SYSTEMATIC REVIEW OPEN

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CBT treatment delivery formats for generalized anxiety disorder: a systematic review and network meta-analysis of randomized controlled trials

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OBJECTIVES: To assess the comparative efficacy and acceptability of different delivery formats of cognitive behavior therapy (CBT) in treating generalized anxiety disorder (GAD).
METHODS: We searched MEDLINE, Embase, PsycINFO, and the Web of Science from database inception to September, 2023, to identify randomized clinical trials (RCTs) of CBT for patients with GAD. Pairwise and network meta-analyses were conducted using a random-effects model.
RESULTS: Finally, 52 trials that randomized 4361 patients (mean age 43 years; 69.7% women) with generalized anxiety disorder met the inclusion criteria. The most studied treatment comparisons were individual and remote CBT versus waiting list. The quality of the evidence was typically of low or unclear risk of bias (39 out of 52 trials, 75%). The network meta-analysis including 30 studies showed that individual CBT was superior to remote CBT (SMD 0.96; 95% CI 0.13–1.79), treatment as usual (SMD 1.12; 95% CI 0.24–2.00) and waiting list (SMD 1.62; 95% CI 1.03–2.22) in relieving anxiety symptoms of GAD. Group CBT (SMD 1.65; 95% CI 0.47–2.84) was more efficacious than waiting list. Remote CBT was not superior to treatment as usual or waiting list. In terms of acceptability CBT delivery formats did not differ significantly from each other.
CONCLUSIONS: Our findings provide evidence for the consideration of group treatment formats as alternative to individual CBT in relieving anxiety symptoms in patients with GAD, but remote CBT may be less effective.

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INTRODUCTION

GAD is a very common mental disorder which has greatly affected the quality of life of patients and results in considerable economic and societal burden [1]. Previous network meta-analysis demonstrated that CBT was the most effective type of psychotherapy for patients with GAD [2]. Although psychotherapy is in great demand, only a small percentage of people actually receive it [3]. Actually, the patient's participation in the treatment may be hindered a range of logistical barriers including making time for treatment and transportation barriers [4]. Therefore, it is important to find more accessible and efficient forms of CBT treatment delivery to reduce the burden of disease.

As we know, in-person CBT is the most common way of treatment in GAD patients, which including individual and group forms [5]. A meta-analysis evaluates the efficacy of group psychotherapy in the treatment of anxiety disorders showed group psychotherapy reduces specific symptoms of anxiety disorders more effectively than no-treatment control group and no significant differences were found compared to individual psychotherapy or pharmacotherapy [6]. Another meta-analysis comparing individual CBT with group CBT for children and adolescents with anxiety disorder showed individual CBT was significantly more effective than group CBT in adolescents, but not in children [7]. To maintain the continuity of psychiatric care in the coronavirus disease 2019 pandemic situation, remote mental health care is encouraged [8]. A meta-analysis comparing face-to-face with internet-based cognitive behavior therapy suggested the effect sizes of the two treatments were similar in GAD patients [9].

However, head-to-head comparisons are limited. Network meta-analysis (NMA) incorporates both direct and indirect effects, and allows to rank the treatments to identify which is the best or worst among them [10]. Ranking forms of CBT delivery based on efficacy for anxiety symptoms is critical for future mental health care system resources, optimization, and organization. Thus, we designed a systematic review and network meta-analysis to assess the comparative effectiveness and acceptability of the different types of CBT for the treatment of GAD in patients participating in randomized clinical trials.

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METHOD

This study report is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines specific for network meta-analysis [11]. The study protocol was registered with PROSPERO (CRD42023493949).

Search strategy

We searched PubMed, Embase, PsycINFO and Web of Science, from database inception to the 1st September 2023, to identify randomized controlled trials (RCTs) examining the effects of psychotherapy for generalized anxiety disorder, compared with any other psychotherapy or control condition. From this pool of RCTs we further selected only those studies testing different CBT delivery formats.

Inclusion and exclusion criteria

Inclusion criteria were: (1) patients with a primary diagnosis of generalized anxiety disorder according to any standard operationalized criteria (Research Diagnostic Criteria, DSM up to the fifth version, ICD-10). It was considered insufficient if the patients were described as "anxious" or "neurotic; (2) the psychotherapeutic intervention had to be CBT, defined as a treatment that focuses on patients interoceptive fears and uses both cognitive restructuring and behavioral procedures to reduce those fears; (3) CBT could be delivered by a therapist or as self-help; (4) being an RCT. Exclusion criteria were: (1) review or meta-analysis not reporting original data; (2) case studies or case series with less than 4 patients; (3) meeting abstract. CBT and comparators were grouped into five homogeneous groups that represented the 'nodes' of the network analysis: in-person face-to-face individual, in-person face-to-face group, remote, treatment as usual and waiting list.

