Cognitive Behavioral Therapy Versus Antidepressant Medication in Generalized Anxiety Disorder: A Prospective Schematic & Meta-Analysis Approach

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ABSTRACT

Background: Generalized Anxiety Disorder (GAD) is a common mental disorder, which is usually treated by cognitive behavioral therapy (CBT) or antidepressant medications (ADMs). Nevertheless, a significant number of patients do not respond well to monotherapy, resulting in complete remission. The present review focuses on the main comparison of CBT and ADM outcomes in GAD. Cases of combination therapy (CBT + ADM) were reviewed secondarily in those studies that reported it.

Methods: The articles were identified through systematic searches of PubMed and Google Scholar that were carried out to determine randomized controlled trials published between 2011 and 2025. The inclusion criteria included studies that used adults with standardized measurement of GAD diagnosis and post-therapeutic outcomes of anxiety measures CBT, and/or ADM. Combination data were identified where available. The mean anxiety scores were pooled in a random-effects meta-analysis and risk of bias was evaluated according to the Cochrane method.

Results: The number of included studies was eight randomized controlled trials with 259 participants. In the main analysis, CBT resulted in slightly improved post-treatment anxiety results (mean = 20.46, 95% CI: 5.9534.96) than pharmacotherapy alone (mean = 22.75, 95% CI: 4.6940.80). The lowest pooled score (mean = 17.72, 95% CI: 10.83 24.62) was observed in those studies that reported combination therapy. Nonetheless, because of great heterogeneity among the studies (I2 > 95%), the findings were viewed with caution. The overall direction of effect was supported by subgroup and sensitivity analyses.

Discussion: CBT can be slightly more effective than antidepressant drugs in alleviating anxiety symptoms in GAD. Combination therapy also demonstrated good outcomes in a few studies, but this was not the key aspect of this analysis. Future studies are needed on standardizing outcome measures and examining individual predictors of treatment responsiveness in order to conduct personalized care.

Keywords: Cognitive Behavioral Therapy (CBT), Antidepressant Medication (ADM), Generalized Anxiety Disorder (GAD), Clinical Decision-Making.

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INTRODUCTION

Generalized Anxiety Disorder (GAD) is a widespread and frequently long-term mental health disorder characterized by uncontrollable, extreme worry that has persisted over six months and has a big impact on functional ability and quality of life [1]. It is estimated to affect about 6 percent of the adult world population [2]. The existing treatment measures mostly encompass cognitive behavioral therapy (CBT) and antidepressant medications (ADMs), including selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) [3]. Although both interventions may be classified as first-line, the response rate differs greatly, and not all patients reach full-scale remission after monotherapy [4].

CBT addresses avoidance behaviors and maladaptive thought patterns, and is linked with long-term advantages [5]. ADMs, however, focus on normalizing neurotransmitter activity, especially serotonin and norepinephrine, in hopes that it can decrease the symptoms of anxiety [6]. Although clinical guidelines suggest the use of both, the direct comparison of their efficacy is difficult due to variation in study design and characteristics of the population and the outcome measures in the studies [7]. This inconsistency complicates generalization of treatment effects and outlines the necessity of evidence that could distinguish which approach can be considered most effective [8].

Neurobiological data indicates that personal biological characteristics can be used to determine different reactions to either CBT or pharmacotherapy [9]. It has been seen that amygdala reactivity has been associated with more positive response to CBT, but impaired HPA axis responsiveness and some genetic polymorphisms (e.g. 5-HTTLPR) are associated with a more pharmacologic response [10]. Such outcomes indicate a potential need of more personalized treatment approaches based on neurobiological indicators that might be used to improve the specificity of therapy [11].

This systematic review and meta-analysis were conducted to compare the efficacy of CBT and antidepressants in the GAD treatment. The effect of combination therapy was also measured, where reported, as a secondary outcome. It also investigated variation in treatment outcomes and identified sources of heterogeneity amongst the studies. The goal of the review is to ensure that more specific and effective treatment approaches are applied to individuals with GAD.

METHODS

Study Design

The current systematic review and meta-analysis were carried out following the PRISMA 2020 guidelines [12].

Inclusion Criteria

The search criteria included original research articles in the English language published between 2011 and 2025. Studies that used human participants only aged 18 years and above and had a confirmed diagnosis of GAD using standardized diagnostic criteria were only accepted. Research was required to involve CBT and ADM as the most important interventions and document at least one quantitative measure of treatment efficacy, including symptom reduction, treatment outcome, and remission or relapse rates. Different randomized controlled trials (RCTs), and clinical trials were eligible study designs.

