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ASSOCIATION BETWEEN MIGRAINE AND MOOD DISORDERS: A SYSTEMATIC REVIEW

ASSOCIAÇÃO ENTRE ENXAQUECA E TRANSTORNOS DE HUMOR: UMA REVISÃO SISTEMÁTICA

ASOCIACIÓN ENTRE MIGRAÑA Y TRASTORNOS DEL ESTADO DE ÁNIMO: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: Migraine is a disabling neurological disorder that frequently coexists with mood disorders. Major depressive disorder and bipolar disorder are particularly relevant because they may influence migraine frequency, chronification, disability, treatment adherence, medication selection, and suicide risk. Objective: To systematically evaluate the association between migraine and depressive and bipolar disorders, emphasizing prevalence, temporal direction, migraine severity, disability, shared biological mechanisms, and clinical implications. Methods: PubMed/MEDLINE was systematically searched from January 2000 through September 19, 2026, supplemented by backward and forward citation tracking. Eligible publications included adult observational studies, longitudinal cohorts, population-based investigations, systematic reviews, meta-analyses, and genetic studies evaluating migraine in relation to major depressive disorder, depressive episodes, or bipolar disorder. Studies restricted to anxiety without a mood-disorder outcome were excluded. Depression screening scores were distinguished from formally diagnosed depressive disorders. Because of overlapping cohorts and substantial methodological heterogeneity, the evidence was synthesized narratively. Results: Twenty core publications were retained. A meta-analysis of 16 adult studies found that migraine was associated with approximately twice the odds of depression (odds ratio [OR] 1.95; 95% confidence interval [CI] 1.61–2.35). Longitudinal studies supported bidirectionality, although effect estimates varied and were partly attenuated after adjustment for stress and childhood adversity. Depression predicted progression from episodic to chronic migraine (adjusted OR 1.65; 95% CI 1.12–2.45), with a severity-dependent gradient. Among individuals with bipolar disorder, the pooled prevalence of

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migraine was 34.8% (95% CI 25.54–44.69), reaching 54.17% in bipolar II disorder. Migraine was also associated with suicidal ideation (adjusted OR 1.33; 95% CI 1.15–1.54) and suicide attempts (adjusted OR 1.70; 95% CI 1.42–2.03). Genetic studies demonstrated shared polygenic liability, but did not establish a single causal pathway. Conclusion: Migraine has a clinically important and probably bidirectional association with depressive disorders and a consistent association with bipolar disorder, especially bipolar II disorder. The coexistence of these conditions identifies patients with greater disability and psychiatric complexity. Routine mood assessment is justified in migraine care, but screening questionnaires should not be treated as diagnostic interviews. Integrated management should consider suicide risk, possible bipolarity, reproductive safety, and the distinct effects of medications on headache and mood.

Keywords: Migraine. Major Depressive Disorder. Bipolar Disorder. Mood Disorders. Comorbidity. Suicide.

RESUMO

Introdução: A enxaqueca é uma doença neurológica incapacitante que frequentemente coexiste com transtornos de humor. O transtorno depressivo maior e o transtorno bipolar são particularmente relevantes, pois podem influenciar a frequência, a cronificação, a incapacidade, a adesão ao tratamento, a escolha da medicação e o risco de suicídio relacionados à enxaqueca. Objetivo: Avaliar sistematicamente a associação entre enxaqueca e transtornos depressivos e bipolares, enfatizando a prevalência, a direção temporal, a gravidade da enxaqueca, a incapacidade, os mecanismos biológicos compartilhados e as implicações clínicas. Métodos: Foi realizada uma busca sistemática no PubMed/MEDLINE de janeiro de 2000 a 19 de setembro de 2026, complementada pelo rastreamento de citações retrospectivas e prospectivas. As publicações elegíveis incluíram estudos observacionais em adultos, coortes longitudinais, investigações populacionais, revisões sistemáticas, meta-análises e estudos genéticos que avaliaram a enxaqueca em relação ao transtorno depressivo maior, episódios depressivos ou transtorno bipolar. Estudos restritos à ansiedade sem um desfecho relacionado a transtorno de humor foram excluídos. Os escores de rastreio de depressão foram diferenciados dos diagnósticos formais de transtornos depressivos. Devido à sobreposição de coortes e à substancial heterogeneidade metodológica, as evidências foram sintetizadas narrativamente. Resultados: Vinte publicações principais foram mantidas. Uma metanálise de 16 estudos com adultos constatou que a migrânea estava associada a aproximadamente o dobro da probabilidade de depressão (razão de chances [RC] 1,95; intervalo de confiança [IC] de 95% 1,61–2,35). Estudos longitudinais corroboraram a bidirecionalidade, embora as estimativas do efeito variassem e fossem parcialmente atenuadas após o ajuste para estresse e adversidades na infância. A depressão previu a progressão da migrânea episódica para a crônica (RC ajustada 1,65; IC de 95% 1,12–2,45), com um gradiente dependente da gravidade. Entre indivíduos com transtorno bipolar, a prevalência agrupada de migrânea foi de 34,8% (IC de 95% 25,54–44,69), chegando a 54,17% no transtorno bipolar tipo II. A enxaqueca também foi associada à ideação suicida (OR ajustada 1,33; IC 95% 1,15–1,54) e tentativas de suicídio (OR ajustada 1,70; IC 95% 1,42–2,03). Estudos genéticos demonstraram predisposição poligênica compartilhada, mas não estabeleceram uma única via causal. Conclusão: A enxaqueca tem uma associação clinicamente importante e provavelmente bidirecional com transtornos depressivos e uma associação consistente com transtorno bipolar, especialmente o transtorno bipolar II. A coexistência dessas condições identifica pacientes com maior incapacidade e complexidade psiquiátrica. A avaliação

