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A Systematic Review and Meta-Analysis: Comparative analysis of psychotherapy and pharmacotherapy for treatment of Depression

Diyasha Chakrabarti* & Seena Thomas K.†

Abstract

Depression represents a significant health issue that may turn into a severe medical condition, particularly when it recurs and manifests at moderate to severe levels of intensity. To identify the most effective treatment for depression, a rigorous study was conducted. The study used grid Hamilton Depression Rating Score (HAMD) scores to assess treatment efficacy and employed R software and MedCalc software to perform a meta-analysis comparing the effectiveness of pharmacotherapy and psychotherapy or the combination of both. After eliminating duplicates, 280 papers were meticulously reviewed, and standardized mean differences and confidence interval of 95% were compared employing a random effect model. The study found that combination therapy (combo-therapy) was more effective in reducing the HAMD than conventional monotherapy. These findings underscore the importance of identifying optimal treatment strategies for individuals suffering from depression.

Keywords — pharmacotherapy, psychotherapy, depression, meta-analysis, systematic review, HAMD

* Department of Statistics and Data Science Christ (Deemed to be University) Bengaluru, India diyasha.chakrabarti@stat.christuniversity.in

† Department of Statistics and Data Science Christ (Deemed to be University) Bengaluru, India seena.thomas@christuniversity.in

I. INTRODUCTION

A. Depression and Treatments

The prevalence of depression in a large section of society is inevitable in the current situation that the world is in. Around 280 million individuals or 3.8% of people worldwide experience depression, with 5.0% of adults and 5.7% of people over 60 afflicted.[1]. The burden of untreated mental illnesses accounts for 13% of all diseases worldwide, according to the World Health Organization [2]. According to current projections, depression will account for the majority of diseases worldwide by 2030. [1]. The supply and demand of mental health therapy differ significantly on a global scale. Between 76% and 85% of people with significant mental health issues in low- and middle-income countries do not receive treatment [1]. Depression is not the same as typical mood swings or transient emotional responses to everyday issues. Depression has the potential to become a serious medical condition, particularly if it is moderately or severely recurring. Options for treatment include brain stimulation, drugs, counseling, and complementary treatments. Depression may worsen and become permanent if left untreated. In extreme circumstances, it may result in death or self-harm. Fortunately, therapies can significantly reduce depressive symptom severity. There are several pharmacotherapy and psychotherapies and a combination of both that guide people towards a depression-free life. The way depression affects people is different when it comes to different age groups. Depression is uncommon in children under the age of 12, although it does occur under specific circumstances. Problems at the academy, a loss of interest in fun activities, different eating habits, weight increase or loss, clinginess, anxiety, troubles with family members, and avoiding academy and socializing are all prevalent indicators. Major mood swings between the ages of 12 and 18 are normal, but sometimes they might indicate signs of depression [3] . If mood swings last for more than a few weeks, it is a serious symptom of depression. Depression may manifest in various symptoms, such as unusual irritability, whiplash, worthlessness, wrath, acute sensitivity, napping or overeating, avoidance of social connections, loss of interest in activities, and self-harm behaviors are all symptoms of depression. Depression is a mental health disease that can affect people of all ages and from all walks of life. Young adults between

the ages of 19 to 29 may be particularly vulnerable to depression due to major life changes such changing locations, or beginning a new job or school, as well as a lack of social support in new surroundings [3]. Other contributing factors may include inadequate coping skills, relationship problems, poverty, trauma, and work-related stress. In contrast, adults between the ages of 30 and 60 may face different challenges that can trigger depression, such as the stress of balancing work and family responsibilities, financial strain, social isolation, relationship difficulties, and physical health problems [3]. Women in this age group may also experience depression related to menopause or perimenopause, which can cause significant hormonal changes and emotional instability. [1]According to [1] depression in both young adults and older adults can manifest in a range of symptoms, including feelings of worthlessness, irritability, lack of motivation, changes in appetite or sleep patterns, and a lack of interest in activities that were formerly pleasant. Some individuals may also engage in self-harming behaviors, such as drug or alcohol abuse or risky behavior. In some cases, depression can also lead to aggressive or violent behavior toward others. Teenagers may also be at risk for depression due to a variety of factors, including hormonal changes, sleep deprivation, peer rejection, and concerns related to sexuality and identity. In addition, they may face family stressors such as domestic violence, parental depression, abuse, and school-related challenges such as poor academic performance or difficulty fitting in. Children may also experience depression related to family stressors, such are difficulties with reading or the death of a pet, acquaintance, or family member or school performance. Overall, depression is a complex and multifaceted issue that can arise due to a variety of environmental, genetic, and psychological causes. Early detection and intervention can help individuals of all ages manage symptoms and improve their overall quality of life. Antidepressants and therapy treatments are widely prevalent and routinely used for the treatment of depression. According to [4], the American Psychiatric Association (APA) and the National Institute for Health and Clinical Excellence (NICE) have established guidelines for the treatment of depression that consider how serious the problem is. These guidelines recommend either pharmacotherapy or psychotherapy as appropriate interventions, depending on the specific needs of the individual. However, various