Study selection and data extraction

All records from all sources were entered into Endnote, and duplicates removed. Two independent researchers checked all resulting records. If one of the researchers indicated a record possibly containing a study meeting the inclusion criteria, the full text of that paper was retrieved. The full texts were read by the same researchers for final inclusion.

In accordance with the study protocol, we worked in pairs and independently extracted the following data from the original reports: mean age, percentage of women, year of publication, study duration, treatment format, number of sessions of the treatment. Any discrepancies were resolved by consensus and arbitration by one of the senior authors.

Risk of bias assessment

We assessed the risk of bias of the included studies using version 2 of the Cochrane risk of bias tool for randomized trials (ROB 2) [12]. Investigators independently used the ROB 2 signalling questions to form judgments on the five ROB 2 domains. Disagreements were resolved by discussion and consensus with a third author.

Outcomes

We measured efficacy in reducing anxiety symptoms (continuous outcome, indicated as 'efficacy') and all-cause discontinuation from the trial (binary outcome, indicated as 'acceptability'). For the efficacy outcome, we selected one scale for each study using a pre-planned hierarchical algorithm. All-cause discontinuation was measured as the proportion of participants who discontinued the trial for any reason. All outcomes referred to the acute phase treatment (post treatment). For both outcomes, we produced a treatment hierarchy by means of surface under the cumulative ranking curve (SUCRA) and mean ranks, having treatment as usual as reference [13].

Data analysis

We conducted a series of pairwise meta-analyses for all direct comparisons using a random-effects pooling model. For each outcome, we performed a NMA with a random-effects model, using the Stata mvmeta package. For the continuous outcome (efficacy) we pooled the standardized mean differences (SMDs) between treatment arms at endpoint. For the dichotomous outcome(acceptability), we calculated relative risks (RR) with a 95% confidence interval (CI) for each study. For continuous variables, we used intention-to-treat (ITT) data when available, and completers data when ITT data were not available. Dichotomous data were calculated on a strict ITT basis, considering the total number of randomized participants as denominator. When a study included different arms of a slightly different version of the same delivery method, we pooled these arms into a single one [14]. Statistical evaluations and production of network graphs and figures were done using the network and network graphs packages in STATA (version 16.1, S.E.) [15].

We statistically evaluated the presence of incoherence by comparing direct and indirect evidence within each closed loop by using the Stata commands mvmeta and ifplot [16] in the Stata network suite. Incoherence was further investigated through the side-splitting approach for each comparison [17].

For the efficacy outcome, we conducted pre-planned sensitivity analyses excluding trials judged to be at 'high risk of bias' to explore the putative effects of the study quality assessed through the ROB 2 on heterogeneity.

If ten or more studies were included in a direct pairwise comparison, we assessed publication bias by visually inspecting the funnel plot, testing for asymmetry with the Egger's regression test [18, 19], and investigated possible reasons for funnel plot asymmetry [20].

RESULTS

After examining a total of 5777 titles and abstracts (1808 after removal of duplicates), we retrieved 157 full-text articles for further consideration and excluded 105 articles. In total, 52 studies with 4361 patients met the inclusion criteria (see Fig. 1). Of these 31 were eligible for the NMA.

The 52 studies included 33 individual CBT arms with 1581 patients, 7 group CBT arms with 343 patients and 13 remote CBT arms with 722 patients. The detailed distribution of these studies and patients is presented in Table 1, which shows selected characteristics of the included studies. The mean age was 40.8 years. The mean proportion of included women was 67.1%. Most studies enrolled adults between 18 and 65 years of age, with five studies including older adults (i.e. ≥ 65 years) and two studies including Children (i.e. ≤ 18 years). Studies were distributed over 33 years (1990–2023) and generally had their main endpoint evaluation around the 12th week of treatment (range: 1–24). The mean number of therapy sessions was approximately 12 (range: 5–29).

