Review Article

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Effectiveness of interventions in the prevention of mood disorders: an overview of systematic reviews with meta-analysis

Eficácia de intervenções na prevenção de transtornos de humor: um overview de revisões sistemáticas com meta-análise

Eficacia de las intervenciones en la prevención de los trastornos del estado de ánimo: una revisión panorámica de revisiones sistemáticas con metaanálisis

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ABSTRACT:
Introduction: Mood disorders are highly prevalent conditions associated with substantial clinical, social, and economic burden worldwide. Despite this impact, evidence-based guidance on preventive interventions remains limited, particularly regarding strategies to prevent disease onset and recurrence. **Objective**: To assess the effectiveness of preventive interventions for depressive and bipolar disorders through an overview of systematic reviews with meta-analyses. **Methods**: This overview followed the PRISMA guidelines and was prospectively registered in PROSPERO (CRD42022323580). Systematic reviews with meta-analyses published between 2010 and 2021 were identified in SciELO, LILACS, MEDLINE/PubMed, and the Cochrane Database of Systematic Reviews. Reviews addressing primary, secondary, or tertiary prevention of mood disorders were included. Methodological quality was assessed using AMSTAR-2. **Results**: Twenty-four systematic reviews met the inclusion criteria. For primary prevention, evidence was available exclusively for depressive disorder, showing that psychological and psychosocial interventions, such as cognitive-behavioral therapy, interpersonal therapy, psychoeducation, mindfulness-based programs, and family-focused interventions, were associated with a reduced incidence of depressive episodes in at-risk populations, including children, adolescents, adults, perinatal women, and post-stroke patients. Secondary and tertiary prevention studies primarily addressed relapse and recurrence. In major depressive disorder, both psychological interventions and pharmacological maintenance treatments significantly reduced relapse risk, with combined approaches often yielding superior outcomes. In bipolar disorder,

maintenance pharmacotherapy with mood stabilizers and second-generation antipsychotics, as well as structured psychoeducational interventions, demonstrated efficacy in preventing mood episode recurrence. However, most reviews were rated as low or critically low methodological quality, reflecting heterogeneity, limited longitudinal data, and small sample sizes. **Conclusions**: Preventive interventions for mood disorders, particularly psychological, psychosocial, and maintenance pharmacological strategies, demonstrate consistent effectiveness in reducing incidence and recurrence across diverse populations. Although the overall evidence is constrained by methodological limitations, the findings support current international guideline recommendations and highlight prevention as a critical component of mental health care. Strengthening preventive psychiatry through robust research and integration into public health policies may substantially reduce the long-term burden of mood disorders.

Keywords: mood disorders, depressive disorder, bipolar disorder, intervention, prevention

RESUMO:
Introdução: Os transtornos do humor são condições altamente prevalentes, associadas a importante carga clínica, social e econômica em todo o mundo. Apesar desse impacto, ainda há escassez de diretrizes baseadas em evidências sobre intervenções preventivas, especialmente no que se refere à prevenção do surgimento e da recorrência dessas condições. **Objetivo**: Avaliar a eficácia de intervenções preventivas para transtornos depressivos e transtorno afetivo bipolar por meio de um overview de revisões sistemáticas com meta-análises. **Métodos**: Este overview seguiu as diretrizes PRISMA e foi prospectivamente registrado no PROSPERO (CRD42022323580). Foram identificadas revisões sistemáticas com meta-análises publicadas entre 2010 e 2021 nas bases SciELO, LILACS, MEDLINE/PubMed e Cochrane Database of Systematic Reviews. Incluíram-se revisões que abordaram prevenção primária, secundária ou terciária dos transtornos do humor. A qualidade metodológica foi avaliada por meio das ferramenta AMSTAR-2. **Resultados**: Vinte e quatro revisões sistemáticas preencheram os critérios de inclusão. Para a prevenção primária, houve evidência apenas para o transtorno depressivo, indicando que intervenções psicológicas e psicossociais, como terapia cognitivo-comportamental, terapia interpessoal, psicoeducação, programas baseados em mindfulness e intervenções familiares, estiveram associadas

à redução da incidência de episódios depressivos em populações de risco, incluindo crianças, adolescentes, adultos, mulheres no período perinatal e indivíduos pós-acidente vascular cerebral. Os estudos de prevenção secundária e terciária concentraram-se principalmente na prevenção de recaída e recorrência. No transtorno depressivo maior, tanto intervenções psicológicas quanto tratamentos farmacológicos de manutenção reduziram significativamente o risco de recaída, sendo que abordagens combinadas frequentemente apresentaram melhores resultados. No transtorno afetivo bipolar, a farmacoterapia de manutenção com estabilizadores do humor e antipsicóticos de segunda geração, assim como intervenções estruturadas de psicoeducação, demonstraram eficácia na prevenção de novos episódios do humor. Entretanto, a maioria das revisões apresentou qualidade metodológica baixa ou criticamente baixa, refletindo heterogeneidade, amostras reduzidas e escassez de dados longitudinais. **Conclusões**: As intervenções preventivas para os transtornos do humor, especialmente estratégias psicológicas, psicossociais e farmacológicas de manutenção, demonstram eficácia consistente na redução da incidência e da recorrência em diferentes populações. Embora a evidência disponível seja limitada por fragilidades metodológicas, os achados sustentam recomendações presentes em diretrizes internacionais e reforçam a prevenção como um componente central do cuidado em saúde mental. O fortalecimento da psiquiatria preventiva, por meio de pesquisas mais robustas e de sua incorporação às políticas públicas de saúde, pode contribuir de forma significativa para a redução do impacto dos transtornos do humor a longo prazo.

Palavras-chave: transtornos de humor, transtorno bipolar, transtorno depressivo, intervenção, prevenção

RESUMEN:
Introducción: Los trastornos del estado de ánimo son condiciones altamente prevalentes, asociadas a una carga clínica, social y económica significativa en todo el mundo. A pesar de este impacto, aún existe una escasez de directrices basadas en evidencia sobre intervenciones preventivas, especialmente en lo que respecta a la prevención de la aparición y la recurrencia de estas condiciones. **Objetivo**: Evaluar la eficacia de las intervenciones preventivas para los trastornos depresivos y el trastorno afectivo bipolar mediante un overview de revisiones sistemáticas con metaanálisis. **Métodos**: Este overview siguió las directrices PRISMA y fue registrado prospectivamente en PROSPERO (CRD42022323580). Se identificaron revisiones sistemáticas con

