Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis

Xinyu Zhou[1], Sarah E. Hetrick[2], Pim Cuijpers[3], Bin Qin[1], Jürgen Barth[4], Craig J. Whittington[5], David Cohen[6], Cinzia Del Giovane[7], Yiyun Liu[1], Kurt D. Michael[8], Yuqing Zhang[1], John R. Weisz[9], Peng Xie[1]

[1]Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; [2]Orygen National Centre of Excellence in Youth Mental Health, University of Melbourne, Melbourne, Australia; [3]Department of Clinical Psychology, VU University Amsterdam, Amsterdam, The Netherlands; [4]Institute of Complementary and Integrative Medicine, University Hospital and University of Zurich, Zurich, Switzerland; [5]Research Department of Clinical, Educational and Health Psychology, University College London, London, UK; [6]Department of Child and Adolescent Psychiatry, Hôpital Pitié-Salpétrière, Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France; [7]Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; [8]Department of Psychology, Appalachian State University, Boone, NC, USA; [9]Department of Psychology, Harvard University, Cambridge, MA, USA

Previous meta-analyses of psychotherapies for child and adolescent depression were limited because of the small number of trials with direct comparisons between two treatments. A network meta-analysis, a novel approach that integrates direct and indirect evidence from randomized controlled studies, was undertaken to investigate the comparative efficacy and acceptability of psychotherapies for depression in children and adolescents. Systematic searches resulted in 52 studies (total N=3805) of nine psychotherapies and four control conditions. We assessed the efficacy at post-treatment and at follow-up, as well as the acceptability (all-cause discontinuation) of psychotherapies and control conditions. At post-treatment, only interpersonal therapy (IPT) and cognitive-behavioral therapy (CBT) were significantly more effective than most control conditions (standardized mean differences, SMDs ranged from −0.47 to −0.96). Also, IPT and CBT were more beneficial than play therapy. Only psychodynamic therapy and play therapy were not significantly superior to waitlist. At follow-up, IPT and CBT were significantly more effective than most control conditions (SMDs ranged from −0.26 to −1.05), although only IPT retained this superiority at both short-term and long-term follow-up. In addition, IPT and CBT were more beneficial than problem-solving therapy. Waitlist was significantly inferior to other control conditions. With regard to acceptability, IPT and problem-solving therapy had significantly fewer all-cause discontinuations than cognitive therapy and CBT (ORs ranged from 0.06 to 0.33). These data suggest that IPT and CBT should be considered as the best available psychotherapies for depression in children and adolescents. However, several alternative psychotherapies are understudied in this age group. Waitlist may inflate the effect of psychotherapies, so that psychological placebo or treatment-as-usual may be preferable as a control condition in psychotherapy trials.

Key words: Psychotherapies, depression, children, adolescents, cognitive-behavioral therapy, interpersonal therapy, psychodynamic therapy, problem-solving therapy, play therapy, waitlist, network meta-analysis

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Depression in young people has significant developmental implications, and accounts for the greatest burden of disease in this age group (1). The point prevalence of depression ranges from 1.9 to 3.4% among primary school children and from 3.2 to 8.9% among adolescents, and the incidence peaks around puberty (2-4). The average duration of a depressive episode in children and adolescents is about nine months, and 70% of patients whose depression remits will subsequently develop another depressive episode within five years, which suggests a substantial continuity between child and adolescent depression and depression in adulthood (3,4). Moreover, due to the atypical presentation and the high frequency of comorbidities (5,6), many cases of child and adolescent depression remain undetected, and do not receive the treatments they need (7-9). Thus, youths with depression experience serious impairment in social functioning, e.g. poor school achievement and relational problems with family members and peers (10), and show an elevated risk of self-harm and suicidal behaviors (11).

Clinical practice guidelines recommend that psychotherapy be considered as the first-line treatment for the management of mild to moderate depression in children and adolescents (12-15), and that medications be reserved for severe cases and those in which psychotherapy does not work (12,13). From the U.S., it is known that approximately three-quarters of the adolescents treated for depression have received some form of psychotherapy (16). Controversy regarding the efficacy and safety of antidepressant medications, along with the evidence of an increased risk of suicidal behavior in children and adolescents treated with some of these medications, has focused attention on the use of psychotherapy for this young population (17-21).

A number of psychotherapies are currently available for treating depression in children and adolescents (22,23). Although there is a broad consensus that various psychotherapies are beneficial for depression in youth patients, recent systematic reviews and meta-analyses have questioned this notion (24-28). The effect sizes of cognitive-behavioral

therapy (CBT) have recently decreased (24) compared to those documented in earlier meta-analyses (25). Some meta-analyses have reported that CBT is superior to other psychotherapies (26,27), whereas others have suggested that non-cognitive treatments (e.g., interpersonal therapy, IPT) work as well as cognitive ones (24,28). However, the conclusions of previous traditional meta-analyses were based on a limited number of trials with direct comparisons between two treatments, while some treatments have rarely or never been directly compared in a randomized controlled trial (RCT).

We implemented a network meta-analysis, a new methodological approach that allows the simultaneous comparison of multiple psychotherapeutic interventions within a single analysis, while preserving randomization (29). This approach was applied to integrate direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator, e.g. waitlist) to estimate the comparative efficacy and acceptability of all treatments (30).

We previously investigated in this way the comparative efficacy of psychotherapies for adult depressed patients (31) and of augmentation agents in adult treatment-resistant depression (32). The aim of the current network meta-analysis was to provide a comprehensive and hierarchical evidence of the efficacy and acceptability of all psychotherapies in the treatment of depression in children and adolescents.

METHODS

Study protocol and search strategy

This systematic review is reported using PRISMA guidelines. The protocol has been registered with PROSPERO (CRD42014010014) and published in BMJ Open (33).

Eight electronic databases – PubMed, EMBASE, Cochrane, Web of Science, PsycINFO, CINAHL, LILACS, and ProQuest Dissertations – were searched from January 1, 1966 to July 1, 2014 with medical subject headings (MeSH) and text words. Also, ClinicalTrials.gov, the World Health Organization's trial portal and U.S. Food and Drug Administration (FDA) reports were reviewed. No language restrictions or restrictions on publication type were applied.

Additional studies were searched for in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews. Relevant authors were contacted to supplement incomplete reports in the original papers or to provide new data of unpublished studies.

Study selection

Two independent researchers (BQ and YYL) selected studies for inclusion, with divergences resolved by consensus. They scanned citations at the title/abstract level and then retrieved a shortlist of potentially relevant studies in full text. These articles were reviewed in full to ensure that they satisfied all of the following criteria.

Only prospective RCTs, including cross-over and cluster-randomized trials, were selected. The study population had to consist of children or adolescents (aged from 6 to 18 years when initially enrolled in the primary study) who either had a diagnosis of major depression, minor depression, intermittent depression, or dysthymia based on standardized diagnostic interviews, or exceeded a predefined threshold for depressive symptoms using a validated depression severity measure.

Interventions included any manualized or structured psychotherapy, such as behavioral therapy, cognitive therapy, CBT, family therapy, IPT, play therapy, problem-solving therapy, psychodynamic therapy, and supportive therapy, regardless of duration and number of treatment sessions. RCTs comparing different modalities of the same type of psychotherapy (face-to-face, Internet or telephone), different treatment conditions (CBT or CBT plus sessions for parents) or different intervention formats (group or individual) were considered as the same node in the network analysis.