Risk of bias of included studies

In most cases (26 RCTs, 50%) studies there were 'some concerns',13 (25%) studies were considered to be at overall high risk of bias, for 13 (25%) studies there were judged to be at low risk of bias. The majority of the studies missed to adequately report the randomization process, leading to 'some concerns' judgment in 19 studies (36.5%).

Network plot

Figure 2 shows the network of comparisons efficacy and acceptability after CBT for GAD patients. In terms of geometry of the networks. Overall, the network was well connected. The most examined comparisons were between individual and remote formats as well as the waiting list and treatment as usual control conditions. We detected a scarcity of direct comparisons between group and remote CBT. Group CBT was compared with only

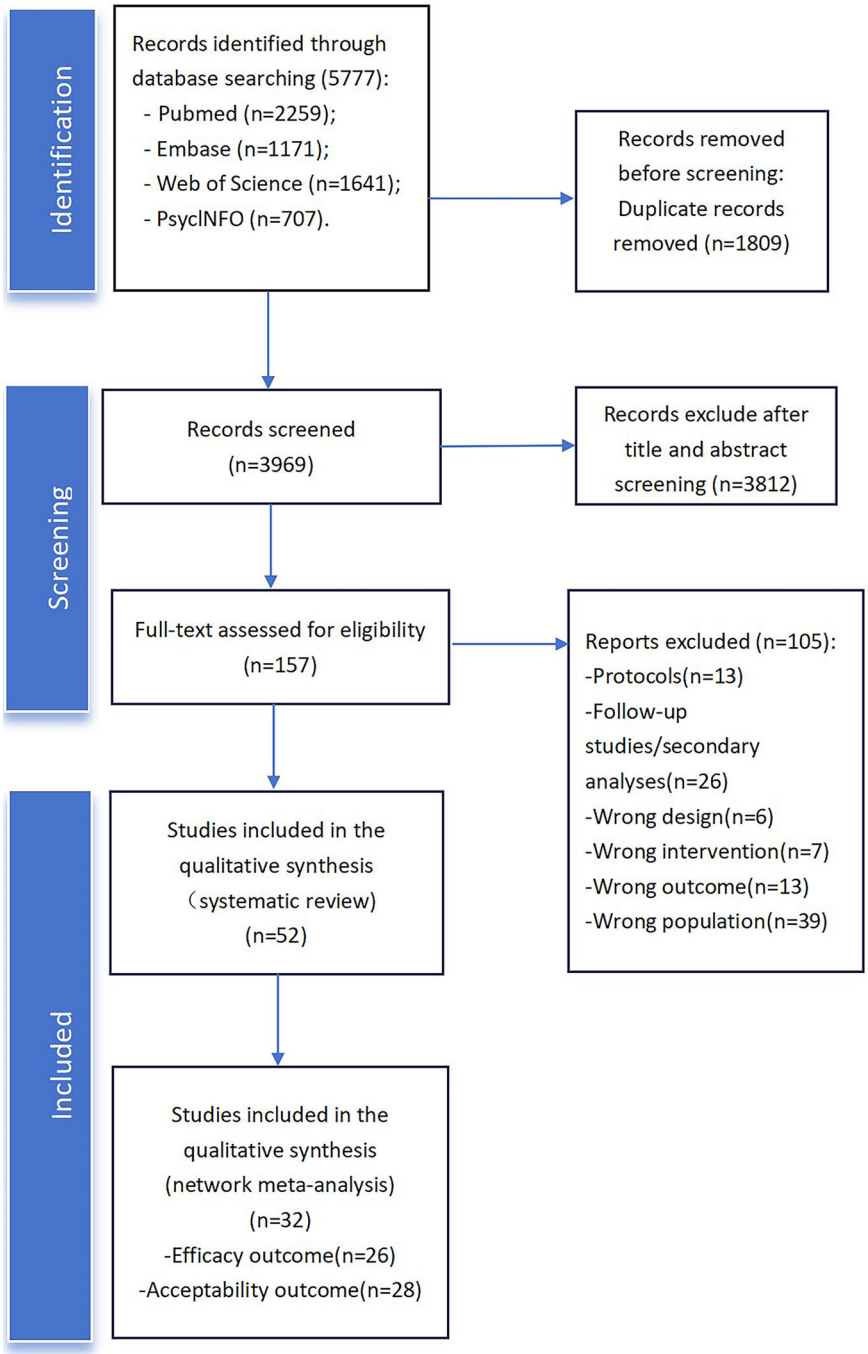

Fig. 1 PRISMA flow diagram. PRISMA flow diagram showing the steps of screening studies included in this systematic review.

waiting list in 2 trials and not with any other format or control condition.