metaanálisis publicadas entre 2010 y 2021 en las bases SciELO, LILACS, MEDLINE/PubMed y Cochrane Database of Systematic Reviews. Se incluyeron revisiones que abordaron la prevención primaria, secundaria o terciaria de los trastornos del estado de ánimo. La calidad metodológica se evaluaron mediante la herramienta AMSTAR-2. **Resultados**: Veinticuatro revisiones sistemáticas cumplieron los criterios de inclusión. Para la prevención primaria, se encontró evidencia únicamente para el trastorno depresivo, indicando que las intervenciones psicológicas y psicosociales, como la terapia cognitivo-conductual, la terapia interpersonal, la psicoeducación, los programas basados en mindfulness y las intervenciones familiares, se asociaron con una reducción en la incidencia de episodios depresivos en poblaciones de riesgo, incluyendo niños, adolescentes, adultos, mujeres en el período perinatal y personas después de un accidente cerebrovascular. Los estudios de prevención secundaria y terciaria se centraron principalmente en la prevención de recaídas y recurrencias. En el trastorno depresivo mayor, tanto las intervenciones psicológicas como los tratamientos farmacológicos de mantenimiento redujeron significativamente el riesgo de recaída, y los enfoques combinados mostraron con frecuencia mejores resultados. En el trastorno afectivo bipolar, la farmacoterapia de mantenimiento con estabilizadores del estado de ánimo y antipsicóticos de segunda generación, así como las intervenciones estructuradas de psicoeducación, demostraron eficacia en la prevención de nuevos episodios del estado de ánimo. Sin embargo, la mayoría de las revisiones presentó una calidad metodológica baja o críticamente baja, reflejando heterogeneidad, tamaños muestrales reducidos y escasez de datos longitudinales. Conclusiones: Las intervenciones preventivas para los trastornos del estado de ánimo —especialmente las estrategias psicológicas, psicosociales y farmacológicas de mantenimiento— demuestran una eficacia consistente en la reducción de la incidencia y la recurrencia en diversas poblaciones. Aunque la evidencia disponible está limitada por debilidades metodológicas, los hallazgos respaldan las recomendaciones presentes en las principales guías internacionales y refuerzan la prevención como un componente central de la atención en salud mental. El fortalecimiento de la psiquiatría preventiva, mediante investigaciones más robustas y su incorporación en las políticas públicas de salud, puede contribuir de manera significativa a la reducción del impacto a largo plazo de los trastornos del estado de ánimo.

Palabras clave: trastornos del estado de ánimo, trastorno bipolar, trastorno depressivo, intervencion, prevención.

Introduction

Mental Disorders (MDs) are defined as conditions that cause clinically significant impairments in an individual's cognition, emotional regulation, or behavior, resulting in substantial distress and functional impairment across multiple domains (including interpersonal relationships and occupational functioning) [1]. It is estimated that worldwide between 7.5% and 20% of the population experiences at least one mental disorder. The most prevalent conditions are anxiety disorders (2.5–7%), depressive disorders (2–6%), and disorders related to the use of alcohol and other substances (0.5–5%) [2 – 3].

Mental Disorders (MDs) rank among the ten leading causes of disability and premature mortality worldwide, accounting for approximately 7% of the total global burden of disease. This burden is quantified using Disability-Adjusted Life Years (DALYs), with depressive disorders representing the largest proportion of DALYs attributable to MDs (37.3% [32.3–43.0]), followed by anxiety disorders (22.9% [18.6–27.5]) and schizophrenia (12.2% [9.6–15.2]) [3 – 4].

The impact is evident across all age groups: children born to mothers diagnosed with anxiety or depressive disorders during pregnancy show a higher likelihood of developing emotional and cognitive problems, and untreated disorders in children and adolescents persist into adulthood in about 10% of cases [5 – 6]. In adulthood, MDs (including anxiety, depression, and substance use disorders) are persistent indicators of the need for medical leave, reduced productivity, and work-related disability, which can lead to premature withdrawal from professional life [7 – 8].

For mental health public policies to be implemented effectively, they must be grounded in robust scientific evidence to ensure safety, cost-effectiveness, and population-level impact [8, 9, 10]. In this context, mood disorders (MDs) constitute one of the most important, complex, and prevalent categories among mental disorders [11 – 12].

At present, data on the effectiveness of preventive interventions for these disorders are sparse. Until now, there has been no robust study compiling high-quality, evidence-based research in a manner that could be readily applied by health professionals and policymakers with the aim of preventing mental disorders and/or mitigating their progression.

Therefore, in response to this gap, this overview was conducted as part of a larger project encompassing multiple groups of mental disorders, with

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the objective of providing a comprehensive approach to the incidence and relapse prevention in mood disorders based on rigorous scientific methodology. Priority was given to the inclusion of systematic reviews with superior methodological quality, indexed in the most authoritative global scientific databases.

For all these reasons the objective of this study is to the effectiveness of interventions for the prevention of incidence and relapse of mood disorders.

Methods

This study is an overview of systematic reviews of the literature, including only those that incorporated meta-analyses. The PRISMA protocol and the Cochrane Handbook for Systematic Reviews of Interventions were used as guides for methodological structuring. The full study protocol was prospectively registered in PROSPERO (National Institute for Health and Care Research) under registration number CRD42022323580.

This article is part of a larger project that assessed systematic reviews across three diagnostic groups: depressive disorders, anxiety disorders, and psychotic disorders. In the present manuscript, we report exclusively the findings related to the spectrum of mood disorders (depressive and bipolar disorders), which constitute the primary focus of the analysis.

Definition of the Research Question

The research question was: Which interventions are effective in the prevention of mood disorders?

Following the PICO framework, the components were defined as follows:
P (Population): men and women of all ages.
I (Intervention): prevention of mood disorders.
C (Comparator): multiple comparators.
O (Outcome): The main outcome measures will be incidence and relapse. Incidence is defined as the occurrence of new cases of a disorder within a population that was initially free of the condition over a specified period, constituting a central epidemiological indicator of disease risk and population burden. Relapse refers to the re-emergence of symptoms within the same disease episode prior to the achievement of full clinical recovery or sustained remission, reflecting persistence or reactivation of the underlying pathological process rather than the onset of a new, independent episode.

Eligibility Criteria
Inclusion Criteria
(a) systematic reviews of randomized controlled trials with meta-analysis.
(b) studies published between January 2010 and December 2021.
(c) studies addressing the prevention of mood disorders.
(d) texts reporting the following measures of association: odds ratio (OR) and/or relative risk (RR).
Exclusion Criteria
(a) case reports.
(b) case series.
(c) studies with fewer than 20 participants.
(d) studies focusing on suicide prevention.
(e) incomplete data.
(f) low statistical quality.
(g) high risk of bias.
(h) studies primarily focused on symptom improvement or treatment.

Data Sources
The systematic review was conducted using the SciELO, LILACS, MEDLINE (via PubMed), and Cochrane Database of Systematic Reviews databases, including studies published between 2010 and 2021.

Search Strategy
The Boolean operator AND was used to combine the Medical Subject Headings (MeSH) terms "mood disorder," "prevention," and "intervention," which were applied individually and in combination.

Study Selection Process
Titles and abstracts identified through the search strategy were independently screened by two reviewers according to predefined inclusion and exclusion criteria. Potentially eligible studies were retrieved and assessed in full text. Discrepancies were resolved by consensus or, when necessary, through consultation with a third reviewer. Duplicate records were identified and removed using reference management software.