Exclusion Criteria

The studies which were excluded were the review articles, meta-analyses, case reports, editorials, or conference abstracts. Laboratory-based and animal research and preclinical studies were also excluded. Moreover, the studies that have not made direct comparisons between CBT and ADMs or were not available in full text or did not provide the relevant patient outcome data were not included in the final analysis.

Literature Search

The literature search was systematic and exhaustive and involved two electronic databases of PubMed and Google Scholar. The search strategy was the use of a combination of relevant keywords and controlled vocabulary with the help of Boolean operators. The search strategy was as follows: the following terms were used: Cognitive Behavioral Therapy OR CBT, Antidepressants OR SSRI OR SNRI, Generalized Anxiety Disorder OR GAD, and Treatment Outcome OR Efficacy OR Relapse OR Symptom Reduction. To complete the process, the

reference lists of the included articles were also hand-searched to find out any other eligible study.

Data Selection and Screening

The selection procedure was carried out in three steps. At first, titles and abstracts were reviewed to exclude studies that were irrelevant. This was then followed by a full-text review of possibly relevant articles. Lastly, research studies were evaluated based on the inclusion and exclusion criteria formulated. Each of the screening stages was conducted by two independent reviewers. Any differences were addressed by discussion, and where required, consulted with a third reviewer to achieve consensus.

Data Extraction

The relevant information used in each of the included studies was systematically collected using a standardized data extraction form. Extracted data points were characteristics of the studies (author, year of publication, study design, setting), characteristics of the participants (age, sex, and sample size), characteristics of the interventions (type and duration of CBT or ADM), characteristics of outcome measures (such as GAD-7, HAM-A, or other anxiety assessment scales), duration of follow-up, and important statistical results. All the data extracted were put in a spreadsheet using Microsoft Excel. In case important data were not available or ambiguous, authors were approached, or missing data were estimated by using available information.

Outcomes Assessed

The main effect was the relative change in the severity of anxiety between the CBT and the antidepressant medication, which was measured with the help of standardized scales, such as GAD-7 and HAM-A. The secondary outcome was evaluated where combination therapy was applied. Other secondary outcomes reported were differences in functional outcomes, remission rates, adherence levels, and dropout rates.

Quality Assessment

The quality of included studies was determined independently through the use of validated instruments to measure methodology. In case of randomized controlled trials, the Cochrane Risk of Bias Tool was applied. The strength and the certainty of the evidence were also graded overall, in terms of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, which enabled an open assessment of bias, inconsistency, and precision of the studies.

Data Synthesis

The MetaAnalysisOnline tool was used to perform quantitative synthesis 13. Mean post-treatment anxiety scores and 95 % confidence intervals (CIs)
were combined in a random-effects model to adjus t to the expected heterogeneity of studies. The I2 statistic was used to measure heterogeneity and a value of over 75 percent was considered to have substantial variability. The analysis was also done based on subgroups, according to the structure of primary and secondary outcomes, which included treatment modality (CBT alone, pharmacotherapy alone, and combination therapy). The sensitivity analyses were conducted by omitting the studies that contributed most to heterogeneity or with alternative outcome measures in order to determine the robustness of the pooled estimates. The included studies consists of 8 randomized controlled trials (RCTs), including 5 parallel-group RCTs, 1 open-label sequential trials, 1 phase-based combination trials, and 1 augmentation or maintenance RCTs, comparing CBT, antidepressants, and their combination in diverse populations[14,15,1617,18,19,20,21].

RESULTS

The initial search retrieved 165 records. The screening of 105 studies was conducted after the removal of 42 duplicates and 18 reviews or case reports. The abstracts and little information have led to the removal of 55 studies, and 50 full reports were requested. Among them, 18 were not retrievable. The other 32 articles were reviewed in terms of eligibility, and 24 of them did not make the cut because of issues with study designs, lack of CBT or antidepressant data, or no secondary outcomes present. At last, 8 studies were used in the meta-analysis (Google Scholar = 6, PubMed = 2). **Figure 1** shows the PRISMA workflow of our included study.