Figure 3 shows the results of the NMAs for each CBT treatment delivery format in the form of a net league table. For each network estimate, all standard pairwise meta-analyses NMAs, and assessments of heterogeneity, incoherence and quality of evidence are reported in the Supplementary material.

Pairwise meta-analyses

The pairwise meta-analyses consisted 6 comparisons. The results of the effect showed that individual, group and remote formats were more effective than the waiting list Fig. 4. And individual and remote formats were more effective than care as usual control conditions. There was no statistical difference between remote and individual treatment. Furthermore, none of the comparisons was statistically significant in acceptability.

Efficacy outcome

Individual CBT (SMD 1.12; 95% CI 0.24–2.00; SUCRA, 82.8%) were superior to treatment as usual in relieving anxiety symptoms of GAD. Group CBT (SMD 1.65; 95% CI 0.47–2.84; SUCRA, 86.9%) was more efficacious than waiting list. Remote CBT was not superior to treatment as usual (SMD 0.16; 95% CI −1.04–1.36; SUCRA, 15.7%) or waiting list (SMD 1.16; 95% CI −0.64–2.95; SUCRA, 11.3%). Individual CBT was more acceptable than remote CBT (SMD 0.96; 95% CI 0.13–1.79; SUCRA, 53.3%). There was perfect consistency between direct and indirect estimates, as investigated through the sidesplit all STATA command in two loops.

Table 1. Characteristics of randomized controlled trials included in the systematic review and in each network of primary outcomes.

Characteristic	Systematic review		Network meta-analysis			
			Efficacy network		Acceptability network	
Number of studies	52		25		26	
Number of patients included	4361		1925		1955	
Women %	69.7		67		68.2	
Mean age (years)	43.0		50.6		46.3	
	N	%	N	%	N	%
Year of publication						
1990–2000	3	5.8	2	8	2	7.7
2001–2010	10	19.2	9	36	10	38.5
2011–2020	28	53.8	13	52.0	12	46.2
2020–2023	11	21.2	1	4	2	7.7
N sessions/modules						
1–6	8	15.4	5	20	5	19.2
7–12	24	46.2	9	36	10	38.5
13–29	18	34.6	9	36	9	34.6
Unclear	2	3.8	2	8	2	7.7
Risk of bias						
High	13	25.0	5	20	5	19.2
Some concerns	26	50.0	11	44	13	50
Low	13	25.0	9	36	8	30.8

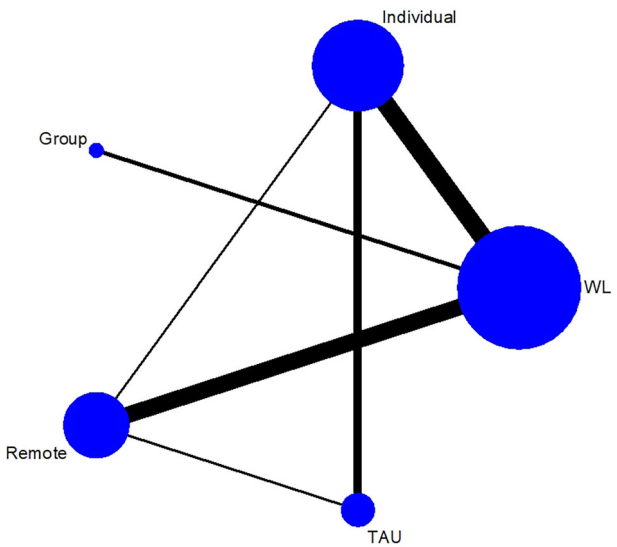

Fig. 2 Network plot of evidence. The size of the node corresponds to the number of participants assigned to each treatment. Treatments with direct comparisons are connected by a line; Its thickness corresponds to the number of tests compared.

Acceptability outcome

No significant differences were found between different delivery formats for the acceptability outcome. There was perfect consistency between direct and indirect estimates, as investigated through the sidesplit all STATA command in two loops.

Sensitivity analysis

After removing the five high risk of bias RCTs (20%) individual CBT retained its superiority over waiting list, and more effective than the remote CBT. In addition, remote CBT was superior to waiting list.