Data Collection and Extraction
Two authors collected the abstracts and distributed the articles among six reviewers for data extraction and organization into tables 1, 2, 3, 4, 5 which included reference, population, assessment, study design, primary outcome, secondary outcome (when applicable), and results.

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Methodological Quality Assessment

The methodological quality of the included systematic reviews was assessed using the AMSTAR-2 tool. A total of twenty-four reviews on the prevention of mood disorders were examined. Out of these, only five reviews were determined to possess high methodological quality, as they did not exhibit any methodological shortcomings based on the criteria outlined in the assessment tool. Five studies were categorized as low quality. These studies were deemed to have only one critical failure. Additionally, thirteen studies were classified as critically low quality. These studies were found to have multiple critical faults according to the AMSTAR-2 criteria. For more details see table 2.

Results

Study Selection

The search strategy on interventions for the prevention of mood disorders yielded a total of 657 potential studies among the databases. After reading the titles and abstracts, 71 articles were selected for complete reading, of which 5 were duplicates and were disregarded. 66 articles remained, which, after reading by peers, 43 were excluded, leaving 24 articles for complete analysis. (Figure 1).

Study Characteristics

Prevention the incidence of depressive disorders

The assessment of interventions aimed at preventing depression in individuals without a prior diagnosis in risk groups was conducted across seven out of the twenty-four papers that were selected. The sample sizes in the research varied from 776 to 14727 people in eight studies [12, 13, 14, 15, 16, 17 ,18, 19]. Different groups were study.

In a sample of 4665 participants psychological interventions as CBT, IPT, escalated care, and problem-solving therapy for 12 months reduced the develop of a depressive disorder in 19%12 (Amstar 2 low). In adults without diagnosed depression psychological intervention decrease de incidence of depression. There was no differences between the type of psychotherapy [18]. Amstar 2 low.

In subjects with 6 to 25 years old with parents with mood disorders, psychoeducation, cognitive-behavioral therapy and family processes. of depressive reduced the chance of develop depressive disorder after 9-18 months and after 24 months or more [15] (Amstar critically low). In children and adolescents (5 to 19 years old), with no previous diagnosis of

depression CBT, IPT, third wave CBT reduced the risk of depression after 12 months [16] (Amstar 2 High).

In post-stroke patients there were low quality evidence for the use of antidepressants, problem solving therapy, CBT, home therapy, and motivational interview to prevent depression incidence in patients without the disorder. There was no found studies for non-invasive brain stimulation [13]; Amstar 2 critically low. In adults after stroke selective reuptake inhibitors reduced the chance of development of post-stroke depression [17]; (Amstar 2 critically low).

In pregnant or postpartum women (less than 6 months postpartum) with or without risk of developing postpartum depression psychosocial and psychological interventions reduced the chance to develop postpartum depressive symptoms [14]; (Amstar 2High). In pregnant women with more than 18 years of age prenatal psychological interventions (CBT, IPT, mindfulness) prevent depression at the prenatal period, but not in postpartum [19]; Amstar 2 low. For more details see table 3.

Preventing relapse of depressive episodes
Ten studies were conducted to investigate therapies for relapse prevention in individuals previously diagnosed with major depressive disorder (MDD). The range of participants varied from 49 to 14,450 [20, 21, 22, 23, 24, 25, 26, 27, 28, 29].

In adults from 18 to 64 years old, psychological interventions (CT, CBT, MBCT, and IPT) were significantly better than TAU in reducing the risk of relapse or recurrence [20]; Amstar 2 critically low. However, in another study for the adults with the same age CBT and MCBT had no significant difference in time to depressive relapse [21] (Amstar 2 low). On the other hand, for adults, 12 months of CBT, mindfulness-based cognitive therapy (MCT) and interpersonal therapy (IPT) were associated with a 22% reduction in relapses compared to controls [22]; Amstar 2 critically low. In an RCT with 49 adults mindfulness-based cognitive therapy group, the incidence of a new depressive episode in winter was lower than in the TAU group [24]; Amstar 2 critically low. Patients who received MBCT had a reduced risk of depressive relapse at a 60-week follow-up period compared with those who did not [27]; Amstar 2 critically low.

In adults with MDD, antidepressants were effective in preventing recurrences, with small differences between the types of drugs [28]; Amstar 2 critically low. Bupropion XL was an effective intervention for

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preventing recurrence of depressive episodes in people with a history of seasonal affective disorder [25]; Amstar 2 low. In adults, Continued use of antidepressants produced a robust reduction in the risk of relapse of depressive episodes [26]; Amstar 2 critically low.

In adults, combination of pharmacotherapy and cognitive behavioral psychotherapy reduced relapse/recurrence prevention in MDD [29]; Amstar 2 critically low. Finally, for children and adolescents' participants treated with antidepressant medication had lower relapse-recurrence rates (40.9%) compared to placebo [23]; Amstar 2 High. For more details see table 4.

Relapse prevention in bipolar affective disorder

In relation to individuals who have a prior medical record of bipolar affective disorder (BD), six systematic reviews have examined various therapies aimed at preventing relapse of manic, depressive, or mixed episodes. These interventions primarily involve the continued utilization of mood stabilizers or antipsychotic medications. The study included a diverse variety of participants, with the sample size varying from 70 to 1580 individuals, all of whom were over the age of 16 [30, 31, 32, 33, 34, 35].

Although the heterogeneity in the data warrants caution, psychoeducation appears to be effective in preventing relapse [30]; Amstar 2 high. A study assessed continuation and maintenance treatment with valproate compared to placebo, lithium, and olanzapine. Valproate was more effective than placebo in preventing the relapse of any mood episode, no difference in efficacy was found between valproate and lithium, and combination therapy with lithium plus valproate was more likely to prevent relapse than valproate monotherapy [31]; Amstar 2 high. Long-acting injectable antipsychotic risperidone was superior to placebo for study-defined relapse rate and relapse of manic symptoms. Pooled long-acting injectable antipsychotics did not outperform oral medications on the primary endpoint, but with significant heterogeneity. Hence, in sensitivity analysis, including only studies with rapid cycling or high frequency of patients with relapse, revealed that long-acting injectable antipsychotics were superior to oral drugs [32]; Amstar 2 critically low. Mood stabilizers (MS) and/or second-generation antipsychotics reduced recurrence [33]; Amstar 2 low. Lamotrigine and lithium were superior to placebo for reducing the rate of relapse due to any mood episode. There were no significant differences in other outcomes between the lithium or lamotrigine and the placebo groups [34]; Amstar 2 critically low. In

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patients over 16 years old lithium was more effective than placebo in preventing general mood episodes, manic episodes, depressive episodes [35]; Amstar 2 critically low.

