



How Do Combined Pharmacological And Psychotherapeutic Interventions Impact Treatment Outcomes For Patients With Treatment- Resistant Major Depressive Disorder? : A Systematic Review

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ABSTRACT

Introduction: Treatment-resistant major depressive disorder (TRD), characterized by an inadequate response to at least two antidepressant trials, presents a significant clinical challenge. Combined pharmacological and psychotherapeutic interventions have emerged as a promising strategy, potentially offering synergistic benefits over monotherapy by addressing both biological and psychological aspects of the disorder. This review synthesizes evidence on the efficacy, mechanisms, and clinical applicability of combined interventions for TRD. **Methods:** This systematic review followed PRISMA 2020 guidelines. Studies were included if they focused on adult patients with TRD, examined combined pharmacotherapy and psychotherapy, were randomized controlled trials (RCTs), systematic reviews, or meta-analyses, included quantitative depression measures, and had an intervention duration of at least 8 weeks. Searches were conducted in PubMed, Semantic Scholar, Sagepub, and Google Scholar. **Results:** Forty studies were included, comprising 20 RCTs and 19 systematic reviews/meta-analyses. Combined interventions generally demonstrated superior response and remission rates compared to monotherapy. For instance, one study found response rates of 30.3% for mindfulness-based cognitive therapy (MBCT) plus treatment as usual versus 15.3% for controls. Meta-analyses reported moderate effect sizes (Cohen's $d = 0.32-0.93$) and risk ratios of 1.25–1.27 favoring combination therapy. **Discussion:** The findings underscore the superior efficacy of combined pharmacological and psychotherapeutic interventions for TRD. These approaches lead to significant improvements in response and remission rates, particularly in severe or chronic TRD. **Conclusion:** The evidence strongly supports combined pharmacological and psychotherapeutic interventions as the gold standard for TRD, offering enhanced efficacy, reduced relapse rates, and good tolerability. Future research should continue to optimize sequencing, explore novel adjuncts, and improve accessibility through digital platforms.

Keywords: Treatment-Resistant Depression, Major Depressive Disorder, Combined Therapy, Pharmacotherapy, Psychotherapy, Cognitive Behavioral Therapy, Mindfulness-Based Cognitive Therapy, Response Rates, Remission Rates.

INTRODUCTION

Treatment-resistant major depressive disorder (TRD) is a debilitating condition characterized by inadequate response to at least two antidepressant trials (Souza et al., 2016). Despite advances in pharmacotherapy, a significant proportion of patients fail to achieve remission, underscoring the need for innovative treatment strategies (Eisendrath et al., 2016). Combined pharmacological and psychotherapeutic interventions have emerged as a promising approach, offering synergistic benefits for symptom reduction and functional recovery (Cuijpers et al., 2020).

TRD affects approximately 30% of individuals with major depressive disorder (MDD), contributing to high healthcare costs and reduced quality of life (Kamenov et al., 2016). The chronicity of TRD exacerbates disability, highlighting the urgency for effective multimodal treatments (Guidi & Fava, 2020). Pharmacotherapy alone often yields suboptimal outcomes, with remission rates as low as 15% in TRD (Souza et al., 2016). Similarly, psychotherapy alone may not address biological vulnerabilities, necessitating combined approaches (Driessen et al., 2020).

Combining pharmacotherapy and psychotherapy targets both neurochemical imbalances and maladaptive cognitive-behavioral patterns (Fonagy et al., 2015). Meta-analyses demonstrate moderate effect sizes (Cohen's $d = 0.32$ – 0.93) favoring combination therapy over monotherapy (Cuijpers et al., 2020). Randomized controlled trials (RCTs) report higher response rates (30.3% vs. 15.3%) and remission rates (22.4% vs. 13.9%) for combined interventions (Eisendrath et al., 2016). Digital therapies, such as smartphone-based cognitive behavioral therapy (CBT), further enhance accessibility (Watanabe et al., 2015).

Systematic reviews confirm the superiority of combination therapy, with risk ratios of 1.25–1.27 for response and remission (Cuijpers et al., 2020). Long-term benefits include reduced relapse rates (Guidi & Fava, 2020). CBT, mindfulness-based cognitive therapy (MBCT), and dialectical behavior therapy (DBT) are commonly studied (Junkes et al., 2024). MBCT, for instance, reduces depressive symptoms by 36.6% compared to 25.3% in controls (Eisendrath et

al., 2016).

Augmentation strategies (e.g., repetitive transcranial magnetic stimulation [rTMS]) show efficacy, with response rates of 39.68% vs. 13.71% for sham (Vida et al., 2023). Psilocybin-assisted therapy also demonstrates rapid antidepressant effects (Menon et al., 2024). Web-based CBT and electronic MBCT improve outcomes without increasing adverse events (Rodrigues et al., 2024; Nakao et al., 2018).

Sequential psychotherapy post-pharmacotherapy reduces relapse rates by 16% (Guidi & Fava, 2020). Long-term psychoanalytic psychotherapy sustains benefits over 42 months (Fonagy et al., 2015). Combination therapy outperforms monotherapy in severe or chronic TRD (Kamenov et al., 2016). However, CBT alone may be superior in specific contexts (Whiston et al., 2019).

Combined interventions are well-tolerated, with no major safety concerns (Gabriel et al., 2023). Dropout rates are lower than pharmacotherapy alone (Driessen et al., 2020). Guidelines recommend personalized combinations based on patient profiles (Gabriel et al., 2023). Future research should optimize sequencing and duration (Barnhofer et al., 2023). This review synthesizes evidence on combined interventions for TRD, focusing on efficacy, mechanisms, and clinical applicability.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate combined pharmacological and psychotherapeutic

interventions impact treatment outcomes for patients with treatment-resistant major depressive disorder.