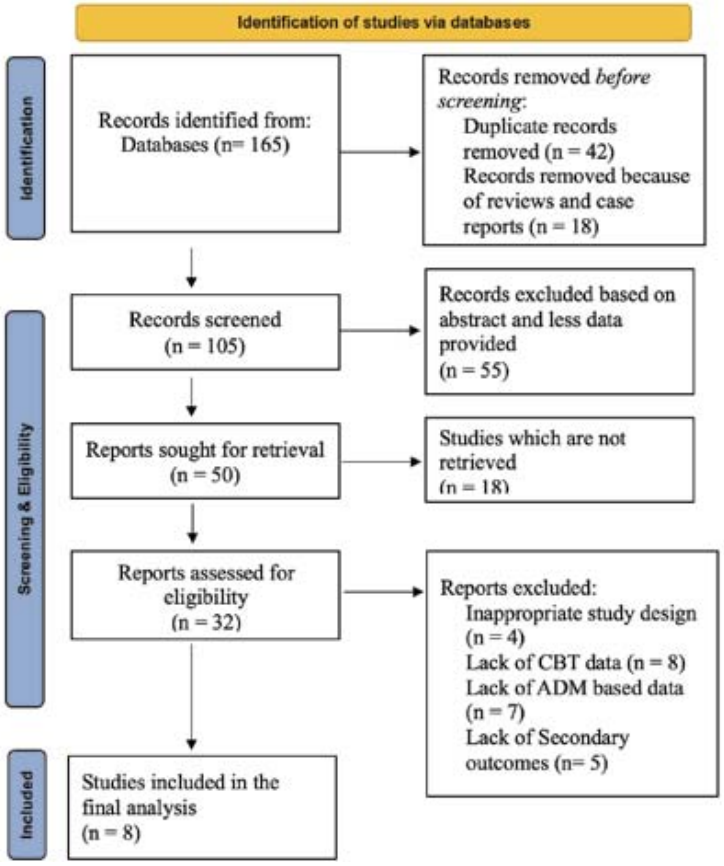

Figure 1: PRISMA workflow diagram

Characteristics of studies

The systematic review included eight papers evaluating the comparative effectiveness of CBT and ADMs for GAD. Some studies also examined the efficacy of combining CBT with pharmacotherapy as an additional therapeutic approach. The type of study designs were randomized controlled trials (RCTs), open-label sequential trials, and augmentation protocols with a small patient size of the pilot trial of 10 participants and a huge size of over 100 participants. The wide range of age diversity across the spectrum of human lifespan was moderated by the age range of participants starting at the age of children (mean age ~10 years) and progressing to older adults (up to ~70 years). All the studies involved both males and females with an overall equal sex distribution. The level of anxiety, response to treatment was primarily measured through such scales included the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), the SCARED questionnaire, and the Penn State Worry Questionnaire (PSWQ). The baseline mean scores of HAM-A assessed during most studies ranged between 21 and 47 with post-treatment measurements that were identified as showing moderate to large reductions of the symptoms across treatment arms. The studies were also targeting the so-called added value of CBT supplemented with SSRIs, such as escitalopram or venlafaxine, or evaluating the predictive validity of CBT responsiveness, or the implications of sequential versus simultaneous treatment. Pediatric results focused on reductions in anxiety symptoms, focused on the quality of life, and depressive symptomology, especially in combined treatment arms. The review also encompasses a variety of methodological studies and participant groups and, therefore, shows an overview of the effects of CBT, pharmacotherapy, and their use in combination on the results of anxiety within groups of different ages.

Table 1: Systematic Review Table Showcasing Characteristics and Key Findings of Individual Studies