Comparators included another class of psychotherapy or a control condition, such as waitlist, no-treatment, treatment-as-usual, or psychological placebo.

To reduce inconsistency among trials, we excluded studies which recruited patients with treatment-resistant or psychotic depression; or involved combination therapies (i.e., combination of different psychological interventions, combination of psychotherapy with pharmacotherapy or another non-psychotherapeutic intervention); or focused on maintenance treatment or relapse prevention; or in which the psychotherapy intervention was not specifically aimed to treat depression. Studies were deemed eligible if they included patients with comorbid psychiatric disorders.

Outcome measures

The primary outcome was efficacy at post-treatment, as measured by mean change scores in depressive symptoms (self- or assessor-rated) from baseline to post-treatment. The secondary outcome was efficacy at follow-up, as measured by mean change scores in depressive symptoms from baseline to the end of follow-up. In addition, we extracted the data for short-term (1 to 6 months) and long-term (6 to 12 months) follow-up in each study. If a study reported data for more than one time within our pre-defined follow-up periods, we considered the last time point within the range. If participants received further treatments after the initial trial (e.g., continuous treatment or booster sessions), they were not included in the follow-up analysis.

Where depression symptoms were measured in a trial using more than one scale, we extracted data for the scale with the highest rank in a pre-defined hierarchy, based on psychometric properties and appropriateness for use with

children and adolescents and on consistency of use across trials (18). The Children's Depression Rating Scale (CDRS-R, 34) was adapted for children and adolescents from the Hamilton Depression Rating Scale (HAMD, 35), a tool validated and commonly used in adult populations. Both the CDRS-R and the HAMD have good reliability and validity (36) and had the highest rank in the hierarchy. The Beck Depression Inventory (BDI, 37) and the Children's Depression Inventory (CDI, 38) were the most commonly used among depression symptom severity self-rated scales and were ranked the second highest in the hierarchy.

The acceptability of treatment was operationally defined as all-cause discontinuation, as measured by the proportion of patients who discontinued treatment up to the post-intervention time point.

Data extraction and risk of bias assessment

Two independent researchers (BQ and YYL) classified psychotherapy approaches, extracted the data and assessed the risk of bias with good inter-rater agreement (kappa=0.86 to 0.90). The researchers independently extracted the key study parameters using a standardized data abstraction form and assessed the risk of bias in trials using the risk of bias tool from the Cochrane Handbook (39). Any disagreements were discussed with a third researcher (XYZ).

Data synthesis and analysis

We performed Bayesian network meta-analysis to compare the relative efficacy and acceptability of different psychotherapies and control conditions with each other from the median of the posterior distribution (29,30). The pooled estimates of standardized mean difference (SMD) with 95% credible intervals (CrIs) were calculated for continuous outcomes, and odds ratios (ORs) with 95% CrIs for categorical outcomes. The SMD is the difference in mean change scores from baseline to post-treatment between two groups divided by the pooled standard deviation (SD) of the measurements, with a negative SMD value indicating greater symptomatic relief (39). In the presence of minimally informative priors, CrIs can be interpreted similarly to confidence intervals, and at conventional levels of statistical significance a two-sided $p<0.05$ can be assumed if 95% CrIs do not include 0 (30).

A Cohen's effect size with Hedges' correction for small sample bias was calculated for all comparisons contained in the studies (40). If means and SDs were not provided, we calculated them from the p value or other statistical indices as described elsewhere (41). Results from intention-to-treat analysis (ITT) or modified ITT were preferred over results from completer analyses.

The pooled estimates were obtained using the Markov Chains Monte Carlo method. Two Markov chains were run simultaneously with different arbitrarily chosen initial values. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic were assessed (42). Convergence was found to be adequate after running 50,000 samples for both chains. These samples were then discarded as "burn-in", and posterior summaries were based on 100,000 subsequent simulations. The node splitting method was used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence (43). Probability values were summarized and reported as surface under the cumulative ranking curve (SUCRA) and rankograms, a simple transformation of the mean rank used to provide a hierarchy of the treatments and accounting for both the location and the variance of all relative treatment effects (44).

Network meta-analysis was performed using the WinBUGS software package (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) with random effects models for multi-arm trials. The other analyses were performed and presented by the Stata 11.0 and R 2.11.1 software packages.

We conducted subgroup analyses of data on primary outcome (efficacy in post-treatment) using the meta-regression model and calculating Somer's D (a correlation coefficient for a dichotomous and an ordinal variable) (45). We considered sex ratio (male-to-female ratio >1 vs. <1); age group (children aged 6-12 years vs. adolescents aged 13-18 years); number of sessions planned (≤ 8 vs. >8 sessions); intervention format (group vs. individual); method for defining the presence of depression (diagnosis of major depression, minor depression or dysthymia vs. severity of depressive symptoms); comorbid psychiatric disorders (with vs. without); risk of bias ("high risk" vs. "unclear risk" or "low risk"); sample size (≤ 50 vs. >50 patients); and year of publication (prior to 2000 vs. 2000 or following).

RESULTS

We analyzed 52 RCTs (46-97), including 116 conditions (psychotherapies and control conditions) and 3,805 patients (see the flow chart in Figure 1). Overall, 2,361 patients were randomized to nine psychotherapies (CBT, N=1149; IPT, N=344; supportive therapy, N=244; cognitive therapy, N=230; family therapy, N=134; play therapy, N=105; behavioral therapy, N=76; problem-solving therapy, N=44; or psychodynamic therapy, N=35). The remaining 1,444 patients were randomized to four control conditions (wait-list, N=419; no-treatment, N=284; treatment-as-usual, N=432; or psychological placebo, N=309).

The RCTs were published between 1980 and 2013. Sample sizes ranged from 9 to 399 patients per trial, with a median of 73. About three-fifths of total participants (59.9%) were females. Ten trials involved children only, 37 adolescents only, and five both. The mean age of participants was 14.7 years (range: 7-18 years). The mean number of sessions planned for psychotherapy was 11.4 (range: 5-36 sessions).

