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EXPLORING THE POTENTIAL BIDIRECTIONAL RELATIONSHIP BETWEEN MIGRAINE AND DEPRESSION: A NARRATIVE REVIEW

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ABSTRACT

Background: Migraine and depression frequently coexist, increasing disability and reducing quality of life. This review evaluated evidence on the direction and mechanisms of their relationship.
Methods: A critical narrative review used targeted searches of PubMed, Scopus, and Google Scholar for English-language publications from January 2016 to June 2026, supplemented by landmark studies. Evidence was synthesised qualitatively according to study design and its ability to inform association, temporal direction, or causality.
Results: Cross-sectional studies consistently associate migraine with depressive symptoms or reported depression. Prospective studies show temporal associations in both directions but do not establish causal bidirectionality. Mendelian randomisation has more often yielded estimates consistent with a potential influence of genetic liability to major depressive disorder on migraine risk than with the reverse pathway. Shared polygenic susceptibility and alterations in pain- and emotion-related neural systems, neurotransmitter and inflammatory signalling, stress regulation, sleep, anxiety, and functional impairment may contribute, but direct mechanistic evidence in clinically diagnosed comorbidity is limited. In a placebo-controlled trial, fremanezumab reduced monthly migraine days and depressive symptom scores in participants with a DSM-5-defined history of major depressive disorder and active symptoms; whether mood improvement was independent of reduced migraine burden remains uncertain.
Conclusions: Reciprocal assessment and coordinated management are reasonable, although their comparative effectiveness remains unproven. CGRP-targeted prevention may improve migraine burden and depressive symptoms in selected patients but should not replace targeted depression treatment. Research should use verified diagnoses, clarify mechanisms and causal direction, and test whether treating either disorder modifies the other.

KEYWORDS

Migraine; Depression; Comorbidity; Bidirectional Association; Mendelian Randomisation; Shared Mechanisms

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1. Introduction

Migraine and depression are distinct disorders that frequently coexist and may substantially increase the overall clinical burden. Individuals with migraine report depressive symptoms and previous diagnoses of depression more often than people without migraine, particularly when headaches are frequent, severe, or disabling (Buse et al., 2020; Duan et al., 2023). Conversely, migraine is common among patients with major depressive disorder and is associated with greater pain and poorer health-related quality of life (Hung et al., 2018).

The frequent co-occurrence of both conditions raises the possibility of a bidirectional relationship. Recurrent pain, disability, and disruption of daily functioning may increase depressive symptom burden; depression, in turn, may heighten pain perception, impair coping, and worsen migraine-related disability. Cross-sectional studies show a strong association, and prospective data identify temporal links in both directions. That pattern is not equivalent to causation, and genetically informed studies indicate that the two pathways may differ aetiologically (Giri et al., 2022; W.-W. Li et al., 2024; Lv et al., 2023).

Several lines of evidence point to a multifactorial relationship. Cross-disorder analyses indicate partially shared polygenic susceptibility between migraine and major depressive disorder (Brainstorm Consortium, 2018). Anxiety, sleep disturbance, stress, and functional impairment may further amplify the combined burden (Duan et al., 2023). Direct studies in patients with verified diagnoses of both disorders are still scarce.

Recognition of this comorbidity has important clinical implications. Patients with frequent or disabling migraine should be assessed for depressive symptoms, while recurrent headache in patients with depression warrants evaluation for migraine and should not be dismissed as a nonspecific somatic complaint. Comprehensive assessment and coordinated management may be beneficial, although the superiority of multidisciplinary care has not been conclusively demonstrated (Dresler et al., 2019).

This narrative review aims to critically evaluate the epidemiological, biological, psychological, and clinical evidence concerning the potential bidirectional relationship between migraine and depression, with particular attention to the distinction between association and causality, the limitations of current evidence, and implications for clinical practice.

2. Methodology

A structured narrative approach was used to critically synthesise heterogeneous epidemiological, genetic, biological, psychological, and clinical evidence concerning the relationship between migraine and depression. The review compares the strengths and limitations of these forms of evidence and does not attempt to calculate a pooled effect estimate.