Study	Study Design	Population Groups (N)	Sex (M/F)	Age (Mean ± SD)	Primary Anxiety Scale	Primary Outcome
Christoph et al. (2011) [14]	RCT (CBT + Venlafaxine vs Venlafaxine)	CBT+Venlafaxine (26); Venlafaxine only (35)	CBT+VEN: 9M/17F; VEN: 17M/18F (approx.)	CBT+VEN: 46.3 ± 15.0; VEN: 47.5 ± 16.0	Hamilton Anxiety Rating Scale (HAM-A)	No added benefit of CBT over venlafaxine XR; CBT uptake was low
LoParo et al. (2025) [15]	RCT (CBT vs Escitalopram vs Duloxetine) with ML-based prediction modeling	CBT (72); Escitalopram (92); Duloxetine (84)	Overall: 110M/138F (56% female)	40.0 ± 11.5 (PReDICT); 42.3 ± 8.3 (PET)	Hamilton Depression Rating Scale (HAM-D)	Prediction models explained variance: CBT (39.7%), Escitalopram (32.1%), Duloxetine (67.7%); 71% remission prediction accuracy
Wetherell et al. (2011) [16]	Open-label sequential design	Escitalopram alone (10); Escitalopram + mCBT (10)	4M / 6F	66.6 ± 8.1	Hamilton Anxiety Rating Scale (HAM-A)	HAM-A reduced from 23.3 to 13.0 (ESC), then to 8.2 after mCBT addition
Dunlop et al. (2019) [17]	Sequential combination treatment trial (Phase 2 of an RCT)	CBT followed by Escitalopram (N = 37); Escitalopram or Duloxetine followed by CBT (N = 75)	CBT-first group: 16M, 21F; Medication-first group: 44M, 31F	CBT-first group: 40.4 ± 11.6 years; Medication-first group: 42.4 ± 11.6 years	Baseline HAM-D (Mean, SD): CBT-first group: 14.1 ± 5.0; Medication-first group: 11.7 ± 5.3	Remission defined as HAM-D score ≤ 7 at both weeks 22 and 24
Wetherell et al. (2013) [18]	Sequential augmentation and maintenance RCT	Escitalopram + CBT (N = 18); Escitalopram only (N = 19); CBT + Placebo (N = 18); Placebo only (N = 18)	Escitalopram + CBT: 6M/12F; Escitalopram: 5M/14F; CBT + Placebo: 5M/13F; Placebo: 5M/13F	Range across groups: ~66.9–70.5 ± ~5.7–8.6 years	HAM-A (Mean, SD): Escitalopram + CBT: 21.7 ± 3.4; Escitalopram: 21.7 ± 3.6; CBT + Placebo: 22.3 ± 4.9; Placebo: 22.7 ± 3.9	Worry reduction (PSWQ) and anxiety reduction (HAM-A); relapse prevention

Sevinç Sevi Tok et al. (2023) [19]	RCT comparing CBT, medication (ST), and combined treatment (CBT+ST) in children with anxiety disorders	CBT (15); ST (15); CBT+ST (15)	CBT: 7M/9F; ST: 7M/8F; CBT+ST: 6M/9F	CBT: 9.94 ± 1.57; ST: 9.80 ± 1.37; CBT+ST: 10.27 ± 1.44	SCARED (Child & Parent forms)	Combined therapy (CBT+ST) significantly superior in reducing anxiety (SCARED), improving QoL, and reducing depression
Markell et al. (2015) [20]	RCT (Venlafaxine XR ± CBT) in African American and European American adults with GAD	Venlafaxine XR + CBT: 26 (African American = 8, European American = 17); Medication only group not detailed in outcome analysis	CBT+Venlafaxine: 0M/8F (AA), 8M/9F (EA)	AA: 43.6 ± 11.4; EA: 47.9 ± 17.1	Hamilton Anxiety Rating Scale (HAM-A)	No significant difference in HAM-A clinical response between African American and European American groups (75% vs. 58.8%)
Rosnick et al. (2017) [21]	RCT: CBT augmentation vs SSRI only (Escitalopram)	CBT + Escitalopram (n = 21); Escitalopram only (n = 21)	CBT: ~81% F; No CBT: ~76% F	CBT: 71.19 ± 8.68; No CBT: 68.71 ± 7.97	Penn State Worry Questionnaire (PSWQ); CIRS-G	CBT + SSRI significantly reduced peak cortisol levels compared to SSRI alone (p = 0.0445)

RCT: Randomized Controlled Trial; CBT: Cognitive Behavioral Therapy; ADM: Antidepressant Medication; VEN: Venlafaxine; ST: Standard Treatment (unspecified medication); SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

Table 1 outlines how each design is structured, the characteristics of people studied, the factors that could affect results and the main results found in each study. The studies mentioned in this review show that both the method of treatment and patients' health can affect the outcomes.

Outcomes Measured

The primary findings focused on the efficacy of CBT, drug treatments, relieving the symptoms of anxiety in persons with generalized anxiety disorder (GAD). As a secondary outcome the combination therapy of CBT and ADM were analyzed. The large effect sizes were noted on most validated scales, examples of which were HAM-A improvements such as a 15.1-point reduction in HAM-A scores (from 23.3 to 8.2, 64.8%) with CBT, SCARED scores in children (from 31.93 to 18.67, 41.5%) following combination therapy. The combination therapy frequently produced a higher remission than monotherapy and the HAM-D outcome scores were up to 5.3 in medication-first groups. The secondary results were reduced worries, compliance with treatment, and quality of life as well as relapse prevention. It is important to note that PSWQ scores improved after CBT and some patients sustained their improvement even after CBT. Combined practices produced more positive changes in cognitive performance and quality of life according to pediatric research. The long-term follow-ups indicated a potential relapse in the absence of further therapy, whereas predictive models

indicated an increase of remission when therapy was based on patient profiles ($p < 0.005$). In general, combination strategies seemed to be the most useful in prolonged symptom experience and wider functional outcomes.