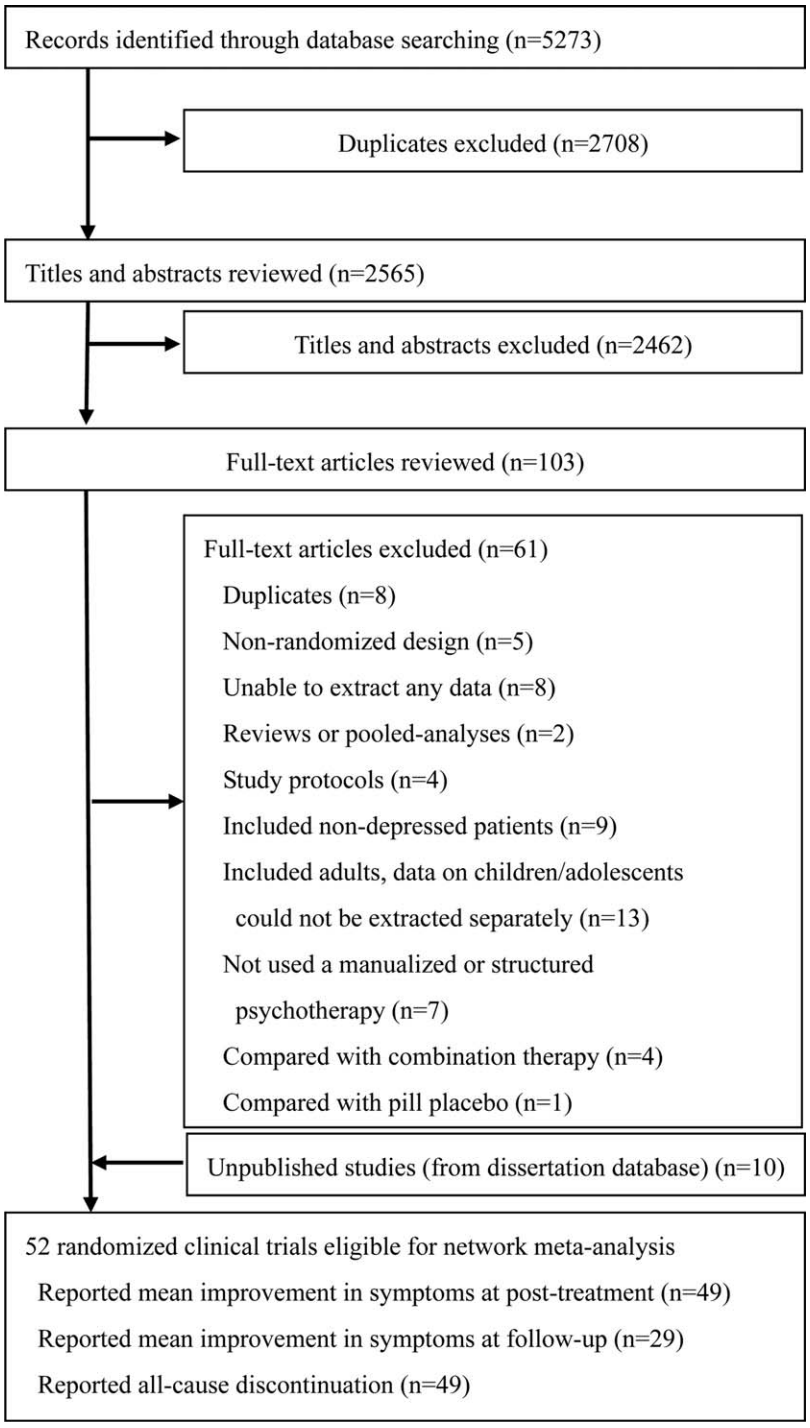

Figure 1 Flow chart of study selection

Further descriptive information about the included studies is given in Table 1.

Twenty-one studies (40%) investigated depressive disorders with standardized diagnostic assessments, while 27 (52%) explored depressive symptoms with a validated depression severity measure, and the remaining four used both methodologies. The median duration of acute phase treatment was 9.5 weeks (range: 4-36 weeks); that of follow-up period was 8.1 months (range: 1-24 months).

The risk of bias was rated as low concerning randomized generation of the allocation sequence in 25 RCTs, allocation concealment in six RCTs, masking of outcome assessors to treatment allocation in 20 RCTs, incomplete outcome data in 28 RCTs, and selective reporting in 46 RCTs.

Table 1 Characteristics of included studies

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Ackerson et al, 1998 (46)	27-item CDI ≥10 and 21-item HAMD ≥10	CT=15 vs. WL=15	7-12	4	NA	NA	CT vs. WL: −2.05 (−3.12, −0.97)	NA
Asarnow et al, 2002 (47)	DSM-IV	CBT=11 vs. WL=12	4th to 6th grade	5	10	NA	NA	NA
Bolton et al, 2007 (48)	APAI ≥32	IPT=105 vs. PT=105 vs. WL=104	14-17	16	16	NA	IPT vs. WL: −0.53 (−0.81, −0.26); PT vs. WL: 0.19 (−0.08, 0.46)	NA
Brent et al, 1997 (49)	DSM-III-R	CBT=37 vs. FT=35 vs. SUP=35	13-18	12-16	NA	NA	CBT vs. SUP: −0.29 (−0.77, 0.19); FT vs. SUP: 0.25 (−0.25, 0.75)	NA
Butler et al, 1980 (50)	Self-report Depression Battery ≥59	CBT=14 vs. CT=14 vs. PBO=14 vs. NT=14	5th to 6th grade	10	10	NA	CBT vs. PBO: −1.12 (−1.94, −0.30); CBT vs. NT: −0.68 (−1.46, 0.10); CT vs. PBO: −0.77 (−1.56, 0.01); CT vs. NT: −0.17 (−0.92, 0.59)	NA
Clarke et al, 1995 (51)	CES-D ≥24	CT=76 vs. TAU=74	9th to 10th grade	5	15	12	CT vs. TAU: −0.21 (−0.57, 0.15)	CT vs. TAU: −0.13 (−0.51, 0.24)
Clarke et al, 1999 (52)	DSM-III-R	CBT=87 vs. WL=36	14-18	8	16	24	CBT vs. WL: −0.27 (−0.72, 0.18)	NA
Clarke et al, 2001 (53)	CES-D ≥24	CT=45 vs. TAU=49	13-18	8	15	24	CT vs. TAU: −0.33 (−0.75, 0.10)	CT vs. TAU: −0.13 (−0.5, 0.27)
Clarke et al, 2002 (54)	DSM-III-R	CBT=41 vs. TAU=47	13-18	8	16	24	CBT vs. TAU: −0.21 (−0.63, 0.21)	CBT vs. TAU: 0.08 (−0.34, 0.50)
Curtis, 1992 (55)	DSM-III-R	CBT=12 vs. WL=11	high school students	8	12	NA	CBT vs. WL: −1.57 (−2.63, −0.51)	NA
Dana, 1998 (56)	27-item CDI ≥12	CBT=10 vs. NT=9	8-13	4	8	1	CBT vs. NT: −0.07 (−0.97, 0.83)	CBT vs. NT: 0.01 (−0.89, 0.91)
De Cuyper et al, 2004 (57)	DSM-III-R	CBT=11 vs. WL=11	9-11	16	16	12	CBT vs. WL: 0.17 (−0.71, 1.05)	CBT vs. WL: −0.57 (−1.47, 0.33)
Diamond et al, 2002 (58)	DSM-III-R	FT=16 vs. WL=16	13-17	12	12	NA	FT vs. WL: −0.35 (−1.05, 0.35)	NA