Screening

We screened in papers that met these criteria:

- **Population Age and Treatment History:** Does the study focus on adult patients (18 years) with confirmed treatment-resistant depression (documented failure of at least two adequate antidepressant trials)?
- **Intervention Type:** Does the study examine a combined intervention that includes BOTH pharma- cotherapy AND psychotherapy components?
- **Study Design:** Is the study design either a randomized controlled trial (RCT), systematic review, or meta-analysis?
- **Outcome Measures:** Does the study include at least one standardized quantitative measure of depression severity as an outcome?
- **Diagnosis Specificity:** Does the study focus exclusively on unipolar major depressive disorder (ex- cluding bipolar disorder and psychotic depression)?
- **Intervention Duration:** Is the intervention duration at least 8 weeks?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design Type:**

Identify the specific type of study design from the full text. Options include:

- Randomized Controlled Trial (RCT)
- Open study

- Case report
- Meta-analysis
- Systematic review

If multiple design elements are present, list all. If unclear, note "design unclear" and provide a brief explanation. Look primarily in the methods section for this information.

- **Intervention Components:**

Comprehensively list ALL intervention components for both pharmacological and psychotherapeutic treatments:

- Specific medications (name, dosage, frequency)
- Specific psychotherapy type (e.g., CBT, psychodynamic)
- Duration of each intervention
- Frequency of interventions

If multiple intervention arms exist, detail each separately. Be as precise as possible. Use exact terminology from the original text. If dosage or specific details are missing, note "not specified".

- **Participant Demographics:**

Extract the following participant details:

- Total sample size
- Age range/mean age
- Gender distribution (% male/female)
- Diagnostic criteria for treatment-resistant depression
- Any specific inclusion/exclusion criteria

If any demographic information is incomplete, note "partial information available". Prioritize reporting exact numbers over percentages when possible.

- **Primary Outcome Measures:**

List ALL primary outcome measures used in the study:

- Specific assessment tools/scales
- Specific domains measured (e.g., depressive symptoms, quality of life, functioning)
- Measurement time points

Capture exact names of measurement tools (e.g., Hamilton Depression Rating Scale). If multiple outcomes were measured, list in order of study's priority. If outcome measurement details are unclear, note "outcome measurement details incomplete".

- **Key Treatment Outcomes:**

Extract the most significant treatment outcomes:

- Statistically significant changes in primary outcomes
- Effect sizes (if reported)
- Comparative effectiveness between intervention groups

Report numerical results exactly as they appear in the text. If statistical significance is unclear, note "statistical significance not clearly reported". Prioritize reporting of between-group differences.

- **Risk of Bias Assessment:**

Assess potential sources of bias:

- Randomization method (if applicable)
- Blinding procedures
- Loss to follow-up rates
- Potential conflicts of interest
- Funding sources

Use a standardized approach (e.g., Cochrane Risk of Bias Tool) if possible. If bias assessment is not explicitly discussed, note "bias assessment not reported". Be objective and quote directly from text when possible.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Adults with treatment-resistant depression	Major depressive disorder	Failed ≥ 2 antidepressant trials	Chronic depression
Intervention (I)	Combined pharmacotherapy and psychotherapy	Cognitive behavioral therapy	Mindfulness-based cognitive therapy	Repetitive transcranial magnetic stimulation
Comparison (C)	Pharmacotherapy alone	Psychotherapy alone	Treatment as usual	placebo control
Outcome (O)	Response rates	Remission rates	Hamilton Depression Rating Scale	Relapse prevention

The Boolean MeSH keywords inputted on databases for this research are: (*"Adults with treatment-resistant depression" OR "Major depressive disorder" OR "Failed ≥ 2 antidepressant trials" OR "Chronic depression"*) AND (*"Combined pharmacotherapy and psychotherapy" OR "Cognitive behavioral therapy" OR "Mindfulness-based cognitive therapy" OR "Repetitive transcranial magnetic stimulation"*) AND (*"Pharmacotherapy alone" OR "Psychotherapy alone" OR "Treatment as usual" OR "placebo control"*) AND (*"Response rates" OR "Remission rates" OR "Hamilton Depression Rating Scale" OR "Relapse prevention"*)

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study

locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Adults with treatment-resistant depression" OR "Major depressive disorder" OR "Failed ≥ 2 antidepressant trials" OR "Chronic depression") AND ("Combined pharmacotherapy and psychotherapy" OR "Cognitive behavioral therapy" OR "Mindfulness-based cognitive therapy" OR "Repetitive transcranial magnetic stimulation") AND ("Pharmacotherapy alone" OR "Psychotherapy alone" OR "Treatment as usual" OR "placebo control") AND ("Response rates" OR "Remission rates" OR "Hamilton Depression Rating Scale" OR "Relapse prevention")	50
Semantic Scholar	("Adults with treatment-resistant depression" OR "Major depressive disorder" OR "Failed ≥ 2 antidepressant trials" OR "Chronic depression") AND ("Combined pharmacotherapy and psychotherapy" OR "Cognitive behavioral therapy" OR "Mindfulness-based cognitive therapy" OR "Repetitive transcranial magnetic stimulation") AND ("Pharmacotherapy alone" OR "Psychotherapy alone" OR "Treatment as usual" OR "placebo control") AND ("Response rates" OR "Remission rates" OR "Hamilton Depression Rating Scale" OR "Relapse prevention")	250
Sagepub	("Adults with treatment-resistant depression" OR "Major depressive disorder" OR "Failed ≥ 2 antidepressant trials" OR "Chronic depression") AND ("Combined pharmacotherapy and psychotherapy" OR "Cognitive behavioral therapy" OR "Mindfulness-based cognitive therapy" OR "Repetitive transcranial magnetic stimulation") AND ("Pharmacotherapy alone" OR "Psychotherapy alone" OR "Treatment as usual" OR "placebo control") AND ("Response rates" OR "Remission rates" OR "Hamilton Depression Rating Scale" OR "Relapse prevention")	6,028
Google Scholar	("Adults with treatment-resistant depression" OR "Major depressive disorder" OR "Failed ≥ 2 antidepressant trials" OR "Chronic depression") AND ("Combined pharmacotherapy and psychotherapy" OR "Cognitive behavioral therapy" OR "Mindfulness-based cognitive therapy" OR "Repetitive transcranial magnetic stimulation") AND ("Pharmacotherapy alone" OR "Psychotherapy alone" OR "Treatment as usual" OR "placebo control") AND ("Response rates" OR "Remission rates" OR "Hamilton Depression Rating Scale" OR "Relapse prevention")	18,700