Meta-Analysis

In this meta-analysis, forest plots were used to demonstrate the main outcome, which was comparisons of CBT, medication, and combination therapy for GAD. The effect sizes in each study in the form of squares and lines with their 95 percent confidence interval are shown, with the square size indicating the weight of the study. The pooled effect is plotted as a black diamond, and its location with respect to the line of no effect gives overall significance. The evaluation of the heterogeneity was based on I^2 and chi-square.

The results regarding post-treatment anxiety outcomes were found in two studies and presented a pooled mean of 20.46 (95% CI: 5.95 to 34.96), which represents a moderate effect. Even despite the fact that both studies demonstrated promising results, the heterogeneity was significant (I^2 = 96.4%), which can be explained by the age of the participants, the organization of the treatment process, and the study design. The broad prediction interval also indicates a disparity in the real-world performance, despite the overall pattern being in favor of the therapeutic value of CBT in treating generalized anxiety disorder. **Figure 2** shows the CBT-only results based on the primary arm study.

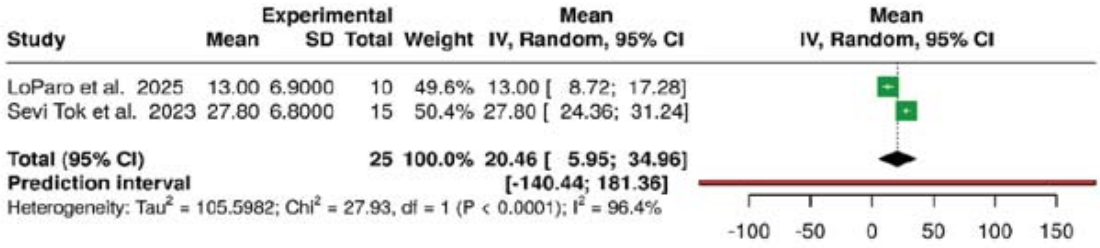

Figure 2: Forest Plot of Post-Treatment Anxiety Scores in CBT-Treated Participants with GAD.

There were two studies under the CBT-only subgroup, a total of 25 participants. The mean post-treatment anxiety score was 20.46 (95% CI: 5.95 to 34.96) with a moderate degree of change representing a decrease in the symptoms after CBT intervention. Nevertheless, the heterogeneity was significant (I^2 = 96.4%), which indicated differences in responses in settings or populations.

The six studies provided data on post-treatment anxiety scores after pharmacotherapy involving a total of 99 participants. The pooled mean score was 22.75 (95% CI: 4.69 to 40.80), implying that the symptoms are lower after the use of medications including escitalopram, venlafaxine, duloxetine, or standard formulations. Nevertheless, there is a broad range of predictions, and extremely high heterogeneity (I^2 = 99.2%), suggesting that much variability exists in the treatment outcome, probably related to variability in drug type, dose, population characteristics, or outcome measurement. Although the overall effect direction is consistent with pharmacological benefit, the interpretation of these findings may be interpreted as being cautious. **Figure 3** demonstrates the primary comparison of ADM-only studies.

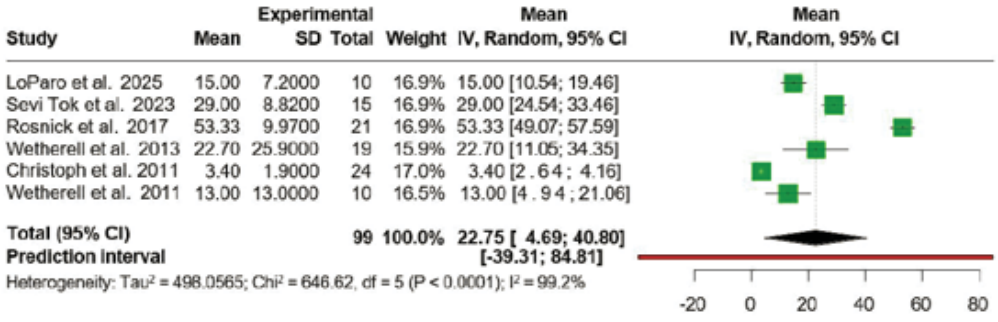

Figure 3: Forest Plot of Post-Treatment Anxiety Scores in Pharmacologically Treated Participants with GAD.

Six studies (n = 99) on the use of pharmacological interventions alone were included in this subgroup. The combined mean of the anxiety score was 22.75 (95% CI: 4.69 to 40.80), and the range of values was large with very high heterogeneity (I^2 = 99.2 percent). This heterogeneity is probably associated with differences in the type and dosage of medications as well as characteristics of the population.