Table 1 Characteristics of included studies *(continued)*

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Diamond et al, 2010 (59)	21-item BDI ≥20	FT=35 vs. TAU=31	12-17	12	12	6	FT vs. TAU: −0.47 (−0.96, 0.02)	FT vs. TAU: −0.30 (−0.78, 0.19)
Eskin et al, 2008 (60)	DSM-IV	PST=12 vs. WL=11	15-18	6	6	12	PST vs. WL: −1.26 (−2.18, −0.35)	NA
Ettelson, 2003 (61)	DSM-IV	CBT=13 vs. WL=12	high school students	8	16	NA	CBT vs. WL: −1.00 (−1.84, −0.16)	NA
Fine et al, 1991 (62)	DSM-III-R	BT=30 vs. SUP=36	13-17	12	NA	9	BT vs. SUP: 0.46 (−0.13, 1.04)	BT vs. SUP: −0.18 (−0.81, 0.45)
Fischer, 1995 (63)	DSM-III-R	CBT=8 vs. PBO=8	12-17	5	5	NA	CBT vs. PBO: −0.47 (−1.47, 0.52)	NA
Fleming et al, 2012 (64)	CDRS-R ≥30	CBT=20 vs. WL=12	13-16	5	7	NA	CBT vs. WL: −1.41 (−2.21, −0.60)	NA
Hickman, 1994 (65)	DSM-III-R	BT=6 vs. TAU=3	8-11	10	10	1	BT vs. TAU: −0.57 (−2.00, 0.86)	BT vs. TAU: −0.68 (−2.13, 0.77)
Hoek et al, 2012 (66)	20-item CES-D ≥16	PST=22 vs. WL=23	12-21	5	5	2.5	PST vs. WL: −0.04 (−0.78, 0.70)	PST vs. WL: 0.04 (−0.73, 0.81)
Israel & Diamond, 2013 (67)	17-item HAMD ≥14	FT=11 vs. TAU=9	13-17	12	12	NA	FT vs. TAU: −1.26 (−2.25, −0.28)	NA
Jeong et al, 2005 (68)	SCL-90-R	PBO=20 vs. WL=20	middle school students	12	36	NA	PBO vs. WL: −0.87 (−1.52, −0.22)	NA
Kahn et al, 1990 (69)	27-item CDI ≥15	BT=17 vs. CBT=17 vs. WL=17	10-14	6-8	12	1	BT vs. WL: −1.03 (−1.75, −0.31); CBT vs. WL: −0.39 (−1.07, 0.29)	BT vs. WL: −0.61 (−1.30, 0.08) CBT vs. WL: −0.88 (−1.59,−0.18)
Kerfoot et al, 2004 (70)	MFQ ≥23	CBT=29 vs. TAU=23	13.7 (2.2), 14.1 (1.6)	8	8	NA	CBT vs. TAU: 0.11 (−0.47, 0.70)	NA
Lewinsohn et al, 1990 (71)	DSM-III	CBT=45 vs. WL=24	14-18	7	14	24	CBT vs. WL: −0.89 (−1.46, −0.32)	NA
Liddle & Spence, 1990 (72)	27-item CDI ≥19 and 17-item CDRS-R ≥ 40	CBT=11 vs. PBO=10 vs. NT=10	7-12	8	8	3	CBT vs. PBO: −0.57 (−1.45, 0.31); CBT vs. NT: −0.45 (−1.32, 0.42)	CBT vs. PBO: −0.25 (−1.11, 0.61) CBT vs. NT: −0.27 (−1.14, 0.59)
Listug-Lunde, 2004 (73)	27-item CDI ≥15	CBT=10 vs. WL=9	middle school students	7	13	3	CBT vs. WL: 0.09 (−0.86, 1.04)	CBT vs. WL: 0.27 (−0.69, 1.23)
Marcotte & Baron, 1993 (74)	21-item BDI ≥15	CBT=15 vs. WL=13	14-17	6	12	2	CBT vs. WL: −0.44 (−1.24, 0.36)	CBT vs. WL: −1.11 (−1.97, −0.26)
McCarty et al, 2013 (75)	MFQ ≥14	CBT=58 vs. SUP=62	11-15	12	12	NA	NA	CBT vs. SUP: −0.46 (−0.84,−0.08)

Table 1 Characteristics of included studies *(continued)*

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Merry et al, 2012 (76)	CDRS-R ≥30	CBT=94 vs. TAU=93	12-19	4-7	7	3	CBT vs. TAU: −0.19 (−0.48, 0.09)	CBT vs. TAU: −0.13 (−0.42, 0.16)
Moldenhauer, 2004 (77)	27-item CDI ≥15	CBT=15 vs. PBO=11	12-17	6	6	1	CBT vs. PBO: −0.49 (−1.29, 0.30)	NA
Mufson et al, 1999 (78)	24-item HRSD ≥15	IPT=24 vs. PBO=24	12-18	12	12	NA	IPT vs. PBO: −0.72 (−1.31, −0.13)	NA
Mufson et al, 2004 (79)	24-item HAMD ≥10	IPT=34 vs. TAU=30	12-18	12-16	12	NA	IPT vs. TAU: −0.64 (−1.15, −0.13)	NA
Phillips, 2004 (80)	21-item BDI ≥10	CBT=33 vs. WL=31	15.5-20.5	6	6	NA	CBT vs. WL: −0.36 (−0.86, 0.13)	NA
Reed, 1994 (81)	DSM-III-R	BT=12 vs. PBO=6	14-19	12	6	2	NA	NA
Reivich, 1996 (82)	27-item CDI >10	CBT=27 vs. SUP=23 vs. NT=24	10-12	12	12	4	CBT vs. NT: −0.19 (−0.79, 0.42); SUP vs. NT: −0.24 (−0.85, 0.37)	CBT vs. NT: −0.45 (−1.04, 0.13); SUP vs. NT: 0.04 (−0.56, 0.65)
Reynolds & Coats, 1986 (83)	20-item BDI ≥12	BT=11 vs. CBT=9 vs. WL=10	Mean 15.65	5	10	5	BT vs. WL: −1.64 (−2.75, −0.53); CBT vs. WL: −1.93 (−3.20, −0.66)	BT vs. WL: −1.29 (−2.46, −0.13); CBT vs. WL: −1.91 (−3.21,−0.61)
Roberts et al, 2003 (84)	27-item CDI ≥15	CBT=25 vs. PBO=27	11-13	12	12	6	CBT vs. PBO: 0.08 (−0.49, 0.66)	CBT vs. PBO: −0.17 (−0.82, 0.47)
Rohde et al, 2004 (85)	DSM-IV	CBT=45 vs. PBO=48	13-17	8	16	12	CBT vs. PBO: −0.48 (−0.90, −0.06)	CBT vs. PBO: 0.20 (−0.22, 0.62)
Rossello & Bernal, 1999 (86)	DSM-III-R	CBT=25 vs. IPT=23 vs. WL=23	13-18	12	12	3	CBT vs. WL: −0.36 (−0.99, 0.28); IPT vs. WL: −0.88 (−1.56, −0.20)	NA
Rossello et al, 2008 (87)	DSM-III-R	CBT=52 vs. IPT=60	12-18	12	12	NA	CBT vs. IPT: −0.51 (−0.89, −0.14)	NA
Spence et al, 2003 (88)	21-item BDI ≥13	CBT=204 vs. NT=195	12-14	8	8	12	CBT vs. NT: −0.51 (−0.74, −0.28)	CBT vs. NT: −0.19 (−0.45, 0.08)
Stark et al, 1987 (89)	27-item CDI ≥16	CBT=9 vs. PST=10 vs. WL=9	9-12	5	12	2	CBT vs. WL: −1.71 (−2.83, −0.59); PST vs. WL: −0.88 (−1.83, 0.08)	NA
Stice et al, 2010 (90)	CES-D ≥20	CBT=89 vs. CT=80 vs. SUP=88 vs. PBO=84	14-19	6	6	24	CBT vs. PBO: −0.65 (−0.95, −0.34); CT vs. PBO: −0.07 (−0.37, 0.24); SUP vs. PBO: −0.26 (−0.56, 0.04)	CBT vs. PBO: −0.17 (−0.47, 0.13); CT vs. PBO: −0.05 (−0.36, 0.25); SUP vs. PBO: −0.32 (−0.62,−0.02)

