapse, benefit from treatment significantly less than patients without CT in the long run. Last, in all included studies, CT was reported retrospectively. Current evidence suggests that the agreement between prospective and retrospective CT reports is low, identifying distinct groups of individuals with potentially different mechanisms through which CT affects mental health outcomes [50,51]. Therefore, the generalizability of our findings is limited to retrospective CT reports.

Conclusion & future research

Patients with MDD, including chronic depression, and CT history, are more severely depressed; however, contrary to previous evidence, they experience similar improvement after pharmacological and psychotherapeutic treatments compared to patients without CT history. Thus, evidence-based psychotherapy and pharmacotherapy should be offered to MDD patients regardless of CT status. To provide further meaningful progress and improve outcomes for individuals with CT, future comprehensive (collaborative) research is necessary to examine long-term treatment outcomes and mechanisms through which CT exerts its long-lasting effects.

References

1. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *The Lancet Public Health* 2017; **2**(8): e356-e66.
2. Hovens JG, Giltay EJ, Wiersma JE, Spinhoven P, Penninx BW, Zitman FG. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatr Scand* 2012; **126**(3): 198-207.
3. Nelson J, Klumparendt A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: Meta-analysis. *Br J Psychiatry* 2017; **210**(2): 96-104.
4. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry* 2012; **169**(2): 141–51.
5. Struck N, Krug A, Yuksel D, et al. Childhood maltreatment and adult mental disorders - the prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Res* 2020; **293**: 113398.
6. Negele A, Kaufhold J, Kallenbach L, Leuzinger-Bohleber M. Childhood Trauma and Its Relation to Chronic Depression in Adulthood. *Depress Res Treat* 2015; **2015**: 650804.
7. Hovens JG, Wiersma JE, Giltay EJ, et al. Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. *Acta Psychiatr Scand* 2010; **122**(1): 66-74.
8. Kuzminskaite E, Penninx BWJH, van Harmelen A-L, Elzinga BM, Hovens JGFM, Vinkers C. Childhood Trauma in Adult Depressive and Anxiety Disorders: An Integrated Review on Psychological and Biological Mechanisms in the NESDA Cohort. *Journal of Affective Disorders* 2021; **283**: 179-91.
9. Teicher MH, Gordon JB, Nemeroff CB. Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry* 2021.
10. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry* 2013; **170**(10): 1114-33.
11. Lippard ETC, Nemeroff CB. The Devastating Clinical Consequences of Child Abuse and Neglect: Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders. *Am J Psychiatry* 2020; **177**(1): 20-36.
12. Hughes K, Ford K, Bellis MA, Glendinning F, Harrison E, Passmore J. Health and financial costs of adverse childhood experiences in 28 European countries: a systematic review and meta-analysis. *The Lancet Public Health* 2021; **6**(11): e848-e57.
13. Kessler RC. The potential of predictive analytics to provide clinical decision support in depression treatment planning. *Curr Opin Psychiatry* 2018; **31**(1): 32-9.
14. Heinonen E, Knekt P, Harkanen T, Virtala E, Lindfors O. Childhood adversities as predictors of improvement in psychiatric symptoms and global functioning in solution-focused and short- and long-term psychodynamic psychotherapy during a 5-year follow-up. *J Affect Disord* 2018; **235**: 525-34.
15. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proceedings of the National Academy of Sciences of the United States of America* 2003; **100**(24): 14293–6.
16. Klein JP, Erkens N, Schweiger U, et al. Does Childhood Maltreatment Moderate the Effect of the Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy in Persistent Depressive Disorder? *Psychother Psychosom* 2018; **87**(1): 46-8.