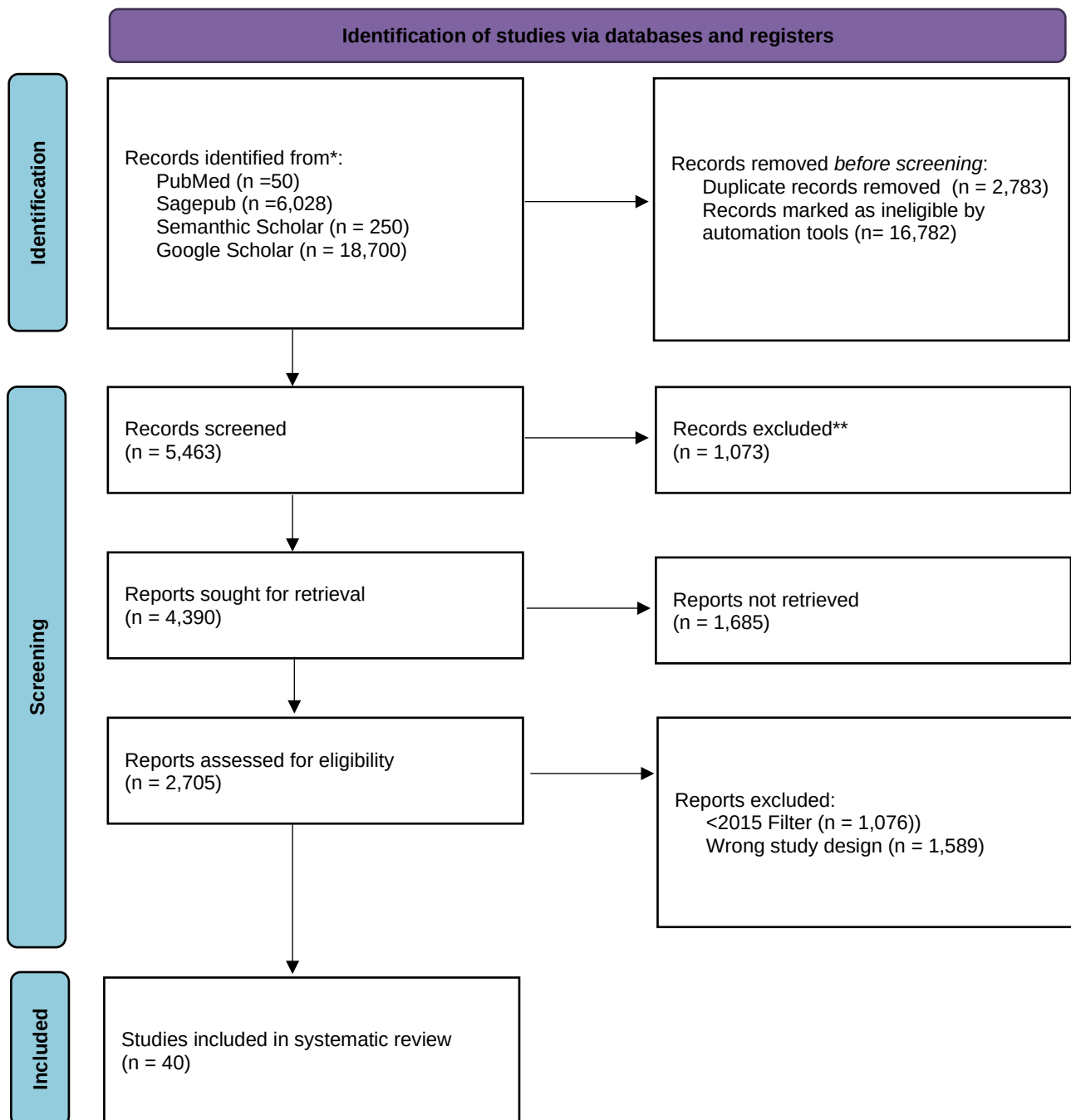


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Souza et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Eisendrath et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Watanabe et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

Rodrigues et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Junkes et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Navarro et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cuijpers et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fonagy et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Vida et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Laws et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nakao et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andrews et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dalhuisen et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Koeser et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
van Bronswijk	✓	✓	✓	✗	✓	✗	✓	✓	✓

et al., 2018									
Yasinski et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Guidi and Fava, 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kamenov et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zakhour et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Driesse et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Schaub et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mantani et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Gabriel et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jia et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Furukawa et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

Barnhofer et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sado et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jones et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Weitz et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Di Salvo et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Whiston et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lin et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
de Roten et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Riese et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fukumori et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhou et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

Menon et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rush and Jain, 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Akpınar et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Study Design	Patient Population	Intervention Combination	Primary Outcome Measures	Full text retrieved
Souza et al., 2016	Randomized controlled trial	40 adults with treatment-resistant depression (major depressive disorder, failed at least one antidepressant)	Treatment as usual (pharmacotherapy) vs. treatment as usual plus interpersonal psychotherapy	Hamilton Depression Rating Scale (weeks 8, 12, 19, 24)	Yes
Eisendrath	Random	173 adults with	Mindfulness-based	Hamilton	Yes

et al., 2016	ized controll ed trial	treatment- resistant depression (major depressive disorder, failed at least two antidepressants)	cognitive therapy plus treatment as usual vs. health enhancement program plus treatment as usual	Depression Rating Scale (17-item), Clinical Global Impression (baseline, 4, 8 weeks)	
Watanabe et al., 2015	Random ized controll ed trial	164 adults with major depressive disorder, antidepressant- resistant	Kokoro-App (cognitive behavioral therapy) plus switch antidepressant vs. switch only	Patient Health Questionnair e-9 (weeks 0, 1, 5, 9)	Yes
Rodrigues et al., 2024	Random ized controll ed trial	28 adults with treatment- resistant depression (median age 50)	Electronic mindfulness-based cognitive therapy plus medication vs. usual care	Beck Depression Inventory, Beck Anxiety Inventory, Mindful Attention Awareness Scale, Self- Compassion	Yes