Table 1 Characteristics of included studies *(continued)*

Trial	Definition of depression	Treatment conditions and sample size	Age (years, range)	Treatment duration (weeks)	Number of sessions	Follow-up duration (months)	Efficacy at post-treatment SMD (95% CI)	Efficacy at follow-up SMD (95% CI)
Tang et al, 2009 (91)	DSM-IV-TR	IPT=35 vs. TAU=38	12-18	6	12	NA	IPT vs. TAU: −1.00 (−1.48, −0.51)	NA
Trowell et al, 2007 (92)	DSM-IV, Kiddie-SADS	DYN=35 vs. FT=37	9-15	9	24.7/11	6	DYN vs. FT: 0.65 (0.18, 1.13)	DYN vs. FT: 0.21 (−0.26, 0.67)
Vostanis et al, 1996 (93)	DSM-III-R	CBT=31 vs. PBO=30	8-17	18	9	9	CBT vs. PBO: −0.38 (−0.91, 0.15)	CBT vs. PBO: −0.31 (−0.83, 0.22)
Weisz et al, 1997 (94)	26-item CDI ≥11	CBT=16 vs. NT=32	9.6	8	8	9	CBT vs. NT: −0.70 (−1.32, −0.08)	CBT vs. NT: −0.63 (−1.25, −0.02)
Wood et al, 1996 (95)	DSM-III-R	CBT=26 vs. PBO=27	9-17	Mean 9.2	Mean 6.4	6	CBT vs. PBO: −0.86 (−1.45, −0.26)	CBT vs. PBO: −0.11 (−0.71, 0.49)
Young et al, 2006 (96)	CES-D ≥16	IPT=27 vs. TAU=14	11-16	10-12	8	6	IPT vs. TAU: −1.04 (−1.72, −0.35)	IPT vs. TAU: −0.60 (−1.26, 0.06)
Young et al, 2010 (97)	CES-D ≥16	IPT=36 vs. TAU=21	13-17	10-12	8	18	IPT vs. TAU: −1.09 (−1.67, −0.51)	IPT vs. SUP: −0.90 (−1.55,−0.25)

APAI – Acholi Psychosocial Assessment Instrument depression symptom scale, BDI – Beck Depression Inventory, BT – behavioral therapy, CES-D – Center for Epidemiologic Study Depression Scale, CI – confidence interval, CDI – Children's Depression Inventory, CDRS-R – Children's Depression Rating Scale-Revised, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, HAMD – Hamilton Rating Scale for Depression, IPT – interpersonal therapy, MFQ – Mood and Feelings Depression Questionnaire, NT – no-treatment control, OR – odds ratio, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SADS – Schedule for Affective Disorders and Schizophrenia, SMD – standardized mean difference, SUP – supportive therapy, SCL-90-R – Symptom Check List-90-Revision, TAU – treatment as usual, WL – waitlist

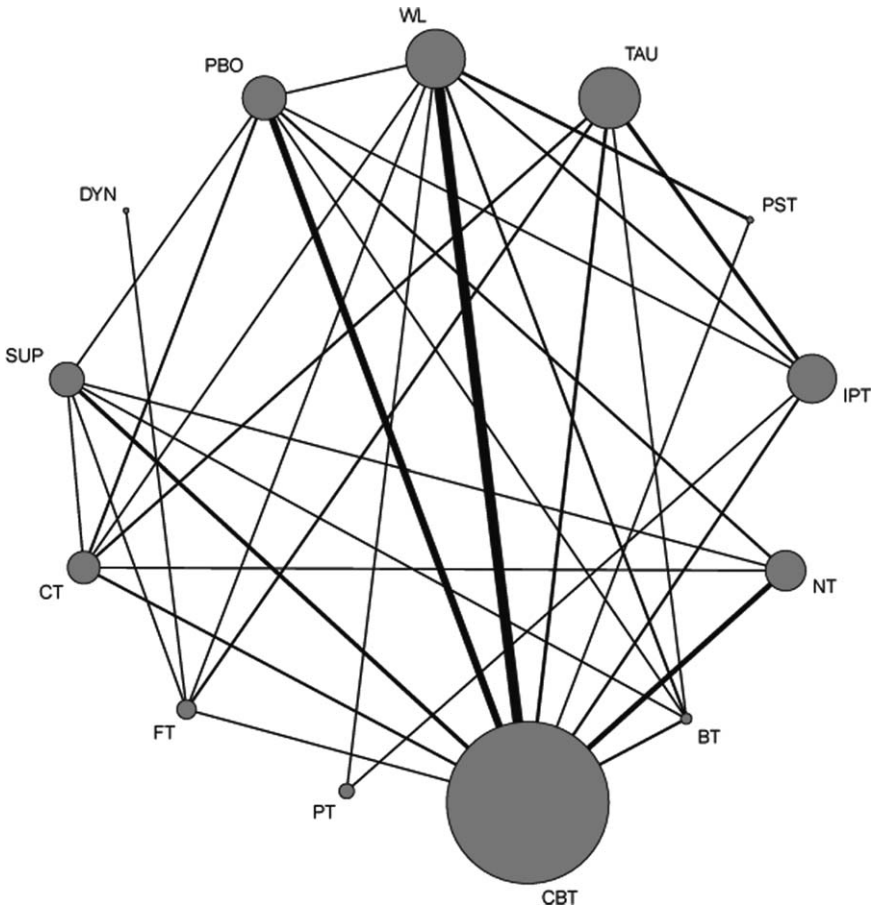

Figure 2 Network plot of evidence of all trials. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomized participants. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, NT – no-treatment control, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SUP – supportive therapy, TAU – treatment-as-usual, WL – waitlist

There were 13 nodes (nine psychotherapies plus four control conditions) and 33 comparisons in the network plot of evidence (Figure 2). Results of efficacy at post-treatment and follow-up assessments are shown in Figure 3. Concerning efficacy at post-treatment, only two psychotherapies (IPT and CBT) were significantly more effective than most control conditions, including psychological placebo, treatment-as-usual and waitlist (SMDs ranged from −0.47 to −0.96). IPT and CBT were also significantly more beneficial than play therapy (SMDs=−0.93 and −0.80, respectively). Among the nine investigated psychotherapies, only psychodynamic therapy and play therapy were not significantly more beneficial than waitlist. Waitlist was significantly inferior to no-treatment (SMD=−0.46).

Concerning efficacy at follow-up, IPT and CBT were significantly more effective than most control conditions, including treatment-as-usual, waitlist and, for CBT, no-treatment (SMDs ranged from −0.26 to −1.05). Also, IPT and CBT were significantly more beneficial than problem-solving therapy (SMDs=−1.10 and −0.90, respectively). Psychodynamic therapy and problem-solving therapy were not significantly more beneficial than waitlist. Waitlist was significantly inferior to all other control conditions, including placebo, treatment-as-usual, and no-treatment (SMDs ranged from −0.53 to −0.67).