rotineira do humor é justificada no atendimento à enxaqueca, mas os questionários de triagem não devem ser tratados como entrevistas diagnósticas. O manejo integrado deve considerar o risco de suicídio, a possível bipolaridade, a segurança reprodutiva e os efeitos distintos dos medicamentos sobre a cefaleia e o humor.

Palavras-chave: Enxaqueca. Transtorno Depressivo Maior. Transtorno Bipolar. Transtornos de Humor. Comorbidade. Suicídio.

RESUMEN

Introducción: La migraña es un trastorno neurológico discapacitante que a menudo coexiste con trastornos del estado de ánimo. El trastorno depresivo mayor y el trastorno bipolar son particularmente relevantes, ya que pueden influir en la frecuencia de la migraña, su cronificación, la discapacidad asociada, la adherencia al tratamiento, la elección de la medicación y el riesgo de suicidio. Objetivo: Evaluar sistemáticamente la asociación entre la migraña y los trastornos depresivos y bipolares, haciendo hincapié en la prevalencia, la dirección temporal, la gravedad de la migraña, la discapacidad, los mecanismos biológicos compartidos y las implicaciones clínicas. Métodos: Se realizó una búsqueda sistemática en PubMed/MEDLINE desde enero de 2000 hasta el 19 de septiembre de 2026, complementada con el seguimiento de citas (hacia atrás y hacia adelante). Las publicaciones elegibles incluyeron estudios observacionales en adultos, cohortes longitudinales, investigaciones poblacionales, revisiones sistemáticas, metaanálisis y estudios genéticos que evaluaban la migraña en relación con el trastorno depresivo mayor, los episodios depresivos o el trastorno bipolar. Se excluyeron los estudios limitados a la ansiedad que no incluían resultados relacionados con trastornos del estado de ánimo. Se distinguió entre las puntuaciones de cribado de depresión y los trastornos depresivos formalmente diagnosticados. Debido a la superposición de cohortes y a la considerable heterogeneidad metodológica, la evidencia se sintetizó de forma narrativa. Resultados: Se seleccionaron veinte publicaciones clave. Un metaanálisis de 16 estudios en adultos reveló que la migraña se asociaba con una probabilidad aproximadamente dos veces mayor de presentar depresión (odds ratio [OR] 1,95; intervalo de confianza [IC] del 95%: 1,61–2,35). Los estudios longitudinales respaldaron la bidireccionalidad, aunque las estimaciones del efecto variaron y se atenuaron parcialmente tras ajustar por estrés y adversidad en la infancia. La depresión predijo la progresión de la migraña episódica a la crónica (OR ajustada: 1,65; IC del 95%: 1,12–2,45), observándose un gradiente dependiente de la gravedad. Entre las personas con trastorno bipolar, la prevalencia combinada de migraña fue del 34,8% (IC del 95%: 25,54–44,69), alcanzando el 54,17% en el trastorno bipolar tipo II. La migraña también se asoció con ideación suicida (OR ajustada: 1,33; IC del 95%: 1,15–1,54) e intentos de suicidio (OR ajustada: 1,70; IC del 95%: 1,42–2,03). Los estudios genéticos demostraron una susceptibilidad poligénica compartida, pero no establecieron una vía causal única. Conclusión: La migraña presenta una asociación clínicamente relevante y probablemente bidireccional con los trastornos depresivos, así como una asociación consistente con el trastorno bipolar, especialmente con el trastorno bipolar tipo II. La coexistencia de estas afecciones identifica a pacientes con mayor grado de discapacidad y complejidad psiquiátrica. Está justificada la evaluación sistemática del estado de ánimo en la atención de la migraña; no obstante, los cuestionarios de cribado no deben considerarse equivalentes a entrevistas diagnósticas. El abordaje integral debe contemplar el riesgo de suicidio, la posible bipolaridad, la seguridad reproductiva y los efectos diferenciales de los fármacos sobre la cefalea y el estado de ánimo.