DISCUSSION

This systematic review and network meta-analysis of CBT for the GAD patients included data from 52 clinical trials including 4361 patients with GAD patients who were randomized to 3 distinct treatment formats or control. The quality of the evidence was typically of low or unclear risk of bias (39 out of 52 trials; 75%). Our findings provide further clarification about the anti-anxiety efficacy of different format of CBT in adults patients with GAD. We found that both individual and group CBT delivery formats are superior to treatment as usual, and individual was more effective than remote CBT. Furthermore, CBT delivered as remote was not superior to treatment as usual. In terms of overall trial dropout rates, CBT delivered in any format was accepted same as treatment as usual.

Our research found the curative effect of group therapy is better than waiting list, and the effect size is large. Group therapy has many advantages such as in structured group format can save time and reduce waiting lists, and also cut down the cost of helping people who are not receiving treatment for financial problems [21]. Furthermore, there are too few professionals are trained in remote rural areas [4]. We also found that the effect size of group therapy was larger than individual therapy, although there was no significant difference in the head-to-head comparison of the two treatments. Previous studies support the efficacy of CBT for anxiety disorders in a group format too, suggesting that it may be as effective or even more effective than CBT that is delivered individually [22, 23]. Group therapy allows group members to get to know each other and exchange experiences. The positive by-products of group treatments include the effects of Alliance and cohesion for group members to serve as co-therapists and offer mutual support [24]. However, drop-out rates is a substantial problem in group CBT [25]. Dropping out of treatment early not only negatively affects outcome but also may leave the patient feeling more symptomatic [26]. Anyway, the large demand of CBT and good curative effect access still make group CBT a cost-effective option to reduce the burden of disability associated with GAD.

Our pairwise comparisons suggested remote CBT was more effective than waiting list. Previous small meta-analysis including 10 studies found that Within-group findings indicate that remote CBT for GAD results in large effect sizes from pretreatment to posttreatment, which is consistent with our results [27]. But in the network meta-analysis, remote was less effective than individual CBT and no significant difference was found in remote and waiting list. On one hand, it is believed that the personal relationship between therapist and patient marked by the extent to which each is genuine with the other and perceives/experiences the other in ways that befit the other is an important factor in the effectiveness of psychotherapy [28]. However, therapists mostly communicate with patients by email in remote CBT, which cannot establish connection well. On the other hand, the specific components such as involve patients or the other helpful person in the treatment protocol are more suitable in individual CBT [29]. Thus, the differences in responses have more to do with the components of CBT than the formats of CBT. Given the fact of limited effect of remote CBT in current stage, we have provided some research directions aimed at enhancing the efficacy of remote therapy. For example, we can train therapists of remote CBT on how to establish and maintain good therapeutic relationships in the remote settings. Alternatively, developing a virtual group therapy environment allows patients to

Group	−0.00 (−0.12, 0.11)	−0.04 (−0.16, 0.07)	−0.02 (−0.15, 0.11)	−0.06 (−0.15, 0.03)
0.03 (−1.29, 1.36)	Individual	−0.05 (−0.11, 0.02)	−0.02 (−0.09, 0.06)	−0.00 (−0.05, 0.05)
0.99 (−0.33, 2.31)	**0.96 (0.13, 1.79)**	Remote	−0.06 (−0.15, 0.03)	−0.04 (−0.10, 0.01)
1.15 (−0.44, 2.74)	**1.12 (0.24, 2.00)**	0.16 (−1.04, 1.36)	TAU	−0.02 (−0.10, 0.07)
1.65 (0.47, 2.84)	**1.62 (1.03, 2.22)**	1.16 (−0.64, 2.95)	**0.66 (0.08, 1.24)**	WL

Fig. 3 Net league table of head-to-head comparisons. The diagonal gives the different nodes that were examined in the study; at the left of the diagonal, the data for the effect sizes are given as standardized mean difference (SMD) with 95% CIs and 95% prediction intervals, with every cell indicating the values for a specific contrast between the nodes. SMDs higher than 0 favour the column-defining treatment. At the right of the diagonal, the values for acceptability are given as relative risk (RR) with 95% CIs and 95% prediction intervals. Data in bold are statistically significant. RRs higher than 1 favour the column-defining treatment.