Data about acceptability are shown in Figure 4. IPT and problem-solving therapy had significantly fewer all-cause discontinuations than CBT and cognitive therapy (ORs ranged from 0.06 to 0.33). Problem-solving therapy also had significantly fewer discontinuations than psychological placebo (OR=0.10; 95% CrI: 0.02 to 0.98).

Concerning efficacy at short-term follow-up, IPT was significantly more effective than problem-solving therapy and waitlist (SMDs=−0.99 and −0.95, respectively), and CBT was significantly more effective than cognitive therapy, problem-solving therapy, psychological placebo, and waitlist (SMDs ranged from −0.35 to −0.91). Behavioral therapy and supportive therapy were superior to waitlist (SMDs=−0.71, and −0.67, respectively). Waitlist was significantly inferior to psychological placebo (SMD=−0.52). In the analysis of efficacy at long-term follow-up, IPT was significantly more beneficial than CBT, cognitive therapy,

IPT	-0.20 (-0.67 to 0.31)	-0.44 (-0.97 to 0.11)	-0.47 (-0.98 to 0.06)	-0.22 (-0.95 to 0.51)	**-1.10 (-1.90 to -0.27)**	-0.33 (-0.95 to 0.31)	-0.46 (-1.01 to 0.10)	-0.38 (-0.91 to 0.17)	**-0.52 (-0.98 to -0.06)**	-0.43 (-1.35 to 0.49)	--	**-1.05 (-1.66 to -0.44)**
-0.13 (-0.49 to 0.23)	CBT	-0.24 (-0.51 to 0.00)	-0.27 (-0.56 to 0.00)	-0.02 (-0.67 to 0.59)	**-0.90 (-1.56 to -0.23)**	-0.14 (-0.54 to 0.27)	**-0.26 (-0.53 to -0.01)**	-0.19 (-0.41 to 0.04)	**-0.32 (-0.60 to -0.08)**	-0.23 (-1.08 to 0.59)	--	**-0.86 (-1.24 to -0.49)**
-0.19 (-0.72 to 0.34)	-0.07 (-0.49 to 0.36)	SUP	-0.03 (-0.36 to 0.31)	0.22 (-0.46 to 0.88)	-0.66 (-1.36 to 0.05)	0.11 (-0.32 to 0.55)	-0.02 (-0.36 to 0.32)	0.06 (-0.23 to 0.37)	-0.08 (-0.42 to 0.25)	0.01 (-0.86 to 0.86)	--	**-0.61 (-1.06 to -0.17)**
-0.27 (-0.75 to 0.23)	-0.14 (-0.54 to 0.27)	-0.08 (-0.60 to 0.46)	CT	0.25 (-0.40 to 0.87)	-0.63 (-1.34 to 0.09)	0.13 (-0.34 to 0.62)	0.01 (-0.37 to 0.38)	0.09 (-0.23 to 0.42)	-0.05 (-0.34 to 0.21)	0.04 (-0.81 to 0.87)	--	**-0.59 (-1.05 to -0.12)**
-0.29 (-0.85 to 0.28)	-0.16 (-0.66 to 0.35)	-0.09 (-0.69 to 0.50)	-0.02 (-0.62 to 0.58)	FT	-0.88 (-1.77 to 0.03)	-0.12 (-0.85 to 0.64)	-0.24 (-0.91 to 0.45)	-0.16 (-0.81 to 0.52)	-0.30 (-0.87 to 0.27)	-0.21 (-0.76 to 0.34)	--	**-0.84 (-1.55 to -0.10)**
-0.33 (-1.05 to 0.39)	-0.20 (-0.85 to 0.45)	-0.13 (-0.90 to 0.62)	-0.06 (-0.82 to 0.69)	-0.04 (-0.84 to 0.76)	PST	0.76 (-0.03 to 1.51)	0.64 (-0.07 to 1.35)	0.72 (0.01 to 1.41)	0.58 (-0.14 to 1.28)	0.67 (-0.42 to 1.72)	--	0.04 (-0.59 to 0.68)
-0.36 (-0.96 to 0.25)	-0.23 (-0.74 to 0.29)	-0.17 (-0.75 to 0.42)	-0.09 (-0.72 to 0.53)	-0.07 (-0.76 to 0.62)	-0.04 (-0.77 to 0.83)	BT	-0.13 (-0.61to 0.35)	-0.05 (-0.50 to 0.41)	-0.19 (-0.67 to 0.26)	-0.09 (-1.03 to 0.82)	--	**-0.72 (-1.21 to -0.23)**
-0.50 (-1.01 to 0.01)	-0.37 (-0.75 to 0.00)	-0.31 (-0.83 to 0.21)	-0.23 (-0.75 to 0.28)	-0.22 (-0.83 to 0.40)	-0.18 (-0.92 to 0.57)	-0.14 (-0.77 to 0.48)	NT	0.08 (-0.24 to 0.42)	-0.06 (-0.43 to 0.30)	0.03 (-0.86 to 0.89)	--	**-0.59 (-1.05 to -0.14)**
-0.60 (-1.03 to -0.18)	**-0.47 (-0.76 to -0.19)**	-0.41 (-0.89 to 0.07)	-0.33 (-0.79 to 0.11)	-0.31 (-0.88 to 0.24)	-0.28 (-0.97 to 0.43)	-0.24 (-0.82 to 0.33)	-0.10 (-0.54 to 0.34)	PBO	-0.14 (-0.48 to 0.17)	-0.05 (-0.92 to 0.80)	--	**-0.67 (-1.11 to -0.25)**
-0.68 (-1.04 to -0.32)	**-0.55 (-0.88 to -0.22)**	-0.49 (-1.00 to 0.01)	-0.41 (-0.84 to 0.00)	-0.39 (-0.91 to 0.10)	-0.35 (-1.07 to 0.36)	-0.32 (-0.91 to 0.26)	-0.18 (-0.67 to 0.30)	-0.08 (-0.49 to 0.33)	TAU	0.09 (-0.70 to 0.88)	--	**-0.53 (-0.97 to -0.08)**
-0.95 (-2.00 to 0.11)	-0.82 (-1.84 to 0.21)	-0.75 (-1.82 to 0.32)	-0.68 (-1.76 to 0.39)	-0.66 (-1.55 to 0.11)	-0.62 (-1.81 to 0.58)	-0.59 (-1.71 to 0.54)	-0.45 (-1.52 to 0.64)	-0.35 (-1.39 to 0.71)	-0.27 (-1.29 to 0.76)	DYN	--	-0.63 (-1.53 to 0.30)
-0.93 (-1.66 to -0.20)	**-0.80 (-1.55 to -0.06)**	-0.74 (-1.59 to 0.10)	-0.66 (-1.49 to 0.15)	-0.64 (-1.52 to 0.22)	-0.61 (-1.56 to 0.35)	-0.57 (-1.46 to 0.30)	-0.43 (-1.26 to 0.39)	-0.33 (-1.11 to 0.45)	-0.25 (-1.02 to 0.52)	0.02 (-1.23 to 1.26)	PT	--
-0.96 (-1.36 to -0.57)	**-0.83 (-1.09 to -0.58)**	**-0.77 (-1.25 to -0.30)**	**-0.69 (-1.15 to -0.25)**	**-0.67 (-1.20 to -0.15)**	**-0.63 (-1.25 to -0.02)**	**-0.60 (-1.12 to -0.09)**	**-0.46 (-0.91 to -0.02)**	-0.36 (-0.72 to 0.00)	-0.28 (-0.66 to 0.10)	-0.01 (-1.05 to 1.01)	-0.03 (-0.76 to 0.70)	WL