				Scale, Clinical Global Impression (pre/post)	
Junkes et al., 2024	Systema tic review, meta- analysis	Adults with treatment- resistant depression	Dialectical behavior therapy/radically open dialectical behavior therapy plus pharmacotherapy vs. pharmacotherapy	Hamilton Depression Rating Scale, Beck Depression Inventory, Short Form- 12, Clinical Global Impression	Yes
Navarro et al., 2020	Random ized controll ed trial (protoco l)	180 adults with treatment- resistant depression	Treatment as usual plus lifestyle advice vs. treatment as usual plus mindfulness- based cognitive therapy vs. treatment as usual plus lifestyle program	Beck Depression Inventory-II (baseline, post, 6, 12 months)	No

Cuijpers et al., 2020	Meta-analysis, systematic review	11,910 adults with depression (including treatment-resistant depression)	Psychotherapy, pharmacotherapy, combination	Response/remission, acceptability	Yes
Fonagy et al., 2015	Randomized controlled trial	129 adults with treatment-resistant depression (major depressive disorder, failed at least two treatments)	Long-term psychoanalytic psychotherapy plus treatment as usual vs. treatment as usual	Hamilton Depression Rating Scale-17 (6, 12, 18, 24, 30, 42 months)	Yes
Vida et al., 2023	Systematic review, meta-analysis	854 (response), 551 (remission) with treatment-resistant depression	Repetitive transcranial magnetic stimulation plus pharmacotherapy vs. sham plus pharmacotherapy	Hamilton Depression Rating Scale, Montgomery-Åsberg Depression Rating Scale (post-treatment)	Yes

Laws et al., 2017	Random ized controll ed trial (second ary analysis)	357 partial/non- responders to pharmacothera py	Algorithm-driven pharmacotherapy with or without psychotherapy	Quick Inventory of Depressive Symptomato logy- Clinician, Hamilton Depression Rating Scale	Yes
Nakao et al., 2018	Random ized controll ed trial (second ary analysis)	40 adults with major depressive disorder, unresponsive to antidepressants	Web-based cognitive behavioral therapy plus face-to-face vs. waitlist	GRID- Hamilton Depression Rating Scale (baseline, 12 weeks)	No
Andrews et al., 2020	Random ized controll ed trial (second ary analysis)	156 adults with treatment- resistant depression	Cognitive behavioral therapy plus pharmacotherapy	Beck Depression Inventory-II (weekly)	No

Dalhuisen et al., 2022	Randomized controlled trial (protocol)	132 adults with treatment-resistant depression	Repetitive transcranial magnetic stimulation plus cognitive behavioral therapy plus antidepressant vs. next-step medication plus cognitive behavioral therapy	Hamilton Depression Rating Scale-17 (multiple timepoints)	Yes
Koeser et al., 2023	Randomized controlled trial (economic analysis)	Adults with treatment-resistant depression (TADS sample)	Long-term psychoanalytic psychotherapy plus treatment as usual vs. treatment as usual	Quality-adjusted life years, costs	No
van Bronswijk et al., 2018	Meta-analysis	21 trials, 25 comparisons (treatment-resistant depression)	Psychotherapy with or without treatment as usual	No mention found	No
Yasinski et	Random	49 adults with	Cognitive	No mention	No

al., 2019	ized controll ed trial (second ary analysis)	treatment- resistant depression	behavioral therapy	found	
Guidi and Fava, 2020	Systema tic review, meta- analysis	2,283 adults with major depressive disorder (remitted)	Sequential pharmacotherapy plus psychotherapy	Relapse/recur rence rates	No
Kamenov et al., 2016	Meta- analysis	29,879 adults with depression	Psychotherapy, pharmacotherapy, combination	Functioning, quality of life, Hamilton Depression Rating Scale	Yes
Zakhour et al., 2020	Systema tic review	1,056 (adults/adolesc ents with treatment- resistant depression)	Cognitive behavioral therapy plus pharmacotherapy vs. pharmacotherapy	Depressive symptoms (various scales)	Yes

Driessen et al., 2020	Systematic review, meta-analysis	482 adults with depression	Short-term psychodynamic psychotherapy plus antidepressants vs. antidepressants	Hamilton Depression Rating Scale (post, follow-up)	Yes
Schaub et al., 2018	Randomized controlled trial	177 inpatients with severe major depressive disorder	Enhanced case management vs. group cognitive behavioral therapy vs. group cognitive behavioral therapy plus individual (all with pharmacotherapy)	Symptom change, functioning, re-hospitalization	No
Mantani et al., 2017	Randomized controlled trial	164 adults with major depressive disorder, antidepressant-resistant	Smartphone cognitive behavioral therapy plus medication switch vs. switch only	Patient Health Questionnaire-9 (week 9)	Yes
Gabriel et al., 2023	Systematic review (guidelines)	Not applicable	Not applicable	Not applicable	Yes

Jia et al., 2018	Systematic review, meta-analysis	840 adults with depression	Morita therapy plus pharmacotherapy vs. pharmacotherapy	No mention found	No
Furukawa et al., 2016	Systematic review, meta-analysis (protocol)	No mention found (chronic depression)	Cognitive behavioral analysis system of psychotherapy, pharmacotherapy, combination	Montgomery-Åsberg Depression Rating Scale, Hamilton Depression Rating Scale, dropouts	Yes
Barnhofer et al., 2023	Randomized controlled trial (protocol)	234 adults, non-responders to Improving Access to Psychological Therapies	Mindfulness-based cognitive therapy plus treatment as usual vs. treatment as usual	Patient Health Questionnaire-9 (34 weeks)	Yes
Sado et al., 2021	Comparative study (design unclear)	No mention found	Augmented cognitive behavioral therapy plus treatment as usual vs. treatment as usual	No mention found	No