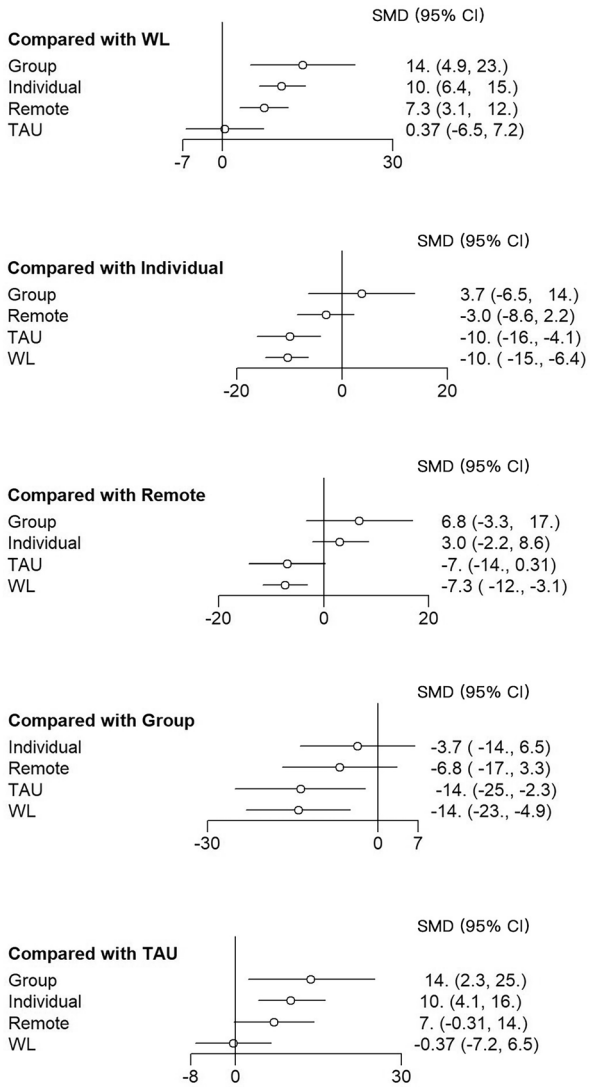

Fig. 4 Forest plots of pairwise meta-analyses. Meta-analysis of the effect between different CBT delivery formats in the GAD patients.

communicate with other patients and therapists in a virtual space to compensate for the lack of interpersonal interaction in remote therapy [30]. In addition, we can develop a remote treatment model suitable for patients with different ages, genders and cultural backgrounds. The inconsistent results of the pairwise comparisons and network meta-analysis suggest that there may be differences between individual and group therapy, but more high-quality RCT studies are needed to verify this.

There are several limitations of this study that should be taken into account when interpreting the results. First, group CBT was only examined in 2 studies and thus should be considered with caution. Second, major heterogeneity was found in several examined comparisons. We defined CBT as a treatment that uses both cognitive restructuring and behavioral procedure. However, most treatments also included other components, such as change exploration, intolerance of uncertainty and interpersonal. The various components included in these treatments varied widely, which may have contributed to statistical heterogeneity as well as clinical heterogeneity. But we did not find indications of significant inconsistency. Third, the assessment scales used at the baseline of the studies we included were not completely consistent. So, we use SMD which is a value without units to eliminate the effect of absolute values. Therefore, the results of SMD analysis should be interpreted with caution. Fourth, risk of bias was judged as high in 25% of the studies included in the systematic review. Most of the risks are caused by inadequate implementation of blind methods and inconsistent interventions. Lastly, we included studies of children and the elderly to take advantage of all available data, which expanded the study population and sample size. Although the responses of different patient groups to various forms of CBT may vary, the current inclusion approach helps present the overall scenario of CBT in treating GAD. Previous meta-analyses already support the effectiveness and safety of CBT for reducing childhood and older anxiety symptoms [31, 32]. However, the effects of various CBT may vary among different groups of patients, and more studies are needed in the future to explore it.” However, the effects of various CBT may vary among different groups of patients, and more studies are needed in the future to explore it.

In summary, current study suggests that group CBT is an effective intervention strategy that may be app as alternative to individual CBT. And remote CBT is less effective than individual CBT. Component analyses and further randomized studies are

warranted to better clarify the role of remote protocols in treating GAD.

CODE AVAILABILITY

Please contact the corresponding author.

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AUTHOR CONTRIBUTIONS

SYL, CJQ and XQH conceived and designed the study. SYL and YXD screened and selected the articles. PW analyzed the data. HQX supervised the data analyses. SLX rated the certainty of evidence. LXC interpreted the data. SYL drafted the manuscript. HLL contributed to revising the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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