studies have produced conflicting results as to which treatment option carries the lowest risk and is the most effective. Antidepressant medications have been widely used for the treatment of mental illnesses, particularly mood and anxiety disorders such as depression and generalized anxiety disorder [5]. The use of antidepressants has surged over the past few decades and they are currently one of the most commonly prescribed classes of medications [6]

Antidepressant drugs are frequently used as a first-line treatment for contemporary mood and anxiety disorders, such as major depressive disorder and generalized anxiety disorder, according to a comprehensive review by Maund [7]. According to Maund [7] these drugs are also increasingly being used off-label for other conditions like fibromyalgia, migraine headaches, eating disorders, smoking cessation, insomnia, and Attention Deficit Hyperactivity Disorder (ADHD). However, the safety and efficacy of using antidepressants for off-label purposes have not been as thoroughly studied as it has for their approved psychiatric applications, so the benefits and risks of using antidepressants for these conditions should be carefully considered on a person-to-person basis [6]. Numerous epidemiological studies conducted over the past 20 years have revealed a rise in the prevalence of antidepressant prescriptions in industrialized nations [8]. Psychotherapy, commonly referred to as talk therapy, is a form of treatment where individuals engage in conversations with a licensed and trained mental health professional, such as a psychotherapist, psychiatrist, therapist, or counsellor. There are various techniques and approaches that therapists may utilize to effectively treat their patients, with Cognitive Behavioral Therapy, Dialectical Behavioral Therapy, Interpersonal Therapy, and Psycho-dynamic Therapy being the four major methods. Each approach aims to address different issues, such as identifying and changing negative thought patterns, developing healthy coping mechanisms, improving communication skills, and exploring past experiences to gain insight into current behaviors and emotions. By working closely with a therapist, individuals can gain tools and strategies to manage their mental health symptoms and improve their overall well-being. Other methods like Chamomile and Lavender Smell Therapy, Dance Therapy, Music Therapy, and Sleep Therapy are also considered to be methods of psychotherapy [9]. According to Harriman [8] they can

be used as standalone treatments or as augmentations to the 4 major psychotherapy. But sometimes, pills or therapy alone are not effective for the treatment of depression. In this study, we aim to see whether monotherapy or combotherapy has a greater efficacy in treating depression by evaluating grid HAMD scores or depression scores.

B. Literature Review

Looking for evidence to support any assertion is not new. Many formal techniques and systematic methods have been developed to improve on classical methods of a systematic review. According to John [10] integrative science as we know it today started to take form in the 20th century. According to Hytten [11] A research review, according to its initial proponent, Scottish scientist Isabella Leitch, "is both a review of research and an inquiry into the deductions that may be drawn from an accumulation of results treated as a new whole," as she wrote in 1959. To prevent the occurrence of bias, a systematic approach to literature review was created. "The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic" is the definition of a systematic review [12]. Although early systematic reviews were carried out in public policy, it was appropriate to apply methodical research to health and medicine initially. Evidence-based medicine, subsequently described by Sackett [14] as "the conscientious, explicit, judicious use of current best evidence in making decisions about the care of individual patients," was advocated by Archie Cochrane in his landmark work "Effectiveness and efficiency" [13]. Evidence-based medicine was first introduced by a group of Oxford health services researchers in the late 1970s and early 1980s. They started a program that involves doing systematic reviews to assess the effectiveness of medical and healthcare initiatives [15]. Since opening its base in Oxford in 1992, the Cochrane Collaboration has grown into an international network of academics, practitioners, researchers, and users dedicated to the quality-assured, cumulative, and accessible principles of knowledge management health. [16]. It was quickly realized that facilities for testing in areas other than health were needed, and a sister organization to Cochrane, the Campbell Partnership, emerged [4]. The concept of systematic reviews was first articulated by Dr. James Lind in the eighteenth century, who stressed the need for an