Discussion

Regarding primary prevention studies, only those focused on depressive disorder were selected. Studies assessing interventions aimed at preventing depression in individuals without a prior diagnosis but belonging to at-risk groups indicate that psychological and psychosocial interventions can significantly reduce the incidence of depressive disorders, although the methodological quality of the evidence varies widely. Across large and heterogeneous samples, interventions such as cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), stepped care, psychoeducation, problem-solving therapy, mindfulness-based approaches, and family-focused interventions were associated with a reduced risk of developing depression in adults, children, adolescents, pregnant and postpartum women, and individuals with a family history of mood disorders, with no consistent differences observed between psychotherapy modalities. In specific contexts, such as the post-stroke period, low-quality evidence suggests potential benefits of antidepressants and psychological interventions for the prevention of depression, while prenatal psychological interventions appear effective in preventing depression during pregnancy but not in the postpartum period. Overall, despite generally favorable findings, many of the included systematic reviews were rated as low or critically low quality according to AMSTAR 2, underscoring the need for more methodologically robust studies to strengthen the evidence base.

Regarding studies on secondary and tertiary prevention, those identified were primarily focused on the prevention of recurrence and relapse. Across ten studies evaluating relapse prevention strategies in individuals previously diagnosed with major depressive disorder, both psychological and pharmacological interventions demonstrated efficacy in reducing the risk of relapse or recurrence, although the methodological quality of the evidence was frequently low. In adults, psychotherapeutic approaches, including cognitive therapy, cognitive-behavioral therapy, mindfulness-based cognitive therapy, and interpersonal therapy, were generally superior to treatment as usual in lowering relapse risk, with some studies reporting clinically meaningful reductions over 12-month follow-up periods, despite inconsistent findings regarding time to relapse across modalities. Mindfulness-based interventions were associated with reduced incidence of

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new depressive episodes and sustained protection against relapse over extended follow-up.

Pharmacological strategies also showed benefit, with continued antidepressant treatment robustly reducing relapse risk and only small differences observed between drug classes; specific agents, such as bupropion XL, were effective in preventing recurrence in seasonal affective disorder. Combined treatment with antidepressants and cognitive-behavioral psychotherapy appeared to confer additional protective effects against relapse. In pediatric and adolescent populations, antidepressant therapy was associated with lower relapse and recurrence rates compared with placebo. Overall, while the findings support the effectiveness of both psychological and pharmacological interventions for secondary and tertiary prevention of depression, most reviews were rated as low or critically low quality according to AMSTAR 2, underscoring the need for more rigorous, high-quality trials to strengthen the evidence base.

Across six systematic reviews involving individuals with a prior diagnosis of bipolar affective disorder, relapse prevention strategies have predominantly focused on the continuation and maintenance use of mood stabilizers and antipsychotic medications to prevent manic, depressive, or mixed episodes. Despite substantial clinical and methodological heterogeneity, psychoeducation demonstrated effectiveness in reducing relapse risk and was supported by higher-quality evidence. Pharmacological maintenance strategies showed consistent benefits, with valproate proving superior to placebo and comparable to lithium, while combination therapy with lithium plus valproate conferred greater protection against relapse than valproate monotherapy. Long-acting injectable antipsychotics, particularly risperidone, reduced relapse rates and manic symptoms compared with placebo, although their superiority over oral formulations was evident mainly in subgroups with rapid cycling or high relapse frequency.

Additionally, mood stabilizers and second-generation antipsychotics were associated with reduced recurrence, and both lithium and lamotrigine were superior to placebo in preventing relapse due to any mood episode. Overall, while maintenance pharmacotherapy appears effective for secondary and tertiary prevention in bipolar disorder, most reviews were rated as low or critically low quality according to AMSTAR 2, highlighting the need for more rigorous, well-designed trials to strengthen the evidence base.

In turn, these findings support practices already recommended by major guidelines [36, 37, 38, 39, 40, 41] worldwide and reinforce the need to incorporate them into public health policies. Psychosocial interventions and pharmacological treatments should be available across the entire healthcare system not only for treatment, but also for the prevention of disease incidence and recurrence [10].

Limitations

The findings of this comprehensive analysis should be interpreted considering several limitations. First, regarding the primary outcome, few studies addressed prevention of first depressive episodes, and those that did were focused on high-risk groups; most studies instead addressed secondary outcomes (i.e., relapse prevention). Second, several reviews—including some rated as methodologically high quality by AMSTAR-2—included primary studies with small samples, insufficient evidence, and limited detail regarding the delivered interventions. Third, most meta-analyses provided limited information on the long-term effectiveness of preventive interventions. Fourth, this overview examined effectiveness but did not assess safety or acceptability.

Finally, because many included reviews incorporated primary studies published before 2013, most relied on DSM-IV (or earlier) diagnostic criteria rather than DSM-5 criteria, published in 2013. Depressive disorder classifications underwent changes that may affect comparability with contemporary diagnostic frameworks.

Conclusion

This overview of systematic reviews with meta-analyses provides convergent evidence that preventive interventions for mood disorders—particularly depressive disorder and bipolar affective disorder—are clinically relevant and potentially impactful across different stages of the disease continuum. Psychological and psychosocial interventions, including cognitive-behavioral therapy, interpersonal therapy, psychoeducation, family-based approaches, and mindfulness-based programs, demonstrated consistent effectiveness in reducing the incidence of depressive episodes among at-risk populations and in preventing relapse and recurrence in individuals with a prior history of major depressive disorder. Pharmacological strategies, especially the continuation and maintenance use of antidepressants in depressive disorders and mood stabilizers or second-generation antipsychotics in bipolar disorder, were also associated with meaningful reductions in relapse and recurrence, with combined

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pharmacological and psychotherapeutic approaches often yielding additional benefits.

Despite the overall coherence of the findings, the strength of the evidence is tempered by substantial methodological heterogeneity and frequent limitations in study quality, as reflected by predominantly low or critically low AMSTAR-2 ratings. These limitations—including small sample sizes, short follow-up periods, variability in intervention protocols, and limited reporting on long-term outcomes—underscore the need for more rigorous, adequately powered, and longitudinally designed studies to refine preventive strategies and enhance their generalizability.

Nevertheless, the collective evidence supports preventive practices already endorsed by major international guidelines and reinforces the imperative to incorporate prevention as a core component of mental health care. Ensuring the availability of psychosocial interventions and pharmacological treatments throughout healthcare systems—not only for treatment but also for primary, secondary, and tertiary prevention—represents a strategic opportunity to reduce the burden of mood disorders, improve long-term outcomes, and inform cost-effective public health policies. Future research should prioritize methodological robustness, safety, acceptability, and real-world implementation to consolidate preventive psychiatry as a foundational pillar of mental health care.