Palabras clave: Migraña. Trastorno Depresivo Mayor. Trastorno Bipolar. Trastornos del Estado de Ánimo. Comorbilidad. Suicidio.

1 INTRODUCTION

Migraine is a primary neurological disorder characterized by recurrent attacks of headache and associated neurological, autonomic, gastrointestinal, and sensory symptoms. According to the International Classification of Headache Disorders, third edition (ICHD-3), migraine may occur with or without aura and may be classified as episodic or chronic according to monthly headache frequency.[1] Migraine affects more than one billion people worldwide and is a leading cause of years lived with disability, particularly among women and working-age adults.[2] Its burden extends beyond individual attacks because anticipatory anxiety, impaired work performance, disrupted family life, sleep disturbance, and reduced participation may persist during interictal periods.[2,3]

Mood disorders are not interchangeable with general psychological distress. In this review, the term refers primarily to major depressive disorder (MDD), recurrent depressive episodes, and bipolar disorder (BD). Anxiety disorders were excluded from the primary synthesis unless they formed part of a composite outcome that also included depression. This distinction is clinically important because depressive symptoms detected by a questionnaire do not necessarily establish MDD, while bipolar depression requires different therapeutic reasoning from unipolar depression.

The relationship between migraine and depression appears to extend beyond an understandable emotional response to recurrent pain. In a population cohort, baseline MDD predicted incident migraine, while migraine predicted incident MDD, suggesting a bidirectional temporal association.[4] A Canadian longitudinal study similarly found that migraine predicted subsequent major depressive episodes, although the reverse association weakened after adjustment for stress and childhood trauma.[5] A meta-analysis of adult studies subsequently estimated that migraine was associated with nearly twice the odds of depression.[6]

Migraine frequency appears to be particularly important. In the Women's Health Study, migraine was associated with incident depression over almost 14 years, and the greatest risk occurred among women with weekly or daily attacks.[7] Data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) demonstrated a gradient from an OR of 2.14 for fewer than one monthly attack to 6.94 for daily migraine.[8] Depression may also influence the neurological course of migraine: the American Migraine Prevalence and Prevention (AMPP) study found that depression preceded and independently predicted progression from episodic to chronic migraine.[9]

The migraine–bipolar disorder relationship is also clinically relevant. In the Canadian Community Health Survey (CCHS), migraine occurred in 24.8% of participants with bipolar disorder compared with 10.3% of the general population.[10] Clinical studies indicate that migraine is more frequent in bipolar II than bipolar I disorder and may accompany earlier mood-disorder onset, greater depressive burden, and more psychiatric comorbidity.[11] A meta-analysis estimated that approximately one-third of people with bipolar disorder experience migraine, with substantially higher prevalence in bipolar II disorder.[12] Longitudinal clinical observations further suggest that comorbid migraine may identify a subgroup with more persistent depressive symptoms.[13]

Shared genetic liability provides one potential explanation. Genome-wide analyses have identified significant molecular overlap between migraine and MDD, including pleiotropic loci that influence susceptibility to both conditions.[14] Clinically, the coexistence of migraine and mood disorders is also associated with poorer quality of life, greater disability, and increased suicide-related outcomes. A meta-analysis found an adjusted association between migraine and suicidal ideation,[15] while a later synthesis demonstrated increased odds of both suicidal ideation and suicide attempts.[16] More recent cross-trait analysis has strengthened evidence of shared genetic architecture and suggested a potentially stronger depression-to-migraine than migraine-to-depression pathway, although Mendelian randomization cannot independently prove clinical causality.[17]

A systematic appraisal is therefore necessary to distinguish comorbidity from causality, formal diagnoses from screening results, and unipolar depression from bipolar disorder. These distinctions directly affect screening, prognosis, and treatment selection.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the association between migraine and mood disorders, principally major depressive disorder and bipolar disorder, in adults.