impartial and thorough analysis of the body of research on scurvy treatment. [17]. According to Hong [17] although there have been several systematic review papers published in the early 20th century, it was not before the 1970s that general science research began to gain prominence and it was realized that clear, transparent, and rigorous methods are needed to enhance the validity of reviews. Originally, systematic reviews were majorly used for clinical trials. Cochrane Cooperation, founded in 1993 [16], is one of the most significant groups created in response to Dr. Archie Cochrane's request for systematic reviews of RCTs. This non-profit, non-governmental organization conducts a systematic examination of medical therapies with the assistance of volunteer specialists worldwide. The Cochrane collaboration is presently home to over 37,000 participants from 130 countries, according to Garritty [18], making it the world's largest developer of systematic reviews in the medical field. Meta-analysis is a statistical technique that is widely used in biostatistics research. It involves combining data from multiple studies to provide a comprehensive summary estimate of the effect size of a particular treatment. Meta-analysis has several advantages in biostatistics research, such as improving the precision of the estimate, increasing statistical power, and identifying sources of variability in the results across studies. However, the validity of the meta-analysis depends on the quality and characteristics of the individual studies included in the analysis. Therefore, biostatistics researchers should adhere to established guidelines and use rigorous methods when conducting and reporting meta-analyses. This includes assessing the quality of the studies, evaluating heterogeneity, and addressing potential biases. Proper implementation of meta-analysis can enhance the credibility and impact of biostatistics research findings, and it is an important tool in producing reliable evidence for clinical decision-making. Meta-analysis has a long history that began in the early 1900s when it was applied to agricultural research to aggregate the findings of several investigations. [19]. However, it was not until the 1970s that meta-analysis became popular in medical research. In 1976, Glass introduced the term "meta-analysis" to describe a statistical method that could be used to combine the results of independent studies [20]. In the late 1970s and early 1980s, a few researchers at the University of Oxford, led by Archie Cochrane, paved the way for evidence-based

medicine by conducting systematic reviews and meta-analyses of clinical trials [21] The establishment of the Cochrane Collaboration in 1993 further solidified the importance of meta-analysis in medical research [16]. Meta-analysis typically involves a systematic search for all relevant studies, followed by a rigorous assessment of the quality of each study, and the extraction of data on the study characteristics, interventions, and outcomes. Once the data is collected, statistical techniques are used to combine the results of individual studies and produce an overall summary effect estimate. The most commonly used methods for combining data in a meta-analysis are the fixed-effect and random-effect models. In the fixed-effect model, it is presumed that all studies evaluate the same treatment effect, however, in the random-effects model, it is supposed that various studies estimate various therapeutic effects due to changes in study design or patient demographics. Publication bias, which happens when research with statistically significant findings are more likely to be published than studies with non-significant results, is one possible problem with meta-analysis. To address this issue, a meta-analysis may include a search for unpublished studies, as well as use statistical methods like as funnel plots to detect and correct for publication bias.