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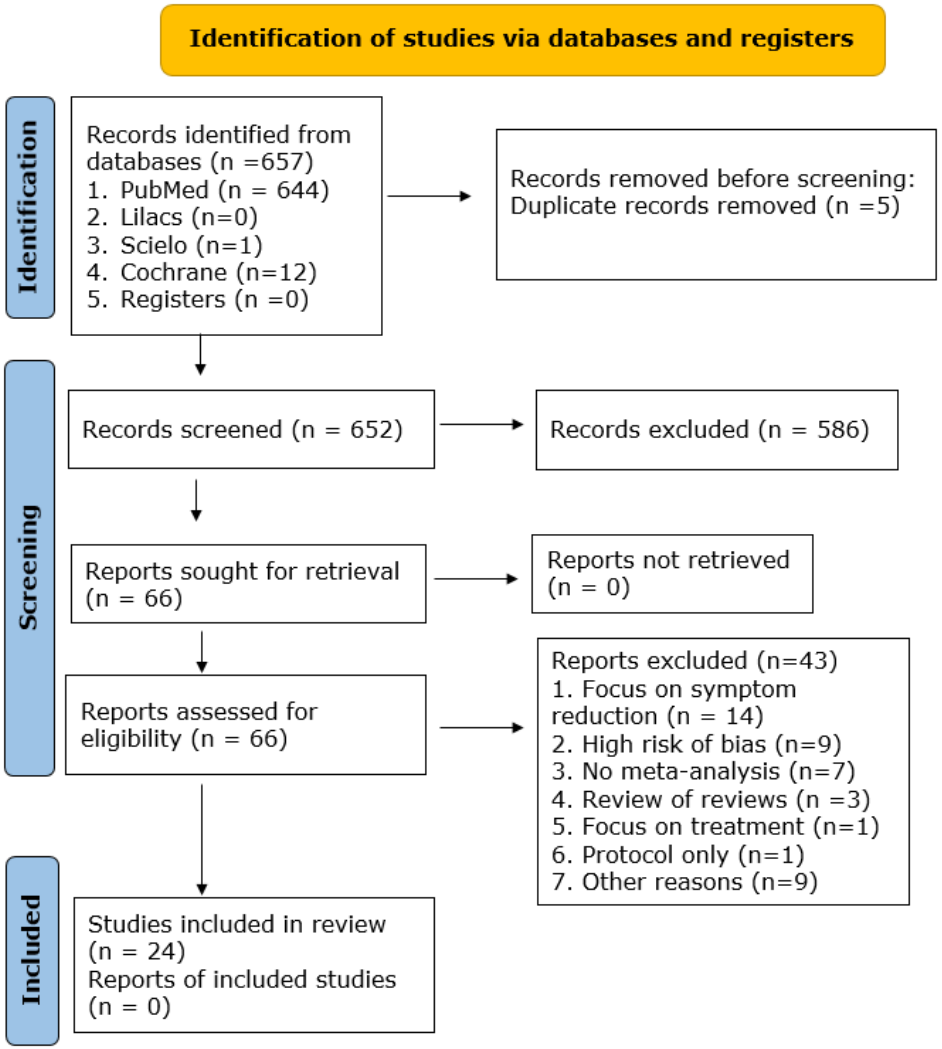

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only – Mood disorders
Source: The authors

Table 1. Characteristics of excluded studies – Mood disorders

N	STUDY	REASONS FOR EXCLUSION
1	Ahlen et al., 2015	Does not specify interventions
2.	Bellón et al., 2015	Review of reviews
3.	Bevan Jones et al., 2018	No meta-analysis
4.	Breedvelt et al., 2021	Focus on symptom reduction
5.	Caldwell et al., 2019	Focus on symptom reduction
6.	Calear & Christensen, 2010	No meta-analysis
7.	Carter et al., 2019	Focus on symptom reduction
8.	Cipriani et al., 2013	Suicide prevention
9.	Cluxton-Keller & Bruce, 2018	Focus on subjective symptoms
10.	Deady et al., 2017	Focus on symptom reduction
11.	Felnhofer et al., 2016	Not a systematic review
12.	Forneris et al., 2015	No meta-analysis
13.	Gartlehner et al., 2015	Initial study of another updated
14.	Grosso et al., 2016	Focus on risk factors
15.	Ho et al., 2016	Focus on symptom reduction and treatment
16.	Huang et al., 2020	Focus on symptom reduction
17.	Kaminski-Hartenthaler et al., 2015	No group control
18.	Lambrichts et al., 2021	High risk of bias
19.	Lin et al., 2018	Focus on symptom reduction
20.	Loechner et. al., 2018	Focus on symptom reduction
21.	Mártin-Gómez et al., 2020	Just protocol
22.	Martinez et al., 2018	No meta-analysis
23.	Merry et al. , 2011	High risk of bias
24.	Miller et al., 2013	No meta-analysis
25.	Mocking et al., 2020.	Focus on treatment
26.	Molyneaux et al., 2018	No meta-analysis

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27.	Morrell et al., 2016	Focus on symptom reduction
28.	Nakamura et al., 2019	Focus on symptom reduction
29.	Nussbaumer et al., 2015	High risk of bias
30.	Nussbaumer-Streit et al., 2019	High risk of bias
31.	O'Connor et al., 2019	Presence of non-randomized clinical trials
32.	Poyatos-León et al.,2017	Focus on symptom reduction
33.	Rigabert et al., 2018	High risk of bias
34.	Sado et al., 2012	High risk of bias
35.	Salazar de Pablo et al., 2021	Review of reviews
36.	Sockol et al., 2013	High risk of bias
37.	Sockol et al., 2015	Focus on symptom reduction
38.	Stockings et al., 2015	Review of reviews
39.	Uguz et al., (2020)	No meta-analysis
40.	Werner-Seidler et al., 2017	Focus on symptom reduction
41.	Zhaid et al., 2020	High risk of bias
42.	Zhang et al., (2018).	High risk of bias
43.	Zhou et al., 2021	Not a systematic review

Source: The authors.

Table 2. AMSTAR 2 classification

QUESTIONS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	QUALITY
STUDY																	
Allida et al., 2020	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Critically low
Biesheuvel-Leliefeld et al., 2015	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	N	Critically low
Bond and Anderson, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Breedvelt et al., 2018	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Carter et. al, 2019	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Cipriani, Reid, et al., 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Hign
Clarke et al., 2015	Y	N	Y	Y	Y	Y	N	P Y	Y	Y	Y	N	Y	N	N	N	Critically low
Cox et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Cuijpers et al., 2021	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Dennis & Dowswell, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Forneris et al., 2019	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Critically low
Gartlehner et al., 2019	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Glue et al., 2010	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	N	Y	N	Y	Critically low
Guidi & Fava, 2021	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	N	N	N	N	Y	Critically low
Havinga et al., 2021	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Critically low
Hetrick et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	High
Kishi et al., 2016	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	Critically low
Kishi et al., 2021	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Kuyken et al., 2016	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	N	Y	Critically low
Oya et al., 2019	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Critically low
Salter et al., 2013	Y	N	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Y	Y	Y	Critically low
Severus et al., 2014	Y	N	Y	Y	Y	Y	P Y	Y	Y	Y	Y	Y	N	Y	N	Y	Critically low
Sim et al., 2016	t	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	N	Y	Critically low
van Zoonen et al., 2014	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Yasuma et al., 2020	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low