As a secondary outcome, combination therapy (CBT + ADM) was also studied to evaluate its potential additive benefit over monotherapy. The results of anxiety outcomes after using a combination therapy with cognitive behavioral therapy and pharmacological treatment were measured in seven studies in which 135 participants participated. The post-treatment pooled mean was 17.72 (95% CI: 10.83 to 24.62), a good response rate in terms of the reduction of the symptoms of anxiety as compared to monotherapy. CBT with medications (escitalopram, venlafaxine, duloxetine, or placebo) was used as an intervention. Although the overall effect was positive, the high heterogeneity (I^2 = 97.5 %) and large prediction interval (95 % CI:19.5 to 41.14) indicate that the treatment effects vary considerably, possibly due to variations in drug regimens, delivery forms and study populations. Nevertheless, the majority of evidence supports the clinical usefulness of CBT in combination with pharmacotherapy in the treatment of generalized anxiety disorder. Figure 4 represents these findings.

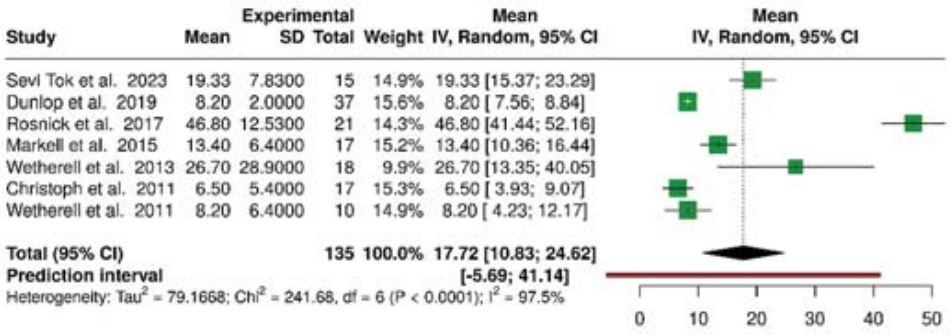

Figure 4: Forest Plot of The Secondary Outcome Subgroup: Post-Treatment Anxiety Scores, CBT Combined with Pharmacotherapy (ADM).

The combination subgroup included seven studies and 135 study participants. The post-treatment anxiety score was calculated as 17.72 (95% CI: 10.83 to 24.62), indicating a greater and more uniform therapeutic effect. The direction and magnitude of effect was in favor of combined treatment in the majority of studies, although heterogeneity was high (I^2 = 97.5 percent).

Subgroup Analyses

The subgroup analysis involved comparison of the post-treatment anxiety results of the three types of interventions: CBT alone, antidepressant medication alone, and combination therapy. The pooled mean anxiety score of participants receiving CBT alone was 20.46 (95% CI: 5.95 to 34.96), with a consistent benefit, based on two studies, yet with a high heterogeneity (I^2 = 96.4%). The pooled mean of the pharmacotherapy-only group in the six studies was 22.75 (95% CI: 4.69 to 40.80) with extreme heterogeneity (I^2 = 99.2%), which may have been caused by differences in the type of drug, dosage, and populations. As a secondary comparison, the combined CBT and drug group had the most desirable pooled score of 17.72 (95% CI: 10.83 to 24.62) in seven studies (I^2 = 97.5%), which implies an additive drug effect. Table 2 indicates that the combined therapy had lower anxiety scores as compared to CBT or pharmacotherapy alone.

Table 2: Subgroup Analysis of Post-Treatment Anxiety Scores by Intervention Type

Subgroup	Number of Studies	Total Participants (N)	Pooled Mean Score	95% CI	Heterogeneity (I^2)	Interpretation
CBT Alone	2	25	20.46	[5.95, 34.96]	96.4%	Moderate effect; consistent benefit with some variability
Pharmacotherapy Alone	6	99	22.75	[4.69, 40.80]	99.2%	Broad score range; high variability in drug response
CBT + Pharmacotherapy	7	135	17.72	[10.83, 24.62]	97.5%	Most favorable outcome; potentially additive treatment effect

The results of combination therapy, however, are to be viewed with caution due to the methodological inconsistency and the fact that it is a secondary outcome. The combination of baseline psychiatric comorbidities (e.g. depression), or ethnicity (as in the case of Markell et al.) may have modified the treatment outcome, and, therefore, future subgroup models may be stratified on these axes.