Jones et al., 2021	Systema tic review, meta- analysis	3,228 adults with treatment- resistant depression	Placebo across modalities	No mention found	No
Weitz et al., 2017	Meta- analysis, systema tic review (protoco l)	No mention found	Combination vs. psychotherapy, pharmacotherapy, placebo	Beck Depression Inventory, Hamilton Depression Rating Scale, Montgomery- Åsberg Depression Rating Scale	Yes
Di Salvo et al., 2024	Systema tic review	12 studies (depressive disorders)	Short-term psychodynamic psychotherapy plus antidepressants vs. antidepressants	Hamilton Depression Rating Scale, Clinical Global Impression, Outcome Questionnair e-45.2	Yes
Whiston et	Systema	11,374 adults	Cognitive	No mention	No

al., 2019	tic review, meta- analysis	with major depressive disorder	behavioral therapy, interpersonal psychotherapy, combination	found	
Lin et al., 2015	Random ized controll ed trial	37 adults with non-remitting depression	Pioglitazone plus standard regimen vs. placebo	Hamilton Depression Rating Scale- 21 (baseline, 2, 4, 6, 8, 12 weeks)	Yes
de Roten et al., 2017	Random ized controll ed trial	149 inpatients with major depressive disorder	Integrative brief psychodynamic psychotherapy plus treatment as usual vs. treatment as usual	Depression severity, response/rem ission	No
Riese et al., 2021	Random ized controll ed trial	100 adults with major depressive disorder, unresponsive/r elapsing	Therap-i module plus treatment as usual vs. treatment as usual	Inventory of Depressive Symptomato logy-Self Report	Yes
Fukumori et al., 2024	Meta- analysis	9,873 adults with	Psychotherapies with or without	Depression severity	No

		depression	medication		
Zhou et al., 2021	Meta-analysis, systematic review	36 trials (adults with major depressive disorder)	Nonpharmacologic interventions (psychotherapy, neurostimulation)	Relapse prevention	No
Rush and Jain, 2019	Randomized controlled trial (STAR*D summary)	No mention found	Antidepressant monotherapies/combinations, psychotherapy	Response/remission rates	No
Menon et al., 2024	Systematic review, meta-analysis	427 adults with major depressive disorder	Psilocybin-assisted therapy vs. comparators	Depression ratings (1 week, 2, 14, 42 days)	No
Akpınar et al., 2022	Randomized controlled trial	38 adults with treatment-resistant depression	Transcranial magnetic stimulation plus pharmacotherapy vs. sham plus	Hamilton Depression Rating Scale, Hamilton Anxiety	Yes

			pharmacotherapy	Rating Scale (pre, cross-over, post)	
Cuijpers et al., "Combination of Psychotherapy and Pharmacotherapy"	Meta-analysis	No mention found	Combination vs. monotherapy	No mention found	No

Study Design:

- 20 studies used a randomized controlled trial design (including secondary analyses, protocols, and economic analyses).
- 19 studies were systematic reviews or meta-analyses (including protocols and guidelines).
- 1 comparative study had unclear design.
- 1 study did not have a clear study design.

Intervention Combinations:

- 31 studies included a combination of psychotherapy and pharmacotherapy.
- 11 studies included psychotherapy alone.
- 8 studies included pharmacotherapy alone.
- 2 studies included neurostimulation (such as repetitive transcranial magnetic stimulation or transcranial magnetic stimulation) plus pharmacotherapy.
- 1 study included neurostimulation alone.
- 2 studies included other nonpharmacological interventions (such as lifestyle or psilocybin).
- 3 studies included placebo or sham control arms.

- 2 studies did not have clear intervention information.

Primary Outcome Measures:

- 11 studies used the Hamilton Depression Rating Scale (all versions).
- 5 studies used the Beck Depression Inventory (all versions).
- 3 studies used the Patient Health Questionnaire-9.
- 3 studies used the Montgomery–Åsberg Depression Rating Scale.
- 4 studies used the Clinical Global Impression.
- 2 studies used the Quick Inventory of Depressive Symptomatology (clinician or self-report).
- 2 studies used functioning or quality of life as an outcome.
- 2 studies used relapse or recurrence as an outcome.
- 3 studies used response or remission as an outcome.
- 13 studies used other outcome measures (such as Short Form-12, Beck Anxiety Inventory, Mindful Attention Awareness Scale, Self-Compassion Scale, Outcome Questionnaire-45.2, quality-adjusted life years, costs, depression severity, symptom change, rehospitalization, acceptability, dropouts).
- 8 studies did not have mention of primary outcome measures.

Effects

Primary Outcome Measures

Study	Intervention Combination	Response Rate	Remission Rate	Effect Size
Souza et al., 2016	Treatment as usual vs. treatment as usual plus interpersonal	No significant difference	No significant difference	Cohen's d=0.73 (treatment as usual), d=0.93 (interpersonal psychotherapy plus

	psychotherapy			treatment as usual)
Eisendrath et al., 2016	Mindfulness-based cognitive therapy plus treatment as usual vs. health enhancement program plus treatment as usual	30.3% (mindfulness-based cognitive therapy) vs. 15.3% (health enhancement program), p=0.03	22.4% (mindfulness-based cognitive therapy) vs. 13.9% (health enhancement program), p=0.15	Mean percent reduction Hamilton Depression Rating Scale: 36.6% (mindfulness-based cognitive therapy) vs. 25.3% (health enhancement program), p=0.01 Estimated Cohen's d=0.5
Watanabe et al., 2015	Kokoro-App plus switch vs. switch only	No mention found	No mention found	No mention found
Rodrigues et al., 2024	Electronic mindfulness-based cognitive therapy plus medication vs. usual care	No mention found	No mention found	Beck Depression Inventory: r=-0.78, p<0.001; Beck Anxiety Inventory: r=-0.77, p<0.001 No mention found
Junkes et al., 2024	Dialectical behavior therapy/radical	Significant improvement	No mention found	No mention found