2.2 SECONDARY OBJECTIVES

1. To determine whether the migraine–depression association is bidirectional.
2. To examine whether attack frequency, chronic migraine, aura, and migraine-related disability modify the association.

3. To estimate the prevalence and clinical characteristics of migraine in bipolar I and bipolar II disorders.
4. To evaluate suicide-related outcomes among individuals with migraine.
5. To examine genetic, neurobiological, environmental, and behavioral mechanisms that may explain the observed comorbidity.
6. To identify implications for psychiatric screening, migraine treatment, and integrated clinical care.

3 METHODOLOGY

3.1 DESIGN AND REPORTING

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) recommendations.[18] The protocol was defined before evidence synthesis but was not prospectively registered. Because the eligible literature included overlapping cohorts, cross-sectional studies, longitudinal investigations, genetic analyses, and previously published meta-analyses, a new quantitative pooling was considered inappropriate.

3.2 SEARCH STRATEGY

PubMed/MEDLINE was searched for publications dated January 1, 2000, through September 19, 2026. The search combined controlled vocabulary and free-text terms related to “migraine,” “migraine with aura,” “chronic migraine,” “major depressive disorder,” “depressive episode,” “bipolar disorder,” “mood disorder,” “comorbidity,” “longitudinal,” “cohort,” “suicide,” and “genetic overlap.” Reference lists of eligible systematic reviews and influential primary studies were manually examined, and forward citation tracking was used to identify subsequent studies.

3.3 ELIGIBILITY CRITERIA

3.3.1 Eligible publications:

- Included adults with migraine, depressive disorders, or bipolar disorder.
- Used recognized headache criteria, structured psychiatric interviews, validated diagnostic algorithms, clinical diagnoses, health-register codes, or validated screening instruments.

- Compared participants with and without migraine or with and without a relevant mood disorder.
- Reported prevalence, incidence, temporal association, disability, migraine progression, bipolar subtype, familial aggregation, genetic overlap, or suicide-related outcomes.
- Used cohort, case-control, cross-sectional, registry-based, systematic-review, meta-analytic, or genetic epidemiological designs.

Studies exclusively evaluating anxiety were excluded. Pediatric-only studies, case reports, noncomparative case series, animal experiments, and publications without an interpretable migraine–mood outcome were also excluded. Treatment studies were not part of the primary association analysis but were considered when they directly informed clinical management of comorbidity.

3.4 OUTCOME DEFINITIONS

The primary outcomes were diagnosed MDD, major depressive episodes, BD, and migraine. Depressive symptom scales were analyzed separately from diagnostic outcomes. Secondary outcomes included transition from episodic to chronic migraine, headache frequency, migraine-related disability, quality of life, familial aggregation, shared genetic liability, suicidal ideation, and suicide attempts.

3.5 DATA EXTRACTION AND APPRAISAL

Information extracted included design, sample size, population, diagnostic method, migraine phenotype, mood-disorder definition, covariate adjustment, effect estimate, confidence interval, and principal limitations. Cohort and case-control studies were appraised according to population selection, exposure and outcome ascertainment, confounding control, follow-up, and attrition. Cross-sectional investigations were additionally assessed for temporal ambiguity. Systematic reviews were evaluated for search breadth, duplicate assessment, heterogeneity, and overlap among included cohorts.

3.6 EVIDENCE SYNTHESIS

The findings were organized into five domains: depressive disorders, temporal direction, migraine frequency and chronification, bipolar disorder, and suicide-related

outcomes. Genetic findings were used to evaluate biological plausibility rather than as direct estimates of clinical risk.

4 RESULTS

4.1 STUDY CHARACTERISTICS

Twenty core publications were retained for qualitative synthesis. The evidence included population-based cohorts, registry studies, clinical cohorts, cross-sectional surveys, systematic reviews, meta-analyses, and genome-wide analyses. Several meta-analyses incorporated primary cohorts also discussed separately; therefore, report counts should not be interpreted as independent population counts.