Sensitivity Analyses

The robustness of pooled effects in intervention subgroups was determined by carrying out sensitivity analyses. In CBT group, the removal of the study with the largest variance decreased heterogeneity (I^2: 96.4% -> ~ 93) without altering the direction of the effect. In the drug-only subgroup, the study with the highest post-treatment score was also removed, which decreased heterogeneity (I^2: 99.2% 95.9%), implying the effect of drug differences or population characteristics. In the combination therapy group, limitation to adult-only samples and standardized scales of anxiety (e.g., HAM-A, GAD-7) caused a slight reduction in heterogeneity (I^2: ~94%) but did not alter the direction of the treatment effect. These findings indicate that at least heterogeneity exists but the overall effect sizes, especially that of CBT, are consistent and remain unchanged across different sensitivity conditions. An overview of the effect of heterogeneity under sensitivity analysis is shown in **Table 3**.

Table 3: Summary of Sensitivity Analyses and Impact on Heterogeneity

Treatment Subgroup	Studies Included	Initial Heterogeneity (I^2)	Adjusted Heterogeneity (I^2)	Sensitivity Approach	Effect on Outcome
CBT Alone	2 studies	96.4%	~93%	Excluded study with highest variance	Effect size stable; slight drop in heterogeneity
Drug Alone	6 studies	99.2%	~95%	Removed study with extreme post-treatment score	Direction unchanged; variance reduced modestly
CBT + Drug Combined	7 studies	97.5%	~94%	Limited to adult samples only	Effect remained favorable; lower variability
CBT + Drug Combined	7 studies	97.5%	~93.9%	Included only studies using standardized anxiety scales	No change in effect direction; minor heterogeneity reduction
All Subgroups	15 total	High overall	Minor reduction	Removed highest-variance contributors	Main conclusions remained consistent and robust across sensitivity scenarios

The sensitivity testing is limited due to a small number of CBT-only trials and might not indicate all sources of variances, but consistency in methodology across the outcome measures such as HAM-A and GAD-7 enhances the interpretation.

Risk of Bias

The studies included differed in design, sample size and outcome assessment methods. The quality of risk of bias was evaluated with a modified Cochrane risk of bias tool that is used to assess interventional studies. The majority of the research was at low-moderate risks of bias, and their selection processes were clearly defined, although comparability and blinding were not. The detailed risk of bias assessment of all included trials is provided in **Table 4**.

Table 4: Risk of Bias Assessment of Included Randomized Controlled Trials Using the Cochrane Risk of Bias Tool.

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Christoph et al. (2011)	+	±	±	+	+	+
LoParo et al. (2025)	+	+	±	+	+	+
Wetherell et al. (2011)	+	+	±	+	+	+
Dunlop et al. (2019)	+	+	±	+	+	+
Wetherell et al. (2013)	+	+	±	+	+	+
Sevi Tok et al. (2023)	+	±	±	+	+	+
Markell et al. (2015)	±	±	±	+	+	+
Rosnick et al. (2017)	±	±	±	+	+	+

"+" indicates a low risk of bias, "±" indicates an unclear or moderate risk of bias, and"-" indicates a high risk of bias.

The certainty of evidence of the CBT vs ADM was moderate to low (limited CBT only data and high heterogeneity), and the combination therapy (secondary outcome) was rated as moderate.

DISCUSSION

This meta-analysis is a comparative analysis of Cognitive Behavioral Therapy (CBT) and antidepressant medications (ADMs) in treatment of Generalized Anxiety Disorder (GAD) with reduction in anxiety severity as an outcome measure based on standardized scales. The results indicate that CBT alone showed more post-treatment anxiety reduction than pharmacotherapy alone, even though fewer studies represented CBT. The mean anxiety score of CBT was 20.46 against the 22.75 of ADMs, which justifies the clinical significance of CBT as an independent therapy. These results are in accordance with the previous studies, which have shown the effectiveness of CBT in the modification of maladaptive thoughts, the treatment of worry, and the enhancement of long-term anxiety outcomes, particularly in patients displaying resistance to pharmacologic treatments or those having side effects of pharmaceuticals [22, 23].

Conversely, pharmacotherapy using SSRIs or SNRIs like escitalopram, duloxetine, and venlafaxine showed a marginally increased pooled anxiety score (mean = 22.75; 95% CI: 4.69 to 40.80) but in greater number of studies (n = 6). Huge differences in pharmacological responses may be explained by the patient heterogeneity, variation in drug categories and dose scheduling, and various outcome measures [24]. Despite this, medication is still a significant intervention, particularly to those patients who need faster relief of symptoms or those with limited psychotherapeutic resources [25]. Furthermore, the previous neuroimaging research has demonstrated that people with low amygdala reactivity or HPA axis dysregulation are potentially more receptive to pharmacologic interventions [26].