II. METHODOLOGY

A. Search Strategy and Selection Criteria

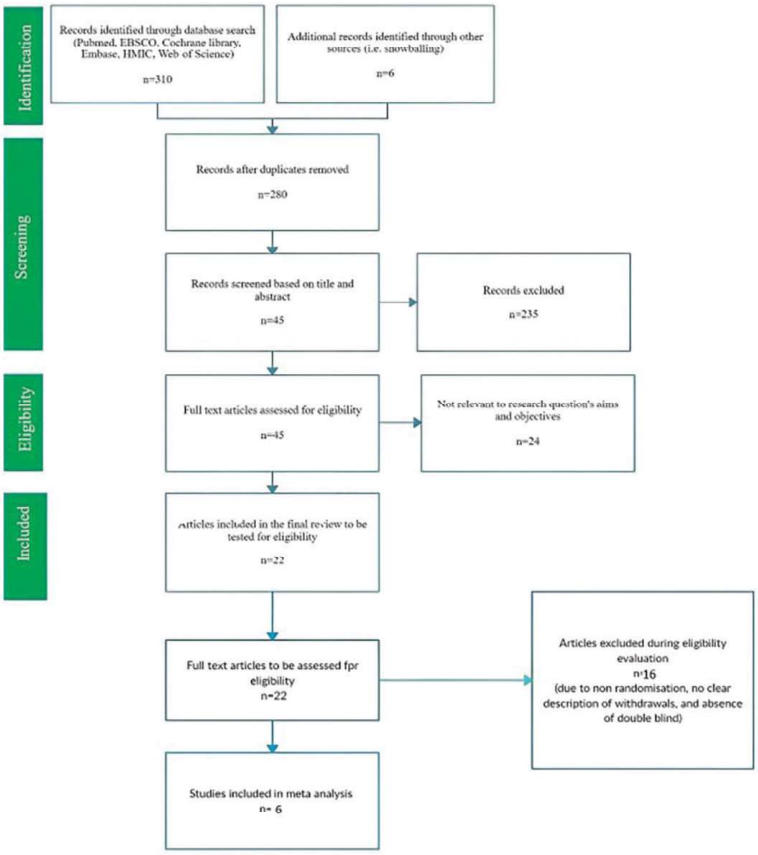
While performing this systematic review and meta-analysis, a thorough search for relevant studies about pharmacotherapy (antidepressants) and psychotherapies was undertaken on PubMed [30], Embase, ClinicalTrialsGov.in, and the Web of Science database. Specifically, randomized controlled trials published from 2017-2022 were scrutinized, utilizing an intricate combination of pivotal keywords to identify eligible studies that could be included in the analysis. This systematic review and meta-analysis included studies that involved active interventions using monotherapies (antidepressants or psychotherapy) or a combination of both, as compared to control conditions or other treatments for the management of depression in individuals aged 18 to 70 years, of both male and female, and utilizing accepted diagnostic standards, with a main diagnosis of depression [22]. The guidelines for treating depression in adults recommend the use of antidepressant medication, psychotherapy, or a combination

of both [22]. According to the guidelines, the decision to opt for either pharmacotherapy or psychotherapy is contingent upon the severity of the depression. Studies in English were [7] only considered and studies in which the treatment of combotherapy or monotherapy timeline was of less than 4 weeks were excluded. Also, studies having a sample size of less than 15 were excluded from the review. Trials with participants having comorbid conditions like anxiety disorder, post-traumatic stress disorder, bipolar disorder were excluded. Pharmacotherapy interventions for depression encompass any orally administered drug that has been approved by the FDA. Drugs like Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Sarafem) , Fluvoxamine (Luvox, Luvox CR) , Sertraline are usually the most commonly administered. Psychotherapy interventions, on the other hand, include an array of approaches such as psychoanalysis and psychodynamic therapies, cognitive behavior therapy, music therapy, and smell therapy. The study also included the combination of interventions as a valid treatment measure for depression. The control condition involved either a placebo, treatment as usual, or any other treatment. The study's inclusion criteria stipulated that appropriately randomized double-blind controlled trials with an adequate elucidation of exclusions and withdrawals were included. In order to reduce clinical heterogeneity, the Jadad Score was used to evaluate these criteria. In compliance with PRISMA-P criteria, the protocol was registered with PROSPERO (the international prospective register of systematic reviews) (PROSPERO CRD42022341888). The authors independently selected the studies and evaluation is done based on inclusion-exclusion criteria, extracted relevant data from the included trials, and did quality assessment (risk of bias). The writers' discussions resolved any disagreements. The assessment of the risk of bias for these studies was done in accordance with Cochrane's handbook for Systematic Reviews and Interventions. Finally, a data extraction sheet (Table 1) was formed which had all the final 6 studies accepted for quantitative analyses along with their 17-point GRID score from baseline to follow-up, as shown in Fig 1.