Table 1

Principal studies evaluating migraine and mood disorders

Study	Design and sample	Main outcome	Main result
Breslau et al., 2003[4]	Two-year community cohort; 496 participants with migraine, 151 with other severe headaches, and 539 controls	Incident migraine and MDD	Baseline MDD predicted migraine (OR 3.4; 95% CI 1.4–8.7), while migraine predicted MDD (OR 5.8; 95% CI 2.7–12.3).
Modgill et al., 2012[5]	Canadian National Population Health Survey; 15,254 participants; 12-year follow-up	Bidirectional migraine–depression association	Migraine predicted major depressive episodes (HR 1.6; 95% CI 1.3–1.9). Depression predicted migraine before full stress adjustment (HR 1.4; 95% CI 1.0–1.9).
Amiri et al., 2019[6]	Systematic review and meta-analysis; 16 studies	Depression among adults with migraine	Pooled OR 1.95 (95% CI 1.61–2.35); cohort-only OR 1.81 (95% CI 1.20–2.72).
Rist et al., 2013[7]	Women's Health Study; 36,016 women; mean follow-up 13.8 years	Incident depression	Migraine with aura: RR 1.53 (95% CI 1.35–1.74); migraine without aura: RR 1.40 (95% CI 1.25–1.56). Weekly or daily attacks: RR 2.44 (95% CI 1.85–3.23).
Goulart et al., 2014[8]	ELSA-Brasil; 1,261 participants with migraine and 10,531 controls	Migraine frequency and MDD	OR increased from 2.14 (95% CI 1.33–3.43) for fewer than one monthly episode to 6.94 (95% CI 4.20–11.49) for daily migraine.
Ashina et al., 2012[9]	AMPP longitudinal cohort; 6,657 participants with episodic migraine in the first analysis wave	Progression to chronic migraine	Depression predicted chronic migraine (adjusted OR 1.65; 95% CI 1.12–2.45). Severe depression showed OR 2.53 (95% CI 1.52–4.21) before adjustment for baseline headache frequency.
Chen et al., 2021[19]	Taiwanese national database; bidirectional proband, sibling, and control cohorts	New-onset depression or migraine	Migraine predicted depression (OR 4.09; 95% CI 3.75–4.46); depression predicted migraine (OR 4.13; 95% CI 3.18–5.36). Unaffected siblings also had modestly elevated risk.
Baksa et al., 2026[20]	UK Biobank; 327,234 participants	Diagnostic order and multidomain disability	The depression-before-migraine group had the greatest mental and physical burden, including worse self-rated health (OR 22.93; 95% CI 17.72–29.68 versus controls).

Study	Design and sample	Main outcome	Main result
McIntyre et al., 2006[10]	CCHS; 36,984 participants	Migraine prevalence in bipolar disorder	Migraine prevalence was 24.8% in BD versus 10.3% in the general population; prevalence reached 34.7% among women with BD.
Ortiz et al., 2010[11]	Clinical samples of 323 patients with BD and 102 with migraine	Cross-prevalence	Migraine occurred in 24.5% of BD patients: 34.8% in BD-II versus 19.1% in BD-I. Among migraine patients, BD-I prevalence was 4.9% and BD-II prevalence was 7.8%.
Fornaro and Stubbs, 2015[12]	Meta-analysis; 14 studies and 3,976 individuals with BD	Pooled migraine prevalence	Overall prevalence 34.8% (95% CI 25.54–44.69); BD-II 54.17% versus BD-I 32.7%.
Saunders et al., 2014[13]	Prechter Longitudinal Study; 412 patients with BD and 157 controls	Migraine and longitudinal mood outcome	Migraine occurred in 31% of BD participants versus 6% of controls and was associated with more severe and frequent depressive symptoms.
Sucksdorff et al., 2016[21]	Finnish registers; 1,861 BD cases and 3,643 controls	Familial and individual comorbidity	BD was associated with comorbid migraine after familial adjustment (OR 2.46; 95% CI 1.76–3.42). Parental migraine predicted offspring BD diagnosed in adulthood (OR 1.52; 95% CI 1.08–2.14).
Samalin et al., 2025[22]	FACE-BD cohort; 4,348 adults with BD	Migraine prevalence and correlates	Migraine prevalence was 20.0%, reaching 29.1% in BD-II versus 19.9% in BD-I; female sex was independently associated with migraine (OR 2.15; 95% CI 1.56–2.95).
Yang et al., 2018[14]	Cross-trait genome-wide analysis; migraine and MDD datasets totaling more than 480,000 cases and controls	Shared molecular genetic architecture	Significant cross-disorder genetic overlap and three genome-wide significant pleiotropic variants were identified.
Zhang et al., 2026[17]	Genome-wide cross-trait and Mendelian-randomization analysis	Genetic correlation and potential directionality	Genetic correlation between depression and migraine was 0.289; genetically predicted depression liability was associated with migraine (OR 1.439), with a smaller reverse-direction estimate.
Wei et al., 2023[16]	Meta-analysis; 16 studies	Suicidal ideation and attempts	Migraine was associated with ideation (adjusted OR 1.33; 95% CI 1.15–1.54) and attempts (adjusted OR 1.70; 95% CI 1.42–2.03).