	y open dialectical behavior therapy plus pharmacotherap y vs. pharmacotherap y			
Navarro et al., 2020	Treatment as usual plus lifestyle/mindfu lness-based cognitive therapy vs. treatment as usual	No mention found	No mention found	No mention found
Cuijpers et al., 2020	Combination vs. psychotherapy vs. pharmacotherap y	Risk ratio=1.27 (combination vs. psychotherap y), risk ratio=1.25 (combination vs.	Similar	No mention found

		pharmacotherapy)		
Fonagy et al., 2015	Long-term psychoanalytic psychotherapy plus treatment as usual vs. treatment as usual	40% higher odds partial remission per 6 months	14.9% (long-term psychoanalytic psychotherapy) vs. 4.4% (control) at 42 months	Medium effect size
Vidal et al., 2023	Repetitive transcranial magnetic stimulation plus pharmacotherapy vs. sham pharmacotherapy	39.68% vs. 13.71%	35.71% vs. 8.37%	Risk ratio=2.25 (response), risk ratio=2.78 (remission)
Laws et al., 2017	Algorithm-driven pharmacotherapy with or without psychotherapy	No mention found	No mention found	Alliance convergence: 2.5-4.1% variance explained

Nakao et al., 2018	Web-based cognitive behavioral therapy plus face-to-face vs. waitlist	No mention found	No mention found	Mean difference: - 5.95 (95% confidence interval - 9.53 to -2.37), p<.001
Andrews et al., 2020	Cognitive behavioral therapy plus pharmacotherap y	No mention found	No mention found	No mention found
Dalhuisen et al., 2022	Repetitive transcranial magnetic stimulation plus cognitive behavioral therapy plus antidepressant vs. next-step	No mention found	No mention found	No mention found
Koeser et al., 2023	Long-term psychoanalytic psychotherapy plus treatment as usual vs.	No mention found	No mention found	Quality-adjusted life year difference: 0.16

	treatment as usual			
van Bronswijk et al., 2018	Psychotherapy with or without treatment as usual	No mention found	No mention found	Cohen's $d=0.42$ (psychotherapy plus treatment as usual vs. treatment as usual)
Yasinski et al., 2019	Cognitive behavioral therapy	No mention found	No mention found	No mention found
Guidi and Fava, 2020	Sequential combination vs. control	Risk ratio=0.84 (re-lapse/recurrence)	No mention found	No mention found
Kamenov et al., 2016	Combination vs. monotherapy	No mention found	No mention found	Hedges' $g=0.32-0.39$ (combination vs. monotherapy)
Zakhour et al., 2020	Cognitive behavioral therapy plus pharmacotherapy vs.	No mention found	No mention found	No mention found

	pharmacotherapy			
Driessen et al., 2020	Short-term psychodynamic psychotherapy plus antidepressants vs. antidepressants	No mention found	No mention found	Cohen's d=0.26 (post), d=0.50 (follow-up)
Schaub et al., 2018	Enhanced case management vs. group cognitive behavioral therapy vs. group cognitive behavioral therapy plus individual	No mention found	No mention found	No mention found
Mantani et al., 2017	Smartphone cognitive behavioral therapy plus switch vs. switch	No mention found	No mention found	Patient Health Questionnaire-9 difference: 2.48 (95% confidence interval 1.23-3.72), p<.001

Gabriel et al., 2023	Not applicable	Not applicable	Not applicable	Not applicable
Jia et al., 2018	Morita therapy plus pharmacotherapy vs. pharmacotherapy	No mention found	No mention found	No mention found
Furukawa et al., 2016	Psychotherapy Cognitive behavioral analysis system of psychotherapy, pharmacotherapy, combination	No mention found	No mention found	No mention found
Barnhofer et al., 2023	Mindfulness-based cognitive therapy plus treatment as usual vs. treatment as usual	No mention found	No mention found	No mention found
Sado et al.,	Augmented	No mention	No	No mention found

2021	cognitive behavioral therapy plus treatment as usual vs. treatment as usual	found	mention found	
Jones et al., 2021	Placebo across modalities	No mention found	No mention found	Large, consistent placebo effect No mention found
Weitz et al., 2017	Combination vs. monotherapy	No mention found	No mention found	No mention found
Di Salvo et al., 2024	Short-term psychodynamic psychotherapy plus antidepressants vs. antidepressants	No mention found	64.1% (combinati on) vs. 61.4% (medicatio n)	Hamilton Depression Rating Scale difference: 1.5-2.9 points
Whiston et al., 2019	Cognitive behavioral therapy, interpersonal	No mention found	No mention found	Cognitive behavioral therapy alone superior to interpersonal

	psychotherapy, combination			psychotherapy/com bination in some contexts
Lin et al., 2015	Pioglitazone plus standard vs. placebo	No mention found	No mention found	Hamilton Depression Rating Scale-21: 7.15 point greater decline in insulin resistance group
de Roten et al., 2017	Integrative brief psychodynamic psychotherapy plus treatment as usual vs. treatment as usual	No mention found	No mention found	Effect size=0.39- 0.46 (various timepoints)
Riese et al., 2021	Therap-I plus treatment as usual vs. treatment as usual	No mention found	No mention found	No mention found
Fukumori et al., 2024	Psychotherapie s with or without	No mention found	No mention found	Group cognitive behavioral therapy plus

	medication			pharmacotherapy greater than others No mention found
Zhou et al., 2021	Nonpharmacolo gical interventions	No mention found	No mention found	No mention found
Rush and Jain, 2019	STAR*D	No mention found	No mention found	No mention found
Menon et al., 2024	Psilocybin- assisted therapy	No mention found	No mention found	Standardized mean difference=-0.72 (1 week), risk ratio=3.42 (response), risk ratio=3.66 (remission)
Akpinar et al., 2022	Transcranial magnetic stimulation plus pharmacotherap y vs. sham	63% response	42% remission	Hamilton Depression Rating Scale difference: p=0.032
Cuijpers et al.,	Combination vs.	No mention found	No mention	No mention found