B. Outcomes

The main outcome was checking the efficacy (change in the average score from baseline to the end of the treatment). This score is based

on GRID-HAMD score which measures symptom severity. The Hamilton Rating Scale for Depression (HRSD), also known as the Hamilton Depression Rating Scale (HDRS) or



abbreviated as HAM-D, is a tool utilized for diagnosing depression and acts as a standard for evaluating improvement in patients. The scale was first published by Max Hamilton in 1960 [23]. The questionnaire, which is intended for adults, evaluates a person's mood, guilt emotions, suicidal thoughts, sleeplessness, restlessness or agitation, nervousness, loss of weight, and physical symptoms to ascertain the degree of their depression. Clinicians evaluate patients using a 3-point or 5-point Likert-type scale based on 17 to 29 items (depending on the version) in the Hamilton Rating Scale for Depression (HRSD), commonly abbreviated as HAMD. For the 17-item version,

a score ranging from 0 to 7 is normal, while a score of 20 or more indicates at least moderate severity [23]. Questions 18-20 provides additional information about depression but are not part of the scale. A structured interview guide is available for the questionnaire [24]. While Hamilton's original scale had 17 items, other versions include up to 29 items, referred to as HRSD-29. Results were noted for over eight weeks. If it was not available, then data from 10-12 weeks were also accepted.

C. Statistical Analysis

The authors performed a meta-analysis using R software (RStudio version 2023.03.3.386) [28] and MedCalc (Version 20.218) [29] software to compare the efficacy of combination therapy and monotherapy for treating depression. The forest plot and funnel plot generated from the data were used to draw conclusions. The study's primary objective was to determine which treatment was more effective by using a random effect model to compare standardized mean differences and confidence intervals of 95%. The effect size of each study was analyzed to identify the optimal type of treatment for depression. Statistical heterogeneity was assessed using the I^2 heterogeneity, and a sensitivity analysis was conducted by removing non-significant studies. Publication bias was identified using the Funnel plot.

III. RESULTS

After identifying 310 published articles and removing duplicates, a total of 280 articles remained. Based on the exclusion criteria outlined in the title and abstract, 235 articles were eliminated, leaving 45 for full-text assessment. Of these, 22 articles met the eligibility criteria for the review, but 15 were later excluded due to non-randomization, lack of double-blind methodology, or unclear explanations of withdrawals. Ultimately, 6 articles were selected for quantitative analysis. The trials compared various combinations of pharmacotherapy and psychotherapy with monotherapy. The comparisons included in the current study were:

- Cognitive Behavioral Therapy and Antidepressants
- Trial-based Cognitive Therapy and Behavioral Activation vs Antidepressants

- Effectiveness of preventive Cognitive Behavioral Therapy and Antidepressants vs Antidepressants
- Fluoxetine and Cognitive Behavioral Therapy vs Cognitive Behavioral Therapy
- ISPRT and Quetiapine vs ISPR
- Computerized Cognitive Behavioral Therapy Antidepressants vs Antidepressants

The main outcome to be considered as the mean Hamilton Depression Score from baseline to 8 weeks of treatment. The software MedCalc provided the forest plot through which it was concluded that a combination of pharmacotherapy and psychotherapy was better than monotherapy for the treatment of depression. The studies involved both males and females belonging to the age group 13 to 80. Participants were randomly assigned to two groups – combotherapy and monotherapy (involving pharmacotherapy and psychotherapy). Mean differences and sample sizes for each group of subjects for each study are given in Table 1. The Mean baseline depression severity score for combotherapy was 20.86 and for monotherapy was 21.30. After 8 weeks of treatment, the mean depression score reduced to 9.9 for combotherapy and 13.83 for monotherapy. The HAMD score significantly reduced to less than 7 with 12 weeks of treatment. The HAMD score of range 0 -10 indicates no depression and a range of 11 to 13 indicates mild depression.