Treatment Efficacy at post-treatment (SMD with 95% CrI) Efficacy at follow-up (SMD with 95% CrI)

Figure 3 Relative effect sizes of efficacy at post-treatment and at follow-up according to network meta-analysis. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For efficacy in post-treatment, standardized mean differences (SMDs) less than 0 favor the column-defining treatment. For efficacy in follow-up, SMDs lower than 0 favor the row-defining treatment. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. Significant results are in bold and underlined. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, NT – no-treatment control, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SUP – supportive therapy, TAU – treatment-as-usual, WL – waitlist

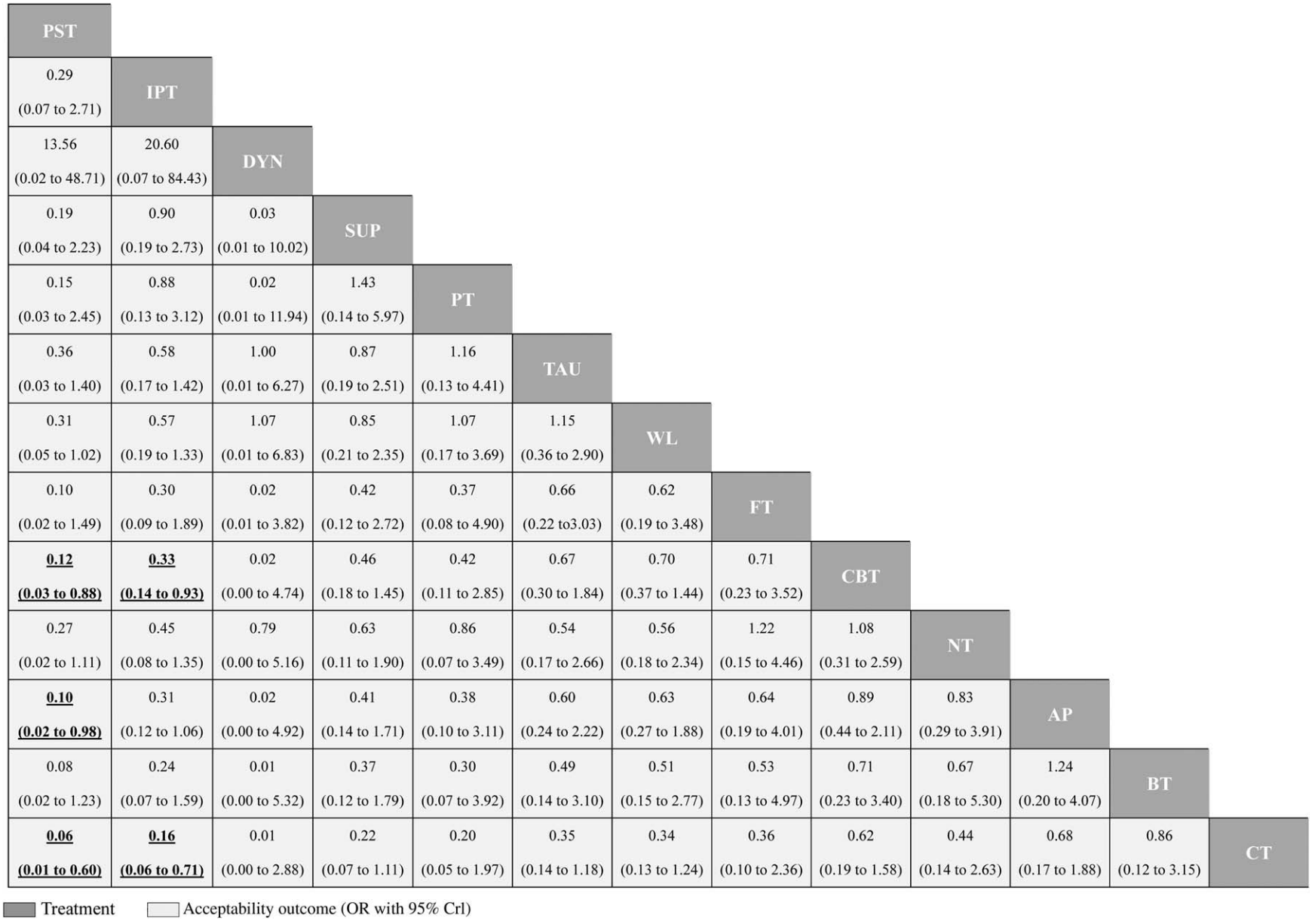

Figure 4 Relative effect sizes of acceptability from network meta-analysis. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For acceptability, odds ratios (ORs) smaller than 1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, NT – no-treatment control, PBO – psychological placebo, PT – play therapy, PST – problem-solving therapy, SUP – supportive therapy, TAU – treatment-as-usual, WL – waitlist