17. Christensen MC, Florea I, Loft H, McIntyre RS. Efficacy of vortioxetine in patients with major depressive disorder reporting childhood or recent trauma. *J Affect Disord* 2020; **263**: 258-66.
18. Lewis CC, Simons AD, Nguyen LJ, et al. Impact of childhood trauma on treatment outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry* 2010; **49**(2): 132-40.
19. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. *European Psychiatry* 2015; **30**(6): 665-80.
20. Cuijpers P, Karyotaki E, Ciharova M, et al. A meta-analytic database of randomised trials on psychotherapies for depression. 2020.
21. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet* 2018; **391**(10128): 1357-66.
22. Vinkers CH, Lamberink HJ, Tijdink JK, et al. The methodological quality of 176,620 randomized controlled trials published between 1966 and 2018 reveals a positive trend but also an urgent need for improvement. *PLoS Biol* 2021; **19**(4): e3001162.
23. Baker AJL, Maiorino E. Assessments of emotional abuse and neglect with the CTQ: Issues and estimates. *Children and Youth Services Review* 2010; **32**(5): 740-8.
24. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
25. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.
26. Cohen J. Weighted kappa: Nominal scale agreement with provision for scaled disagreement or partial credit. *Psychological Bulletin* 1968; **70**(4): 213–20.
27. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**(1): 159-74.
28. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: A practical tutorial. *Evidence-Based Mental Health* 2019; **22**(4): 153-60.
29. Schwarzer G. meta: An R package for meta-analysis. *R News,* 2007; (7): 40–5.
30. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
31. RStudio Team. RStudio: Integrated Development for R. Boston, MA: RStudio, PBC; 2020.
32. Cuijpers P, Weitz E, Cristea IA, Twisk J. Pre-post effect sizes should be avoided in meta-analyses. *Epidemiol Psychiatr Sci* 2017; **26**(4): 364-8.
33. Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press; 1985.
34. Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Erlbaum; 1988.
35. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014; **14**: 25.
36. Sidik K, Jonkman JN. A comparison of heterogeneity variance estimators in combining results of studies. *Stat Med* 2007; **26**(9): 1964-81.
37. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis With R: A Hands-On Guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021.
38. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc* 1995; **57**(1): 289–300.

39. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**(7414): 557-60.
40. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**(7109): 629-34.
41. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**(2): 455–63.
42. Cuijpers P, Griffin JW, Furukawa TA. The lack of statistical power of subgroup analyses in meta-analyses: a cautionary note. *Epidemiol Psychiatr Sci* 2021; **30**: e78.
43. van Bronswijk SC, Koster EM, Peeters F. Effectiveness of Acute-Phase Treatment of Depression Is Not Influenced by Comorbid Personality Disorders: Results from a Meta-Analysis and Meta-Regression. *Psychother Psychosom* 2020; **89**(2): 109-10.
44. Heinonen E, Knekt P, Harkanen T, Virtala E, Lindfors O. Associations of early childhood adversities with mental disorders, psychological functioning, and suitability for psychotherapy in adulthood. *Psychiatry Res* 2018; **264**: 366-73.
45. Klein DN, Arnow BA, Barkin JL, et al. Early adversity in chronic depression: clinical correlates and response to pharmacotherapy. *Depress Anxiety* 2009; **26**(8): 701-10.
46. De Bolle M, Johnson JG, De Fruyt F. Patient and clinician perceptions of therapeutic alliance as predictors of improvement in depression. *Psychother Psychosom* 2010; **79**(6): 378-85.
47. Klein DN, Schwartz JE, Santiago NJ, et al. Therapeutic alliance in depression treatment: controlling for prior change and patient characteristics. *J Consult Clin Psychol* 2003; **71**(6): 997-1006.
48. Rosenman S, Rodgers B. Childhood adversity in an Australian population. *Soc Psychiatry Psychiatr Epidemiol* 2004; **39**(9): 695-702.
49. Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry* 2020; **19**(1): 92-107.
50. Baldwin JR, Reuben A, Newbury JB, Danese A. Agreement between prospective and retrospective measures of childhood maltreatment: A systematic review and meta-analysis. *JAMA Psychiatry* 2019; **76**(6): 584-93.
51. Danese A, Widom CS. Objective and subjective experiences of child maltreatment and their relationships with psychopathology. *Nat Hum Behav* 2020; **4**(8): 811-8.