To check for efficacy, a forest plot is a crucial tool for academics to compile data from various articles into a unified vision. In terms of efficacy, from the forest plot as shown in Fig 3, it can be observed that all the studies are statistically significant except one. The central line indicates the line of no difference between two groups also called the line of null effect. Studies on the left of it are significant and are more effective. So, since all the studies are mostly to the left of the vertical line it implies that combo-therapy is more effective than monotherapy for the treatment of depression. To reach the objective, the effect sizes were compared. A statistical metric known as an effect size is used to quantify the strength of the link or difference between two variables [22]. It is a standardized measure that enables researchers to compare the strength of effects across different studies, experiments, or

samples. It explains the magnitude of the impact of any intervention (which in this case would be pharmacotherapy or psychotherapy or combotherapy) on the outcome (depression). In this study, Cohen's D measure was used to calculate and analyze effect sizes. The measure of effect size was used to quantify the difference between two means, typically in experimental or quasi-experimental designs. Cohen's D represents the standardized difference between the two means, divided by the pooled standard deviation [22] Effect sizes can be checked from the forest plot (Fig I) .The effect size in a forest plot is typically represented by a point estimate, such as the mean difference or odds ratio, with confidence intervals displayed as lines extending from the point estimate. The size of the point estimate and the width of the confidence interval provides information about the magnitude and precision of the effect size, respectively [25]. The larger the point estimate more is the effect size. Effect sizes for this study ranged from -1.49 to -0.38. The pooled effect size was 0.83 which was statistically significant (p value). A study of publication bias was conducted using a funnel plot.

Researchers can utilize a funnel plot as a graphical tool to evaluate possible publication bias, which happens when studies with unfavorable or non-significant results are less likely to be published. The plot displays the effect size of each study on the x-axis and a measure of precision on the y-axis, with the studies represented by dots or circles. Funnel lines are drawn to represent the expected range of effect sizes if there were no publication bias. If publication bias exists, the plot will be asymmetrical, with missing small studies that do not report significant results. The plot can be used to identify studies contributing to bias and to estimate the extent of publication bias using statistical tests [26]. The plot given in Figure 4 is symmetrical, indicating an absence of publication bias in this study.

The heterogeneity measure I^2 is a statistical measure used in meta-analysis to estimate the degree of variability among the effect sizes of the included studies. It is expressed as a percentage and ranges from 0% to 100%, where a higher value indicates greater heterogeneity [27]. It estimates the percentage of the variability in effect sizes that is due to factors other than sampling error. I^2 can be used to determine whether a fixed-effect or random-effect model should be used in the

meta-analysis. If I^2 is low (less than 50%), a fixed-effect model may be appropriate, whereas if I^2 is high (greater than 50%), a random-effects model may be more appropriate [27]. In Fig 2 it can be observed that the Q statistic value is 30.52 and the I^2 value is 83.62 (95% CI, 65.77 to 92.16). This indicates substantial heterogeneity among the included studies in a meta-analysis.

IV. DISCUSSION

Majority of the studies in the literature compared combotherapy and monotherapy with the Odds Ratio as an effect size. This is the first attempt to compare combotherapy and monotherapy by analyzing the Cohen's D as an effect size. The forest plot utilizes the size of the box to represent the weight of the study, with larger boxes indicating greater information and effect. From the forest plot (Fig. III) it can be concluded that for patients suffering from depression, the overall treatment was in favor of combotherapy. More specifically, combotherapy was associated with a lower HAMD score as compared to conventional monotherapy (mean difference, -0.93, 95% CI, -1.49 to -0.38). In more specific terms, the combination of fluoxetine with Cognitive Behavioral Therapy resulted in the greatest reduction in depression within an 8-week treatment period. An I^2 score of 83.62% indicates the presence of substantial heterogeneity. This suggests that the variation in effect sizes is likely related to factors such as variations in study design, demographic characteristics, intervention or exposure, or outcome assessment rather than just being random. Hence for this study, a random effects model was applied. More specifically, the I^2 statistic quantifies the proportion of variation in effect sizes that is due to heterogeneity rather than chance. An I^2 value of 83.62% means that 83.62% of the variation in effect sizes is due to heterogeneity, while the remaining 16.38% is due to chance. The funnel plot (Fig II) indicates the absence of publication bias. This report summarizes the efficacy of various combo therapies and monotherapies, but this study should be assessed with caution due to the small number of treatments and substantial heterogeneity. In summary, meta-analysis is a powerful statistical technique for synthesizing evidence from multiple studies, which can provide a more precise and reliable estimate of treatment effects compared to individual studies. However, it is important to conduct meta-

analysis using rigorous methods and to interpret the results with caution, taking into account the quality and heterogeneity of the included studies. Yet despite these limitations, the findings of this meta-analysis are quite comprehensive with respect to the available evidence.