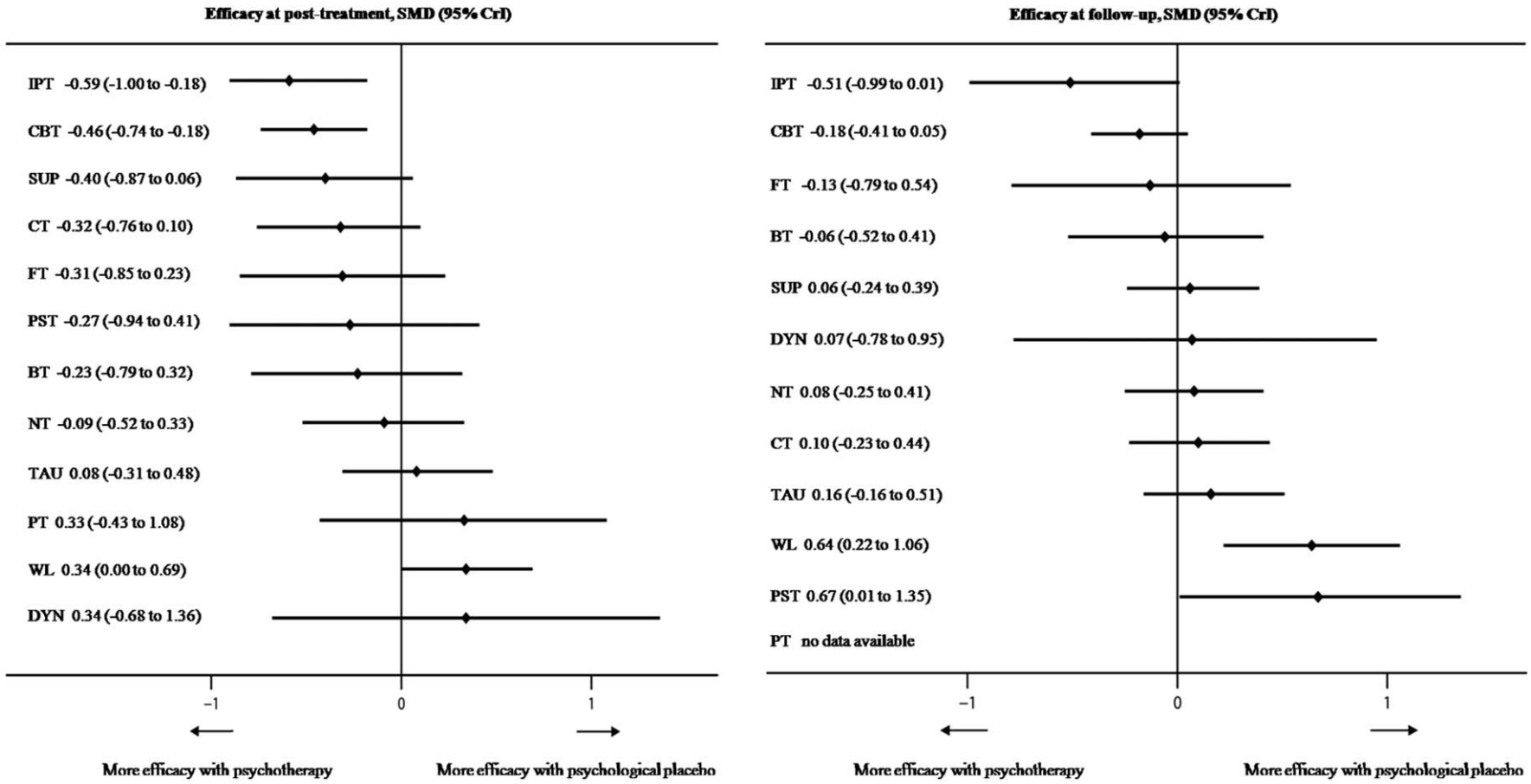

Figure 5 Forest plots of network meta-analysis results for efficacy with psychological placebo as reference. Standardized mean differences lower than 0 favor psychotherapy. BT – behavioral therapy, CBT – cognitive-behavioral therapy, CT – cognitive therapy, FT – family therapy, IPT – interpersonal therapy, PT – play therapy, PST – problem-solving therapy, DYN – psychodynamic therapy, SUP – supportive therapy, SMD – standardized mean difference, CrI – credibility interval

psychological placebo, treatment-as-usual, and no-treatment (SMDs ranged from −0.78 to −1.08), while CBT was not superior to any control condition.

There was no significant heterogeneity in the network meta-analysis concerning efficacy at post-treatment (SD =0.38; 95% CrI: 0.25 to 0.53), efficacy at follow-up (SD=0.12; 95% CrI: 0.01 to 0.31), and acceptability (SD=0.69; 95% CrI: 0.25 to 0.98), which suggests good interpretability of the results. There was very little evidence that direct and indirect effects were inconsistent (95% CrIs of differences between direct and indirect estimates included 0).

Forest plots of the network meta-analysis results for efficacy at post-treatment and at follow-up, with psychological placebo as reference, are shown in Figure 5. We also created hierarchies of effect size on the basis of SUCRA rankings for efficacy outcomes. The best treatment, according to the curves, was IPT at post-treatment (SUCRA=90.5%) and at follow-up (SUCRA=90.3%). The worst treatment, according to the curves, was waitlist at post-treatment (SUCRA=9.39%) and at follow-up (SUCRA=6.26%).

There was no evidence that the treatment effect was significantly modified by patients' clinical characteristics or risk of bias in the trials. However, IPT and CBT had less significant effects in studies in which patients were children, comorbid psychiatric disorders were present, and the year of publication was 2000 or following.

DISCUSSION

Our review of 52 RCTs suggests that, among the psychotherapies tested in children and adolescents with depression, only IPT and CBT are significantly more beneficial than most control conditions at post-treatment and at follow-up. Compared with other psychotherapeutic interventions, IPT and CBT were significantly more effective than play therapy at post-treatment, and more effective than problem-solving therapy at follow-up. Psychodynamic therapy and play therapy were not significantly more effective than waitlist in reducing depression symptoms at post-treatment and follow-up, although the limited number of trials available suggests the need for further research.

The acceptability of psychotherapies for depressed children and adolescents has seldom been investigated in previous meta-analyses. We found that IPT and problem-solving therapy had significantly fewer all-cause discontinuations than CBT and cognitive therapy. A possible interpretation is that a protocol putting emphasis on cognitive changes is more difficult for young people to engage in.

Our finding that waitlist was inferior to other control conditions (including no-treatment, treatment-as-usual and psychological placebo) seems to support the idea that waitlist may act as a "nocebo condition" in psychotherapy trials (98). In the case of child and adolescent depression, alternative hypotheses may be proposed to interpret this finding. First, placebo response in child and adolescent depression may be particularly high (17,99). Second, patients who are allocated to no-treatment may actively seek other treatments, while those on waitlist do not, as they are waiting for the intervention to be delivered (98). Anyway, the use of waitlist may inflate the treatment effect of psychotherapies in clinical trials, and the use of psychological placebo or treatment-as-usual is likely to provide a more robust comparison.

In our analysis, IPT and CBT demonstrated a robust effect over short-term follow-up, but only IPT had a beneficial effect over long-term follow-up. The theory behind IPT may particularly ring true for young people, as interpersonal difficulties may be more likely to drive psychopathology at this age (100). However, this finding was based on few trials, and requires further validation.

Subgroup analyses suggested no significant moderation of the treatment effect by different patient characteristics and intervention settings. Nonetheless, compared to psychological placebo, IPT and CBT showed less robust effects in studies on children with depression or on patients with comorbid disorders, and in more recently published trials. These findings are consistent with those from previous literature (26,101,102), but require further confirmation due to the relatively small size of the subgroups.

There were some limitations in the current study. Network meta-analysis assumes that some treatment arms are similar in rationale and procedure, allowing us to group them together as one node in the network (103). However, the classification of psychotherapeutic interventions for child and adolescent depression remains provisional. For instance, the treatments implemented in the trials we included under the heading "family therapy" were somewhat heterogeneous. Moreover, treatment-as-usual may be very different in various mental health care contexts, and it may be difficult to differentiate between no-treatment and treatment-as-usual in clinical practice, because when someone is assigned to no treatment, he/she can seek some form of usual care (98).

We excluded studies on treatment-resistant depression and psychotic depression, to reduce heterogeneity and inconsistency among trials. This may have led, however, to an overestimation of the effect size in the present meta-analysis, because the most difficult cases were not considered. Also, we could not include data on adverse effects, cost-effectiveness, quality of life outcomes and suicide, because they were lacking in almost all studies, although these variables are important for clinicians and patients to make decisions on selecting appropriate treatment.

In conclusion, our review supports the notion that IPT and CBT, when available, should be the initial choice of psychological treatment for depression in children and adolescents. However, several alternative treatment options are understudied in this age group, and further research on moderators of treatment effect are needed. Waitlist may inflate the treatment effect of psychotherapies, and psychological placebo or treatment-as-usual are likely to provide a more robust comparison in psychotherapy trials.

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Author/s:
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