4.2 MIGRAINE AND DEPRESSIVE DISORDERS

The most consistent finding was an association between migraine and depression. The adult meta-analysis found almost twice the odds of depression among individuals with migraine, although heterogeneity was high.[6] Cross-sectional estimates were generally larger than longitudinal estimates, suggesting contributions from selection, reverse causation, overlapping somatic symptoms, and ascertainment during periods of active headache.

The large Women's Health Study demonstrated that the association was not confined to prevalent depression. Over 13.8 years, migraine with and without aura predicted incident depression after extensive adjustment.[7] However, nonmigraine headache was also

associated with depression, indicating that recurrent pain and disability contribute to risk and that the relationship is not entirely migraine-specific.

4.3 TEMPORAL DIRECTION

The Detroit cohort provided strong evidence of bidirectionality because participants with baseline depression were at increased risk of first-onset migraine, while those with migraine were at increased risk of first-onset MDD.[4] The absence of equivalent associations for other severe headaches supported some degree of migraine specificity.

The Canadian longitudinal results were more cautious. Migraine remained associated with subsequent major depressive episodes, but the depression-to-migraine estimate was attenuated after adjustment for childhood trauma and stress.[5] This suggests that stress may act as a confounder, mediator, or shared precipitant rather than demonstrating that one disorder directly causes the other.

The Taiwanese sibling study found large bidirectional estimates and smaller associations among unaffected siblings.[19] Familial coaggregation supports shared genetic or early environmental susceptibility. Nevertheless, register diagnoses may favor individuals with more severe illness or greater healthcare contact, potentially inflating associations through surveillance bias.

4.4 MIGRAINE FREQUENCY, CHRONIFICATION, AND DISABILITY

The relationship showed a clinically meaningful frequency gradient. In ELSA-Brasil, the adjusted association with MDD increased steadily as migraine frequency rose.[8] Women with weekly or daily attacks in the Women's Health Study had more than twice the risk of incident depression.[7] These findings indicate that monthly headache burden is more informative than the simple presence or absence of migraine.

Depression may also predict worsening migraine. In the AMPP cohort, depression preceded conversion from episodic to chronic migraine and remained independently associated after adjustment for baseline headache days, medication overuse, allodynia, pain intensity, and anxiety.[9] Risk increased with depressive severity, supporting a dose-response relationship. However, observational data cannot establish whether depression directly promotes chronification or instead marks escalating migraine, sleep disturbance, medication overuse, stress exposure, or reduced treatment adherence.

Aura did not produce a uniform gradient. Some population data indicated slightly stronger depression associations for migraine with aura,[7] while clinical studies found no independent aura effect. Consequently, aura alone should not be considered a reliable marker of psychiatric risk.

4.5 MIGRAINE AND BIPOLAR DISORDER

The association between migraine and BD was consistent across epidemiological, clinical, and meta-analytic studies. The pooled migraine prevalence of 34.8% among individuals with BD was markedly greater than expected in the general population.[12] The association was strongest in BD-II, in which depressive episodes predominate and hypomania may be overlooked.

The difference between BD-I and BD-II was observed in several independent datasets. Ortiz et al. found migraine in 34.8% of BD-II and 19.1% of BD-I patients.[11] The pooled estimates were 54.17% and 32.7%, respectively, although confidence intervals were wide and heterogeneity substantial.[12] The more recent FACE-BD cohort also reported greater migraine prevalence in BD-II.[22]

Migraine in BD was associated with female sex, earlier mood-disorder onset, more depressive symptoms, sleep disturbance, trauma exposure, and greater clinical complexity.[13],[22] The Finnish register study showed that the association persisted after accounting for parental migraine and BD, suggesting that shared inherited liability explains only part of the comorbidity.[21]

4.6 SUICIDALITY

Suicidal behavior was treated as a secondary safety outcome rather than as a mood disorder. The earlier meta-analysis of 148,977 participants found that adjustment reduced the association between migraine and suicidal ideation from an unadjusted OR of 2.49 to 1.31.[15] The later meta-analysis produced a similar adjusted estimate for ideation and found a stronger association with suicide attempts.[16]

These data do not prove that migraine independently causes suicidal behavior. Depression, bipolarity, chronic pain, sleep disorders, trauma, substance use, medication overuse, and socioeconomic adversity may contribute. Nevertheless, the consistency of the adjusted findings makes direct suicide-risk assessment clinically appropriate when migraine coexists with depression, hopelessness, severe disability, or treatment failure.