Table I. Final Study Details

Study name	***Mean1***	***SD1***	***N1***	***Mean2***	***SD2***	***N2***
Atsuo	12.1	5.2	40	14.2	6	40
Curt	9.84	5.9	14	17.98	6.3	10
Davey	12.3	8.2	27	11.9	5.3	27
Holly	8.3	3.9	44	13.2	4.6	44
Liu	8.19	3.54	26	15.2	3.54	26
Gukaysan	8.7	7.6	27	15.2	3.64	27

Table II. Output For Meta Analysis

Study	***N1***	***N2***	***To-tal***	***SMD***	***SE***	***95% CI***	***t***	***p***	***Weight %***	
									Fixed	***Ran-dom***
Atsuo	40	40	80	-0.370	0.223	-0.815 to 0.0743			25.25	18.13
Curt	14	10	24	-1.295	0.441	-2.211 to -0.380			6.471	13.70
Davey	27	27	54	0.0729	0.268	-0.486 to 0.611			17.50	17.28
Holly	44	44	88	-1.139	0.228	-1.592 to -0.688			24.21	18.04
Liu	26	26	52	-1.950	0.333	-2.620 to -1.281			11.33	15.95
Guka-ysan	27	27	54	-1.075	0.287	-1.652 to -0.498			15.24	16.9
Total (Fixed Effect)	178	174	352	-0.825	0.112	-1.046 to -0.604	-7.532	< 0.001	100	100
Total (Random Effect)	178	174	352	-0.930	0.285	-1.491 to -0.370	-3.26	0.0012	100	100

Q	30.519

DF	5
Significance Level	P<0.0001
I^2 (inconsistency)	83.62%
95 % (CI) for I^2	65.77 to 92.16

Egger's Test	
Intercept	-4.826
95%(CI)	-17.9490 to 8.2231
Significance Level	p = 0.3605
Begg's Test	
Kendall's Tau	-0.3333
Significance Level	p = 0.3476

Table III. Publication Bias

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Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Code , Data And Material Availability

The final dataset with all its relevant information collected from the articles has been brought together in a single excel sheet given in Table 2. It has information regarding the authors, the sample size, the control, the intervention, and Jadad Score.

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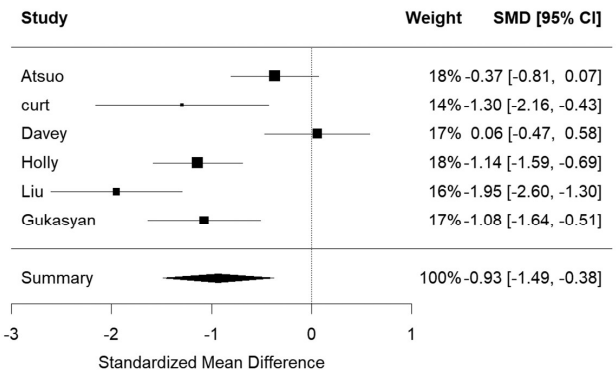

Fig. 1 Forest plot for overall efficacy of combotherapy vs monotherapy on the reduction of depression (difference from mean at baseline to end of treatment) . 95 % ci : 95 % confidence interval