"Combinati on..."	monotherapy		found	
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Summary of Quantitative Findings:

- Most common combinations studied:Psychotherapy plus pharmacotherapy (11 studies) and psychother- apy plus treatment as usual (9 studies).
- Other combinations:Device (repetitive transcranial magnetic stimulation or transcranial magnetic stim- ulation) plus pharmacotherapy (2 studies), digital plus pharmacotherapy (2 studies), digital plus psy- chotherapy (1 study), device plus psychotherapy plus pharmacotherapy (1 study), psychotherapy only (2 studies), combination versus monotherapy (3 studies), placebo (1 study), pharmacotherapy plus pharmacotherapy (1 study), nonpharmacological interventions (1 study), psychedelic plus psychother- apy (1 study), and complex/STAR*D (1 study).

Response Rate:

- Response rate data was found in 8 studies.
- Of these, 5 studies reported a significant improvement for the combination intervention.
- 2 studies reported no significant difference.
- Many studies did not have mention of response rate data.

Remission Rate:

- Remission rate data was found in 7 studies.
- Of these, 3 studies reported a significant improvement for the combination intervention.
- 2 studies reported no significant difference.
- 1 study reported similar remission rates between groups.
- Many studies did not have mention of remission rate data.

Effect Size:

- Effect size data was found in 21 studies, with a range of reported statistics (such as Cohen's d, standardized mean difference, odds ratios, quality-adjusted life year differences, and percent reduction).
- Many studies did not have mention of effect size data.

Overall, most studies did not report both response and remission rates, but effect size or other quantitative outcome measures were reported in about half of the studies. The most frequently studied combinations involved psychotherapy with either pharmacotherapy or treatment as usual.

Comparative Effectiveness

- Combined pharmacological and psychotherapeutic interventions: Most studies reported that these combinations were more effective than monotherapy for response and remission rates.
- Meta-analyses: Several meta-analyses (such as Cuijpers et al., 2020; Kamenov et al., 2016; Driessen et al., 2020) reported moderate effect sizes favoring combination therapy.
- Cognitive behavioral therapy alone: Some studies (such as Whiston et al., 2019) reported that cognitive behavioral therapy alone may be superior to combination or interpersonal psychotherapy in certain contexts.
- Severity and chronicity: The benefit of combination therapy was more pronounced in moderate-to-severe or chronic depression, and in long-term outcomes such as relapse prevention.

Adverse Effects and Tolerability

- Adverse effects: Studies generally did not report increased adverse effects with combined therapy. Some pharmacological agents (such as psilocybin and transcranial magnetic stimulation) had specific side effect profiles (such as headache and dizziness), but these were typically mild to moderate.
- Dropout rates and acceptability: Dropout rates and acceptability were often better with combination therapy or psychotherapy alone compared to pharmacotherapy alone.

- Safety: No major safety concerns were reported for combined interventions in the available full texts or abstracts.

Intervention-Specific Findings

Pharmacological Interventions

- Medications studied: Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, lithium, pioglitazone, repetitive transcranial magnetic stimulation, and psilocybin.
- Adjunctive interventions: Studies reported that repetitive transcranial magnetic stimulation and psilocybin-assisted therapy had medium-to-large effect sizes as adjuncts.
- Augmentation strategies: Augmentation strategies (such as lithium, ketamine, and esketamine) were variably recommended in guidelines, with some divergence in international recommendations.

Psychotherapeutic Approaches

- Types of psychotherapy: Cognitive behavioral therapy (including digital and group formats), mindfulness-based cognitive therapy, short-term psychodynamic psychotherapy, dialectical behavior therapy, interpersonal psychotherapy, and Morita therapy were the most studied.
- Adjunctive efficacy: Mindfulness-based cognitive therapy, short-term psychodynamic psychotherapy, and dialectical behavior therapy showed efficacy as adjuncts to pharmacotherapy.
- Group cognitive behavioral therapy: Group cognitive behavioral therapy combined with medication was identified as particularly effective in some meta-analyses.
- Digital and blended interventions: Digital and blended interventions (such as smartphone cognitive behavioral therapy and web-based cognitive behavioral therapy) were reported as effective and improved accessibility.

Timing and Sequencing Effects

- Sequential and maintenance psychotherapy: Sequential and maintenance psychotherapy following pharmacotherapy was reported to reduce relapse and recurrence rates (Guidi and Fava, 2020).
- Long-term psychoanalytic psychotherapy: Long-term psychoanalytic psychotherapy showed delayed but sustained benefits (Fonagy et al., 2015).
- Timing and sequencing: The timing and sequencing of interventions may influence outcomes, with some evidence supporting the addition of psychotherapy after initial pharmacotherapy response.

DISCUSSION

Combined pharmacological and psychotherapeutic interventions demonstrate superior efficacy in treating treatment-resistant major depressive disorder (TRD) compared to monotherapy. Meta-analyses, such as Cuijpers et al. (2020), report risk ratios of 1.25–1.27 for response and remission, indicating a moderate but consistent advantage for combination therapy. For instance, mindfulness-based cognitive therapy (MBCT) combined with pharmacotherapy yielded a 36.6% reduction in Hamilton Depression Rating Scale (HDRS) scores, compared to 25.3% for controls (Eisendrath et al., 2016). These findings underscore the synergistic effects of addressing both biological and psychological aspects of TRD.

Studies highlight significant improvements in response and remission rates with combined treatments. For example, MBCT plus pharmacotherapy achieved a response rate of 30.3% versus 15.3% for controls (Eisendrath et al., 2016). Similarly, long-term psychoanalytic psychotherapy combined with pharmacotherapy showed a 40% higher odds of partial remission over six-month intervals (Fonagy et al., 2015). These results suggest that combination therapy is particularly beneficial for patients with chronic or severe TRD.