Source: The authors

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Table 3. Prevention incidence of depressive disorders

AUTOR, YEAR	POPULATION (number and setting)	ASSESSMENT	TYPE OF STUDY	COMPARATOR	OUTCOME	SECOND OUTCOME	MAIN FINDINGS
Allida et. al., 2020	19 RCT (n=1771) post-stroke patients without diagnosis of depressive disorder	1. Pharmacological interventions (antidepressants) 2. Psychological interventions: Problem solving therapy (2); CBT (1); solution-focused therapy(1); home therapy (1); motivational interview(2) 3. Non-invasive brain stimulation	Systematic review with meta-analysis	1.placebo 2. usual care 3. simulated stimulation or usual care	Prevention of depression in post-stroke patients DSM IIIR/ DSM IV/ DSM 5	Improvement of depressive symptoms (Hamilton, MADRS, GDS)	There is very low quality evidence from eight trials (9 interventions) that pharmacologic interventions decrease the number of people who meet study criteria for depression (RR=0.50, 95% CI 0.37 to 0.68; 734 participants) compared to placebo). There is very low-quality evidence from two studies that psychological interventions reduce the proportion of people meeting study criteria for depression (RR=0.68, 95% CI 0.49 to 0.94, 607 participants) compared with usual care and/or attention control. Non-invasive brain stimulation studies not found.
Cuijpers et. al., 2021	50 RCTs (4665 Participants) in risk groups without a diagnosis of depression	Psychological interventions (CBT, IPT, escalated care, problem-solving therapy, and others)	Systematic review with meta-analysis	Usual care	Prevention of depression (diagnostic interview)	N/A	One year after the preventive interventions, the relative risk of developing a depressive disorder was RR = 0.81

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							(95% CI: 0.72–0.91), indicating that those who received the intervention were 19% less likely to develop a depressive disorder. - does not specify which diagnostic criteria are indicated in the interview
Dennis et. al. 2013	28 RCT, (n=14727) Pregnant or postpartum women (less than 6 months postpartum) with or without risk of developing postpartum depression	Psychosocial and psychological interventions	Systematic review with meta-analysis	Usual postpartum	Prevention of postpartum depression (Edinburgh Postnatal Depression Scale (EPDS)	- morbidity maternal mortality. -maternal-intantil attachment -Anxiety -maternal stress	Women who received a psychosocial or psychological intervention were significantly less likely to develop postpartum depression compared to those who received standard care (mean RR 0.78, 95% confidence interval (CI) 0.66 to 0.93 ; The combined results showed that the differences between the groups were not statistically significant. Interventions: (1) the provision of intensive, individualized postpartum home visits provided by public health nurses or midwives (RR=0.56, 95% CI 0.43 to 0.73; two trials, 1262 women);

							(2) lay-based (pair) telephone support (RR 0.54, 95% CI 0.38 to 0.77; one study, 612 women); It is (3) Interpersonal psychotherapy (standardized mean difference -0.27, 95% CI -0.52 to -0.01; five trials, 366 women). Professional and lay interventions were both effective in reducing the risk of developing depressive symptoms. Interventions initiated in the postpartum period also significantly reduced the risk of developing depressive symptoms (RR=0.73, 95% CI 0.59 to 0.90; 12 trials, 12,786 women). Identifying 'at-risk' mothers helped prevent postpartum depression (RR= 0.66, 95% CI 0.50 to 0.88; eight trials, 1853 women).
Havinga et. al. 2021	22 RCTs (n=1258 children and youth) (6 to 25 years old)	Prevention programs (psychoeducation, cognitive-behavioral	Systematic review with	Usual treatment	Prevention of depressive	Improvement of depressive	A significant risk difference was found in favor of prevention

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	with parents with mood or anxiety disorders	therapy and family processes. of depressive and anxiety disorders in children of parents with these disorders)	meta-analysis		and anxiety disorders (criteria of DSM IV)	or anxious symptoms	programs on the risk of developing a depressive/anxiety disorder in offspring in: a) short term (9-18 months of; RR = 0.37, 95% CI [0.21; 0.66]) b) Long-term (24 months or more of follow-up; RR = 0.71, 95% CI [0.57; 0.87]
Hetrick et. al., 2016.	83 RCT (n=11913) Children and adolescents (5 to 19 years old), with no previous diagnosis of depression	Psychological interventions (CBT, IPT, third wave CBT)	Systematic review with meta-analysis	Multiple	Prevention of depression (DSM IV, DSM IV-TR; ICD 10)	Reduction of post-interventio ndepressive symptoms (1.CDRS 2. (HAM-D 3.MADRS 4. K-SADS 5. BID	The risk of having a diagnosis of depression at 12 months (32 trials, n=5965) was reduced for participants who received an intervention compared to those who received no intervention (risk difference – RD=-0.03, 95% CI= -0.05 to -0.01; P value = 0.01). Moderate evidence (GRADE). For tests implemented in cognitive, there was no effect for diagnosing depression (RD=-0.01, 95% CI -0.03 to 0.01). For assays implemented in potentially targeted, there was a statistically beneficial effect significance of the intervention (diagnosis of

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							depression RD=-0.04, 95% CI -0.07 to -0.01.
Salter et. al. 2013	8 RCT (n 776) Adults after stroke	prophylactic pharmacotherapy	Systematic review with meta-analysis	Placebo	Prevention of depression after stroke HRSD,; DSM-IV; MADRS	N/A	Pooled analyzes demonstrated reduced odds for the development of post-stroke depression associated with pharmacological treatment (OR: 0.34; 95% CI: 0.22-0.53; P , 0.001), a treatment duration of 1 year (OR 0.31; 95%CI 0.18-0.56; P .001), selective serotonin reuptake inhibitor (OR 0.37; 95% CI 0.22-0.61; P .001).

Van zoonen et. al,et. al., 2014	32 RCTs (n= 6214) Adults without diagnosed depression	psychological interventions	Systematic review with meta-analysis	Multiple	Prevention of depression (criteria of DSM III-R; -IV	-	RR of developing a depressive disorder = 0.79 95% CI: 0.69–0.91), indicating a 21% decrease in incidence in prevention groups compared to control groups. Heterogeneity was low (I2=24%). NNT = 20. Sensitivity analyzes show that there are no differences between the type of prevention (selective, indicated or universal) or between the type of psychotherapy (CBT, IPT, other) by NNT, TIP(NNT=7) is more effective than TCC (NNT=71) Several studies with different populations and different interventions and different times limit the results

Yasuma et al., 2020	18 ECR (n=7.416) Pregnant women > 18 years of age	Prenatal psychological interventions (CBT, IPT, mindfulness)	Systematic review with meta-analysis	Usual prenatal care (CBT, TIP, mindfulness)	Prevention of prenatal and perinatal depression		The effect size of prenatal psychological intervention on universal prevention of prenatal depression (SMD= 0.28, 95% CI 0.11, 0.44) and postnatal depression (SMD= 0.37, 95% CI 0.08, 0.66). The cognitive-behavioral approach had a significant effect on the prevention of prenatal depression SMD= 0.53 95% CI 0.13, 0.94. Postpartum results were not significant SMD=0.45 95% CI 0.03, 0.92. Language bias (English only), included low-quality studies

Source: The authors.
RCT: Randomized controlled trial; **CBT:** Cognitive Behavioral Therapy; **DSM:** Diagnostic and Statistical Manual of Mental Disorders; **IPT:** interpersonal therapy; **MADRS:** Montgomery-Asberg Depression Rating Scale; **K-SADS** Schedule for Afective Disorders and Schizophrenia for School; **BID** Bellevue Index of Depression.