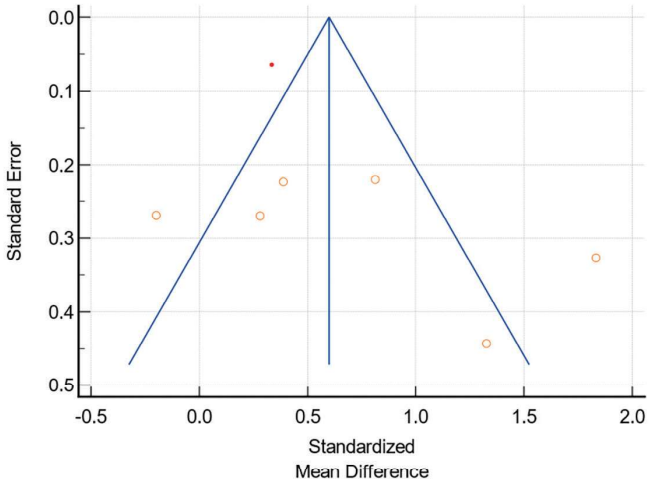

Fig. 2 funnel plot

Table IV Data Extraction Sheet

Study Title	Authors	citation	Journal//Book	Jadad Score	study characteristics		size		
					Type of Comparison	Type of Control	sample size	treatment size	control size
Effectiveness of Supplementary Cognitive-Behavioral Therapy for Pharmacotherapy-Resistant Depression: A Randomized Controlled Trial	Nakagawa A, Mitsuda D, Sado M, Abe T, Fujisawa D, Kikuchi T, Iwashita S, Mimura M, Ono Y.	J Clin Psychiatry. 2017 Sep/Oct;78(8):1126-1135. doi: 10.4088/JCP.15m10511.	J Clin Psychiatry	3/5	Pharmacotherapy +Cognitive Behavioral Therapy	Pharmacotherapy	78	39	39
Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial	Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, Finan PH, Griffiths RR.	JAMA Psychiatry. 2021 May 1;78(5):481-489. doi: 10.1001/jamapsychiatry.2020.3285.	JAMA Psychiatry	5 /5	Psilocybin+Pharmacotherapy	Pharmacotherapy	27	15	12
The Efficacy of Computerized Cognitive Behavioral Therapy for Depressive and Anxiety Symptoms in Patients With COVID-19: Randomized Controlled Trial	Liu Z, Qiao D, Xu Y, Zhao W, Yang Y, Wen D, Li X, Nie X, Dong Y, Tang S, Jiang Y, Wang Y, Zhao J, Xu Y.	J Med Internet Res. 2021 May 14;23(5):e26883. doi: 10.2196/26883.	J Med Internet	3/5	Computerized Cognitive Behavioral Therapy+Antidepressants	Antidepressants	252	126	126
Efficacy of trial-based cognitive therapy, behavioral activation and treatment as usual in the treatment of major depressive disorder: preliminary findings from a randomized clinical trial	Hemanny, C., Carvalho, C., Maia, N., Reis, D., Botelho, A. C., Bonavides, D., Seixas, C., & de Oliveira, I. R	CNS spectrums, 25(4), 535–544. https://doi.org/10.1017/S1092852919001457	CNS Spectrums	5/ 5	Trial based Cognitive Behavioral Therapy +Antidepressants	Antidepressants	24	14	10
The addition of fluoxetine to cognitive behavioural therapy for youth depression (YoBA-C): study protocol for a randomised control trial	Davey, C. G., Chanen, A. M., Hetrick, S. E., Cotton, S. M., Ratheesh, A., Amminger, G. P., Koutsogiannis, J., Phelan, M., Mullen, E., Harrison, B. J., Rice, S., Parker, A. G., Dean, O. M., Weller, A., Kerr, M., Quinn, A. L., Catania, L., Kazantzis, N., McGorry, P. D., & Berk, M.	The lancet. Psychiatry. 6(9), 735–744. https://doi.org/10.1016/S2215-0366(19)30215-9	The lancet. Psychiatry	4/5	Cognitive Behavioral Therapy + Fluoxetine	Cognitive Behavioral Therapy	54	27	27
Psychotherapy Alone and Combined With Medication as Treatments for Depression: A Randomized Controlled Trial	Swartz, H. A., Rucci, P., Thase, M. E., Wallace, M., Carretta, E., Celedonia, K. L., & Frank, E.	The Journal of clinical psychiatry. 79(2), 16m11027. https://doi.org/10.4088/JCP.16m11027	The Journal of clinical psychiatry	4/5	interpersonal and social rhythm therapy+Quetiapine	interpersonal and social rhythm therapy	88	44	44
Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up	Gukasyan, N., Davis, A. K., Barrett, F. S., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., & Griffiths, R. R.	*Journal of psychopharmacology (Oxford, England)*, 36(2), 151–158. https://doi.org/10.1177/0269881121107375 9	Journal of psychopharmacology	4/5	Psilocybin+Pharmacotherapy	Pharmacotherapy	54	27	27