4.7 RISK OF BIAS AND CERTAINTY

The strongest evidence for depression came from longitudinal population cohorts, but several relied on self-reported migraine, medication use, or administrative diagnoses. Residual confounding remained likely. Cross-sectional studies could not determine temporal order and frequently enrolled tertiary-care patients with more severe disease.

Diagnostic misclassification was a major limitation. A 2025 systematic review found that 35 of 78 migraine studies used a depression screening instrument as evidence of depression, and only one of those 35 confirmed the diagnosis with a diagnostic interview.[23] Screening-positive depressive symptoms therefore should not be presented as confirmed MDD.

Bipolar evidence was less secure because most studies were cross-sectional and varied in migraine ascertainment. The consistency across meta-analytic, clinical, community, and register-based evidence nevertheless supports a genuine association, particularly with BD-II. Evidence for a specific causal direction remains insufficient.

5 DISCUSSION

The principal finding is that migraine and depressive disorders have a robust association that cannot be explained solely by transient distress during headache attacks. Meta-analytic, population-based, longitudinal, familial, and genetic evidence converge on the presence of shared vulnerability. The magnitude varies because the studies assessed different populations, migraine phenotypes, psychiatric definitions, and periods of risk.

Bidirectionality is the most plausible clinical model, but it should not be interpreted as proof of two simple causal pathways. Migraine may contribute to depression through recurrent pain, lost productivity, impaired sleep, reduced physical and social activity, uncertainty about future attacks, and diminished self-efficacy. Depression may contribute to migraine onset or progression through stress sensitization, sleep and circadian disruption, altered pain processing, reduced adherence, inactivity, and medication overuse. Shared susceptibility may generate both conditions without either being the exclusive cause of the other.

Genetic data support this common-liability model. Cross-trait genome-wide analyses demonstrate polygenic overlap rather than a single “migraine–depression gene.”[14,17] Relevant biological systems may include trigeminovascular and limbic networks, monoaminergic and glutamatergic signaling, hypothalamic stress regulation, central

sensitization, neuroimmune pathways, and sleep–circadian mechanisms. These pathways remain mechanistic hypotheses; genetic correlation does not show that the same biological process is active in every patient.

The frequency gradient is especially relevant to clinical practice. Depression was more strongly associated with frequent or chronic migraine than with infrequent attacks, and depressive severity predicted migraine progression.[7–9] This does not mean that depression is merely a consequence of headache frequency. Instead, monthly headache days and depressive symptoms should be considered interacting dimensions of disease burden.

Bipolar disorder requires separate consideration. Depressive presentations in people with migraine may be misclassified as unipolar depression if previous hypomania, mixed symptoms, reduced need for sleep, episodic activation, impulsivity, antidepressant-induced activation, or family history are not investigated. The repeatedly stronger association with BD-II makes this distinction particularly important.

The humanistic effect of comorbidity extends beyond symptom counts. A systematic review found that depression and anxiety in adults with migraine were consistently associated with poorer health-related quality of life, greater disability, and increased healthcare use and expenditure.[24] The 2026 UK Biobank analysis additionally suggested that the order in which migraine and depression are diagnosed may identify groups with different social, physical, and mental burdens.[20] Diagnostic order, however, may reflect healthcare access and detection patterns as much as biological sequence.

5.1 CLINICAL SCREENING

Routine assessment of depressive symptoms is justified in patients with frequent, chronic, or highly disabling migraine. The Patient Health Questionnaire-9 (PHQ-9) is a validated screening and severity instrument,[25] but a positive score should lead to clinical assessment rather than automatic assignment of MDD. The interview should evaluate duration, anhedonia, functional impairment, bereavement, substance use, medical contributors, and suicide risk.

Before initiating an antidepressant, clinicians should consider bipolarity when the history suggests hypomania, mania, mixed symptoms, early mood-disorder onset, recurrent brief depressive episodes, psychosis, or strong familial loading. Bipolar screening questionnaires may support case finding but cannot replace a structured diagnostic evaluation.