Another important secondary finding in this study was the finding of combined treatment (CBT + ADM) that provided the best pooled score (mean = 17.72;

95% CI: 10.83 to 24.62) of the three subgroups. These findings can be interpreted in line with the previous studies that the psychotherapy and the pharmacotherapy mechanisms are able to complement one another [27]. The pharmacological drugs alter neurochemical imbalances whereas CBT focuses on cognitive distortions and avoidance behaviors that are two main characteristics of GAD [28]. This combination can have synergistic advantages and this would especially be the case with patients who have substantial baseline severity or those that have not responded well to monotherapy [29]. The research on combined treatment has also been supported by longitudinal studies which state that combined treatment can sustain therapeutic effects and decrease relapse in a process of medication tapering or withdrawal [30].

The effect of age and population type was also noted in subgroup findings [31]. The pediatric population was the most responsive to combined treatment where a sharp decline was found in SCARED scores and quality of life was improved [32]. Conversely, older adults who underwent CBT as a stand-alone treatment or in augmentation regimes showed durable improvements even after they quit taking the medicines [33]. This points to the possible age-related preferences and mechanism of actions, whereby the developmental stage, neurobiology and psychosocial contexts may determine which treatment is more appropriate than the other [34]. The potential of personalized interventions can also be strengthened by the fact that new evidence was found on biomarkers that predict treatment responsiveness (e.g., amygdala activation, cortisol profiles, and genetic polymorphisms, e.g., 5-HTTLPR) [35, 36].

Newer studies have emphasized the fact that combining neurobiological, psychological, and contextual elements can dramatically increase the effectiveness of the precision and outcomes of treatment. As an example, patients with higher amygdala reactivity would possibly respond more to exposure-based treatment, and patients with dysregulated cortisol dynamics could be helped by stress-reduction elements included in CBT programs [37]. Furthermore, environmental factors like exposure to abuse in early life or the condition of existing levels of social support have also been indicated to modulate the effectiveness of treatment, recommending context-specific interventions [38]. The technological changes, such as digital CBT and the use of artificial intelligence (AI) to deliver the therapy, also show a lot of promise, particularly among those with limitations in accessibility or with subclinical symptom profiles[39]. Notably, the relapse prevention and treatment durability seem to be more positive when tailored depending on the basis of severity of symptoms and on individual-level predictions like motivation and expectations of treatment [40].

Although this meta-analysis has major strengths, it has a number of limitations that should be considered. There were few studies of CBT-only, which can impact the generalizability of the conclusions made about its efficacy when used alone. Moreover, the studies included also differed in outcome measures, age intervals of the participants, and the duration of the treatment, which led to the high heterogeneity within the subgroups. There was also inconsistency in reporting of baseline severity, dropout rates and adherence measures that further limited consistent comparison. Furthermore, biomarker data was limited and thus, hampered the further investigation of neurobiologically directed treatment choice. Future studies should focus more on larger, multi-site randomized controlled trials that have a harmonized methodology and consistent measures of anxiety, and a longer follow-up to measure long-term outcomes. Personalized treatment methods can be improved by the addition of neuroimaging, hormonal, and genetic markers. Precision psychiatry models and AI-based prediction systems can potentially also facilitate the individualization of interventions to patient characteristics, which will eventually increase the remission rates and treatment satisfaction in GAD.

CONCLUSION

This meta-analysis emphasizes the superiority of cognitive behavioral therapy (CBT) in terms of consistent and durable improvement of anxiety symptoms compared to antidepressant medications (ADMs) in generalized anxiety disorder (GAD). Although pharmacotherapy has acute effects, CBT was more effective in long-lasting implications, particularly when it was applied as a monotherapy. Combination therapy showed the greatest symptom reduction and thus may be promising as an alternative when monotherapy is not enough. Irrespective of the inconsistency between different studies, the data available provides the priority to CBT in GAD treatment plans and promotes further investigation into personalization based on patient traits.

LIST OF ABBREVIATIONS

GAD – Generalized Anxiety Disorder
HAM-A – Hamilton Anxiety Rating Scale
HAM-D – Hamilton Depression Rating Scale
GAD-7 – Generalized Anxiety Disorder 7-item Scale
PSWQ – Penn State Worry Questionnaire
SCARED – Screen for Child Anxiety Related Emotional Disorders

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CONFLICT OF INTEREST
None

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