Table 4. Preventing relapse of depressive episodes

AUTOR, YEAR	POPULATION (number and setting)	ASSESSMENT	TYPE OF STUDY	COMPARATOR	OUTCOME	SECOND OUTCOME	MAIN FINDINGS
Biesheuvel-Leliefeld, et al, 2015	25 RCTs(n=2055) adults 18-64 years old, with Recurrent MDD, in remission.	Psychological interventions: CT, CBT, Mindfulness based cognitive therapy (MBCT), and IPT.	Systematic review with meta-analysis	1. Usual care (UT): clinical routine, no treatment, waiting list 2.antidepressants	Preventing relapse of depressive episodes in MDD (Hamilton, HRSD, BDI, SCID-1)	N/A	Preventive psychological interventions were significantly better than TU in reducing the risk of relapse or recurrence (RR = 0.64, 95% CI = 0.53–0.76, z = 4.89, p < 0.001 , NNT = 5) - also more successful than antidepressants (RR=0.83, 95% CI=0.70–0.97, z=2.40, p=0.017, NNT=13). The preventive effect of psychological intervention was generally better when prevention was preceded by treatment in the acute phase. The effect size between the psychological interventions was similar. low quality studies
Breedvelt et. al, 2021	714 (4 RCTs) adults (18-65 years old) with depression total or partially in remission	Psychological interventions (CBT, MBCT)	Systematic review with	Monoterapy with antidepressants	Preventing relapse of depressive	N/A	There was no significant difference in time to depressive relapse between use of a

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			meta-analysis		episodes in MDD (critérios do DSM IV)		psychological intervention during tapering of antidepressant medication versus antidepressant therapy alone (hazard ratio [HR], 0.86; 95% CI, 0.60-1, 23)
Clarke et. al., 2015	29 RCTs (2742 adults), any age, in full or partial remission of depression	Psychological interventions (CBT, mindfulness-based cognitive therapy, interpersonal psychotherapy)	Systematic review with meta-analysis	1. Usual treatment 2. Assessment Only control	Preventing relapse of depressive episodes in MDD (DSM IV)	-prevenção de novos episódios depressivos	- 12 months of CBT, mindfulness-based cognitive therapy (MCT) and interpersonal therapy (IPT) were associated with a 22% reduction in relapses compared to controls (95% CI 15% to 29%). - The mean risk of developing a new episode of depression at 12 months was reduced by 25% for TCC (RR = 0.75; 95% CI 0.64 to 0.89, I^2 = 8%), 21% for TCM (RR= 0.79, CI 95% 0.69 to 0.91, I^2 = 0%) and 22% for IPT (RR= 0.78, 95% CI 0.65 to 0.95, I^2 = 0%) . - The effect of CBT at 24 months was similar to the effect at 12 months, but with greater heterogeneity (RR=0.72,

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							95% CI is 0.57-0.91, I^2 = 63%), but the effect of IT { was not sustained (RR = 0.92, 95% CI is 0.81-1.05, I^2 = 0%).
Cox et. al., 2012	9 RCTs (882 children and adolescents) with a history of depression in remission	Psychological and pharmacological interventions	Systematic review with meta-analysis	Placebo	Preventing relapse of depressive episodes in MDD (critérios do DSM IV ou ICD 10)		Three studies indicate that participants treated with antidepressant medication had lower relapse-recurrence rates (40.9%) compared to those treated with placebo (66.6%) during a relapse prevention phase (OR) 0, 34; 95% (CI) 0.18 to 0.64, P = 0.02). A study that compared a combination of psychological therapy (CBT) and medication with medication favored a combined approach, but did not reach statistical significance (OR 0.26; 95% CI 0.06 to 1.15) Little evidence due to the limitation of the number of studies and with different types of assays
Forneris et. al., 2019	1 RCT 49 adults with a history of seasonal depression	Psychological Interventions (TCM)	Systematic review with meta-analysis	Usual treatment (UT)	Prevention of seasonal affective disorder recurrence in adults	N/A	In the mindfulness-based cognitive therapy group, the incidence of a new depressive episode in winter was lower than in the TAU group. RR =

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					(criteria of (criteria of DSM 5)		0.88, 95% CI 0.60 to 1.30
Gartlehner et. al , 2019	3 RCTs (n=1100) adults with a history of seasonal affective disorder (SAD) without symptoms at baseline	Prophylactic use of second-generation antidepressants (SGAs),	Systematic review with meta-analysis	Placebo	Prevention of seasonal affective disorder recurrence in adults (criteria of (criteria of DSM 5)	N/A	Moderate-quality evidence indicates that bupropion XL is an effective intervention for preventing recurrence of depressive episodes in people with a history of SAD RR = 0.56, 95% CI 0.44 to 0.72;
Glue et. al., 2010	54 RCTs (n = 9268 Adults) with a history of depression with a good response to antidepressants in the acute phase	Maintenance of antidepressant treatment	Systematic review with meta-analysis	Placebo	Preventing relapse of depressive episodes in MDD (criteria of DSM III, DSM IVA)		Continued use of antidepressants produced a robust reduction in the risk of relapse of depressive episodes (OR 0.35; 95% CI 0.32 – 0.39).
Guidi and Fava, 2021	70 RCTs (2283 Adults) with history of remitted MDD	Sequential combination of pharmacotherapy and cognitive behavioral psychotherapy	Systematic review with meta-analysis	Usual treatment	Prevention of depressive episode relapse in MDD (criteria of DSM III, DSM IV, DSM 5)	N/A	The pooled hazard ratio for MDD relapse/recurrence was 0.84 (95% CI, 0.74-0.94), suggesting a relative advantage in relapse/recurrence prevention for the sequential combination of treatments compared with the control conditions.