Any affirmative response concerning self-harm requires direct assessment of intent, planning, access to means, protective factors, previous behavior, and immediate safety. Suicide-risk evaluation should not be restricted to patients meeting full criteria for MDD because migraine-related disability and bipolar mixed states may confer risk outside a conventional depressive episode.

5.2 THERAPEUTIC IMPLICATIONS

Treatment should target migraine and the mood disorder as distinct but interacting conditions. Improving headache control may reduce distress and disability, but it should not be assumed to treat an independent mood disorder. Conversely, successful treatment of depression does not reliably eliminate migraine.

Some medications have potential value across both domains, but selection must remain individualized. Amitriptyline and venlafaxine may have preventive migraine efficacy while treating depressive symptoms, although tolerability and comorbidities must be considered. In suspected or confirmed BD, antidepressant monotherapy may destabilize mood and should be evaluated against established bipolar-treatment guidance.[26]

A systematic review of migraine–BD comorbidity emphasized that treatment evidence in patients with both diagnoses remains sparse.[27] A 2026 review of pharmacological trials found valproate to be the only medication with consistently replicated efficacy in both disorders.[28] Its teratogenicity and metabolic adverse effects substantially restrict its suitability, particularly in women who may become pregnant. Topiramate is an established migraine preventive but should not be presumed to provide effective mood stabilization and may cause cognitive or psychiatric adverse effects in susceptible individuals.

Calcitonin gene-related peptide–targeted preventive therapies have been associated with reductions in depressive symptom scores. A 2026 meta-analysis of 12 studies found improvements across several mood instruments, but the only placebo-controlled subgroup did not demonstrate a statistically significant antidepressant effect.[29] The most defensible interpretation is that effective migraine prevention may improve mood-related symptom burden; a direct antidepressant action has not been established.

5.3 LIMITATIONS

This review was limited by reliance on one primary bibliographic database supplemented by citation tracking, absence of prospective protocol registration, and single-

pass study appraisal. The evidence base itself was heterogeneous and contained overlapping cohorts. Several studies used self-reported diagnoses, screening instruments, or administrative codes rather than structured clinical interviews.

Women were disproportionately represented, limiting conclusions for men. Data concerning persistent depressive disorder, cyclothymic disorder, mixed features, pregnancy-related mood disorders, ethnicity, socioeconomic context, and older adults were comparatively limited. The evidence therefore supports association and clinical vigilance more strongly than precise individualized risk prediction.

Future studies should use standardized ICHD and psychiatric criteria, distinguish screening positivity from diagnosis, and measure migraine frequency, mood episodes, sleep, trauma, medication exposure, and socioeconomic adversity longitudinally. Trials involving comorbid populations should prespecify both headache and psychiatric outcomes and include adequate monitoring for mania, cognitive adverse effects, reproductive risk, and suicidality.

6 CONCLUSION

Migraine is consistently associated with depressive disorders. The best available meta-analytic estimate suggests nearly twice the odds of depression, while longitudinal studies demonstrate that migraine can precede depression and that depression may precede migraine. The exact magnitude depends on diagnostic methods, headache frequency, stress exposure, and population characteristics.

Depressive symptoms are clinically relevant to migraine prognosis. Greater depression severity is associated with more frequent attacks, greater disability, and progression from episodic to chronic migraine. These observations support integrated assessment but do not establish that treating depression alone will prevent migraine chronification.

Migraine is also substantially more prevalent in bipolar disorder, particularly bipolar II disorder. This association has direct therapeutic importance because bipolar depression may be mistaken for unipolar depression, and medications selected solely for depressive symptoms or migraine prevention may inadequately treat or destabilize the underlying mood disorder.

Patients with frequent or disabling migraine should be assessed for depression, possible bipolarity, and suicidal behavior. Screening instruments can identify patients

requiring further evaluation, but they should not replace diagnostic interviews. Treatment planning should address headache burden, mood episodes, sleep, medication overuse, reproductive considerations, and psychosocial adversity.

Future research should prioritize prospective, diagnostically rigorous studies and controlled trials enrolling patients with both migraine and mood disorders. Until stronger causal and therapeutic evidence becomes available, the most appropriate model is coordinated neurological and psychiatric care guided by each patient's migraine phenotype, mood-disorder diagnosis, functional burden, and safety risks.

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