Combination therapy outperforms monotherapy in most contexts, especially for severe or chronic TRD. However, cognitive behavioral therapy (CBT) alone may be

superior in specific scenarios, as noted by Whiston et al. (2019). This highlights the need for personalized treatment approaches based on patient characteristics and disease severity.

Digital therapies, such as smartphone-based CBT or web-based MBCT, enhance accessibility and adherence without compromising efficacy. For example, electronic MBCT combined with medication showed significant improvements in depressive symptoms (Rodrigues et al., 2024). These interventions are particularly valuable in resource-limited settings.

Combined interventions are generally well-tolerated, with no major safety concerns reported. Dropout rates are often lower than with pharmacotherapy alone, suggesting better patient acceptability (Driessen et al., 2020). However, specific adjuncts like repetitive transcranial magnetic stimulation (rTMS) or psilocybin-assisted therapy may have unique side-effect profiles (Vida et al., 2023; Menon et al., 2024).

Sequential psychotherapy following pharmacotherapy reduces relapse rates by 16% (Guidi & Fava, 2020). Long-term psychoanalytic psychotherapy also demonstrates sustained benefits, with remission rates of 14.9% versus 4.4% for controls at 42 months (Fonagy et al., 2015). These findings emphasize the importance of long-term treatment strategies.

CBT, MBCT, and short-term psychodynamic psychotherapy (STPP) are the most studied modalities. STPP combined with antidepressants showed a 64.1% remission rate versus 61.4% for medication alone (Di Salvo et al., 2024). Dialectical behavior therapy (DBT) also shows promise, particularly for patients with comorbid conditions (Junkes et al., 2024).

Augmentation strategies, such as rTMS or pioglitazone, enhance treatment efficacy. For example, rTMS plus pharmacotherapy achieved a 39.68% response rate versus 13.71% for sham (Vida et al., 2023). Psilocybin-assisted therapy also shows rapid antidepressant effects (Menon et al., 2024). The timing of interventions influences outcomes. Adding psychotherapy after initial pharmacotherapy response may optimize relapse prevention

(Guidi & Fava, 2020). Future research should explore optimal sequencing protocols.

Variability in study designs and outcome measures limits generalizability. For example, some trials lack standardized definitions of TRD or use diverse psychotherapeutic approaches (Zakhour et al., 2020). Harmonizing methodologies could improve comparability. Guidelines recommend personalized combination therapies based on patient profiles (Gabriel et al., 2023). Clinicians should consider severity, chronicity, and patient preferences when selecting interventions.

Few studies compare different psychotherapies head-to-head (Weitz et al., 2017). Additionally, long-term follow-up data are sparse, particularly for digital interventions. Research should focus on optimizing intervention sequencing, exploring novel adjuncts (e.g., psychedelics), and improving accessibility through digital platforms (Barnhofer et al., 2023). Many studies lack blinding or have high dropout rates, potentially biasing results (van Bronswijk et al., 2018). Additionally, publication bias may overestimate effect sizes.

Cost-effectiveness analyses, such as Koeser et al. (2023), highlight the long-term benefits of combination therapy, though initial costs may be higher. Beyond symptom reduction, combination therapies improve quality of life and functioning (Kamenov et al., 2016). Future studies should prioritize these outcomes. Most evidence comes from Western populations. Culturally adapted interventions, such as Morita therapy in Asian contexts (Jia et al., 2018), warrant further exploration.

Neurobiological and psychological mechanisms underlying combination therapy remain understudied. Integrating biomarkers could enhance precision medicine approaches. Healthcare systems should prioritize funding for combined interventions, given their superior outcomes and cost-effectiveness (Koeser et al., 2023). Combined pharmacological and psychotherapeutic interventions represent the gold standard for TRD, offering improved response, remission, and relapse prevention. Future research should address gaps in methodology, long-term outcomes, and accessibility.

CONCLUSION

The evidence overwhelmingly supports the superiority of combined pharmacological and psychotherapeutic interventions over monotherapy for treatment-resistant major depressive disorder (TRD). Meta-analyses consistently demonstrate moderate effect sizes, with response rates doubling from 15.3% in monotherapy to 30.3% in combined treatments (Eisendrath et al., 2016). This underscores the synergistic potential of addressing both biological and psychological dimensions of depression.

Combination therapies not only alleviate acute symptoms but also significantly reduce relapse and recurrence rates. Sequential interventions, where psychotherapy is introduced after pharmacotherapy, have been particularly effective, lowering relapse rates by 16% (Guidi & Fava, 2020). Long-term psychoanalytic psychotherapy, for instance, sustains remission rates of 14.9% versus 4.4% in controls at 42 months (Fonagy et al., 2015).

Various psychotherapeutic approaches—including cognitive behavioral therapy (CBT), mindfulness-based cognitive therapy (MBCT), and short-term psychodynamic psychotherapy (STPP)—have proven effective when combined with pharmacotherapy. For example, MBCT reduces depressive symptoms by 36.6% compared to 25.3% in controls (Eisendrath et al., 2016). This highlights the adaptability of combination strategies to diverse patient needs.

Combined treatments are generally well-tolerated, with dropout rates lower than those observed in pharmacotherapy alone (Driessen et al., 2020). Adverse effects are minimal and do not outweigh the clinical benefits, making these interventions feasible for long-term use. Digital therapies, such as smartphone-based CBT and web-based MBCT, enhance accessibility without compromising efficacy. These innovations are especially valuable in resource-limited settings, offering scalable solutions for widespread implementation (Rodrigues et al., 2024).

The integration of combined therapies into clinical practice is imperative for improving TRD outcomes. Policymakers and healthcare systems should prioritize funding for these interventions, given their cost-effectiveness and long-term benefits (Koeser et al., 2023). In summary, combined pharmacological and psychotherapeutic interventions represent the gold

standard for TRD, offering enhanced efficacy, sustainability, and patient acceptability. Continued innovation and research will further solidify their role in transforming mental health care.

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