Kuyken et. al. , 2016	9 RCTs (1,258 patients included, mean (SD) age was 47.1 (11.9) years, 944 (75.0%) were female.	Mindfulness-based cognitive therapy (MCBT)	Systematic review with meta-analysis	Usual treatment	Preventing relapse of depressive episodes in MDD (DSM III, DSM-III, -III-R, -IV, ou -IV-TR ou ICD 10)	N/A	Patients who received MBCT had a reduced risk of depressive relapse at a 60-week follow-up period compared with those who did not (hazard ratio, 0.79; 95% CI, 0.64-0.97). MBCT (hazard ratio, 0.69; 95% CI, 0.58-0.82) Comparisons with active treatments suggest a reduced risk of depressive relapse over a 60-week follow-up period (hazard ratio, 0.79; 95% CI, 0.64-0.97).
Sim et. al., 2015	72 RCTs (n=14,450) Adults with MDD	Use of antidepressants	Systematic review with meta-analysis	Placebo	Preventing relapse of depressive episodes in MDD (DSM IV)	N/A	Antidepressants were more effective than placebos in preventing relapse (response rates [RR] = 1.90, confidence interval [CI]: 1.73–2.08; NNT = 4.4; p < 0.0001) - duration of 33.4 weeks Antidepressants were effective in preventing recurrences (RR = 2.03, CI 1.80–2.28; NNT = 3.8; p < 0.0001), with small differences between the types of drugs. Psychosocial interventions produced

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							inconsistent or inconclusive results

Source: The authors
HRSD: such as the Hamilton Rating Scale of Depression, **BDI:** Beck Depression Inventory, **SCID-1:** Structured Clinical Interview for DSM-IV Axis 1 Disorders.

Table 5. Relapse prevention in bipolar affective disorder

AUTOR, YEAR	POPULATION (number and setting)	ASSESSMENT	TYPE OF STUDY	COMPARATOR	OUTCOME	SECOND OUTCOME	MAIN FINDINGS
Bond and Anderson, 2015	Participants with bipolar disorder who are not in the acute phase 16 RCTs (average of 70 participants)	Psychoeducation (i) a discrete psychological intervention involving primarily the patient with bipolar disorder; (ii) providing information about bipolar disorder and/or its treatment; and (iii) relating this information to aiding self-management of the disorder.	Systematic review with meta-analysis	1.Usual treatment 2. placebo	Relapse prevention in bipolar affective disorder (BD) any episode (critérios do DSM IV)	N/A	Although the heterogeneity in the data warrants caution, psychoeducation appears to be effective in preventing: a) any relapse [n = 7; OR: 1.98–2.75; (NNT)***: 5–7, depending on the analysis method] b) relapse/manic/hypomanic (n = 8; OR: 1.68–2.52; NNT: 6–8), c) depressive relapse was not effective Caution: relatively few studies, with different methodologies and small number of participants
Cipriani, Reid, et al., 2013	6 RCTs (875 participants) with BAD on long-term treatment with valproate or any other mood stabilizer, antipsychotic drug or placebo	Continuation and maintenance treatment with valproate	Systematic review with meta-analysis	1. placebo 2. lithium 3. olanzapine	Relapse prevention in bipolar affective disorder (BD) any episode (critérios do DSM IV)	Improved overall funcioning	Valproate was more effective than placebo in preventing the relapse of any mood episode (RR 0.68, 95% CI 0.49 to 0.93; NNTB 8), No difference in efficacy was found between

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							valproate and lithium (RR 1.02, 95% CI 0.87 to 1.20). Combination therapy with lithium plus valproate was more likely to prevent relapse than valproate monotherapy (RR 0.78, 95% CI 0.63 to 0.96).
Kishi, et. al., 2016	7 RCTs (n=1016) Adults) with bipolar disorder in remission	Use of long-acting injectable antipsychotics: flupentixol risperidone	Systematic review with meta-analysis	1. Placebo 2. Oral medication (MS, antidepressant, AP)	Relapse prevention in bipolar affective disorder (BD) (criteria of DSM IVA)		Long-acting injectable antipsychotic risperidone was superior to placebo for study-defined relapse rate (hazard ratio = 0.63, p<.0001), relapse of manic symptoms (hazard ratio = 0.42, P <.(hazard ratio=0.75, P=0.007). Pooled long-acting injectable antipsychotics did not outperform oral medications on the primary endpoint, but with significant heterogeneity (I2 = 74%). Sensitivity analysis, including only studies with rapid cycling or high frequency of patients with relapse, revealed

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							that long-acting injectable antipsychotics were superior to oral drugs (I2=0%, RR=0.58, P=0.0004)
Kishi, 2021	8 RCTs (1456 Stable adults with bipolar disorder using: 3 aripriprazole + mood stabilizer (EH) 1 lurasidone + EH 2 quetiapine + EH 1 Ziprasidone + EH 1 olanzapine + EH	Use of a mood stabilizer (MS) and/or second-generation antipsychotic	Systematic review with meta-analysis	Mood stabilizer + placebo and discontinuation of AP Second generation antipsychotics (SGA) Limitations – small samples in some included studies	Relapse prevention in bipolar affective disorder (BD) (criteria of DSM IV)	recurrence of manic/hypomanic/mixed and depressive episodes and all causes discontinuation within 6 months.	RR (95% CI) of recurrence at 6 months was: 0.51 (0.39–0.86) for any mood episode, 0.42 (0.30–0.59) for manic/hypomanic/mixed episodes - 0.39 (0.28–0.54) for depressive episodes. The RR for all-cause discontinuation was 0.67 (0.50–0.89). Both aripiprazole+SH and quetiapine+SH outperformed placebo+SH in recurrence of any mood, manic/hypomanic/mixed, and depressive episodes at 6 months.
Oya et. al., 2019	Stable adults with bipolar disorder 2 RCT with lithium (n=218) 4 RCTs with lamotrigine (n=706)	use of lamotrigine or lithium	Systematic review with meta-analysis	Placebo	Relapse prevention in bipolar affective disorder (BD) (criteria of DSM IV)	N/A	Both drugs were superior to placebo for reducing the rate of relapse due to any mood episode [lithium: RR = 0.52 (0.41-0.66), P < 0.00001, I 2 = 0%, NNT = 2.3 (1.6-4.2); lamotrigine: RR = 0.81 (0.70-0.93), P = 0.004, I 2 = 0%, NNT = 8.3 (5.0-

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							25.0)] and discontinuation for all causes. There were no significant differences in other outcomes between the lithium or lamotrigine and the placebo groups. Few studies and small samples
Severus et. al., 2014	7 RCT (n= 1580) Adults over 16 years of age with total or partial remission of a mood episode in bipolar disorder.	use of lithium	Systematic review with meta-analysis	1. Placebo 2. Anticonvulsivants	Relapse prevention in bipolar affective disorder (BD) (criteria of DSM III-R, -IV; ICD 10)	N/A	Lithium was more effective than placebo in preventing general mood episodes (random effects RR 0.66, 95% CI 0.53 to 0.82), manic episodes (random effects RR 0.52, 95% CI 0. 38 to 0.71) and, depressive episodes (random effects RR 0.78, 95% CI 0.59 to 1.03; fixed effect RR 0.73, 95% CI 0.60 to 0.88). In preventing manic episodes, lithium showed superiority over anticonvulsants (random effects RR 0.66, 95% CI 0.44 to 1.00)

Source: The authors

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