2.1. Search Strategy

A targeted literature search of PubMed and Scopus, supplemented by Google Scholar, was used to identify English-language peer-reviewed publications from January 2016 through June 2026. Earlier landmark studies were considered when they remained important to the interpretation of directionality or proposed mechanisms.

Medical Subject Headings (MeSH), where applicable, and free-text terms were combined using AND and OR. The core association and directionality search combined terms for migraine (Migraine Disorders, migraine, or chronic migraine) with terms for depression (Depressive Disorder, depression, major depressive disorder, or depressive symptoms) and terms describing directionality or design (bidirectional, longitudinal, prospective, cohort, incidence, genetic correlation, or Mendelian randomisation). Additional thematic searches used terms relating to proposed mechanisms (genetic susceptibility, serotonin, calcitonin gene-related peptide, anti-CGRP monoclonal antibodies, inflammation, hypothalamic–pituitary–adrenal axis, cortisol, central sensitisation, sleep, insomnia, mediation, and brain imaging) and clinical management (screening, treatment, fremanezumab, mindfulness, and multidisciplinary care). Search syntax was adapted to the requirements of each source.

Reference lists of relevant reviews and eligible primary studies were also examined to identify additional publications. Greater weight was given to systematic reviews, meta-analyses, prospective cohort studies, genetically informed analyses, large observational studies, randomised clinical trials, and relevant professional guidance.

2.2. Inclusion and Exclusion Criteria

Eligible sources included original human studies, systematic reviews, meta-analyses, and professional guidance that addressed at least one of the following: the epidemiological association or temporal direction between migraine and depression; genetic or biological pathways potentially relevant to both conditions; psychological and functional interactions; or clinical assessment and management. Studies of a single disorder were retained only when they were used to assess the plausibility of a proposed shared mechanism or when a migraine intervention reported depressive symptom outcomes. Such studies were treated as indirect evidence and were not interpreted as demonstrating a mechanism specific to comorbidity.

Conference abstracts, editorials, letters, case reports, non-peer-reviewed publications, and animal studies were excluded. Studies without a clear connection to the review questions or without sufficient methodological information to interpret their findings were also excluded.

2.3. Study Selection, Data Extraction, and Evidence Appraisal

Titles and abstracts were screened for relevance to the review questions, followed by full-text evaluation of publications selected for inclusion. Information was extracted on study design, population and sample size, definitions or diagnostic methods for migraine and depression, principal effect estimates, follow-up duration where applicable, and major methodological limitations.

Evidence was appraised qualitatively; no formal risk-of-bias instrument was applied. Prospective studies with incident outcomes, structured diagnoses, and adjustment for important confounders were considered more informative about temporal direction than cross-sectional studies. Mendelian randomisation studies were evaluated separately because they address genetically predicted liability and depend on instrument validity and other model assumptions. Mechanistic findings from separate migraine and depression populations were assigned less weight than studies of patients with both conditions. Treatment evidence was interpreted in relation to study design, including whether depressive symptoms were primary or secondary outcomes, whether major depressive disorder was clinically established, and whether a control group was present.

2.4. Narrative Synthesis and Methodological Limitations

Findings were synthesised narratively across epidemiological, biological, psychological, and clinical domains. The interpretation explicitly distinguished coexistence or statistical association from temporal direction and from causal inference. Quantitative meta-analysis was not undertaken because of heterogeneity in study populations, diagnostic definitions, exposures, outcomes, and research designs.

Although the literature search was structured, study selection was purposive and did not include duplicate independent screening, a PRISMA flow diagram, or a validated certainty-of-evidence framework. Accordingly, this work is a critical narrative synthesis, not an exhaustive systematic review.

3. Literature Review

3.1. Epidemiological Evidence for a Potential Bidirectional Association

3.1.1. Depression in Patients with Migraine

Depression is consistently reported as one of the most common psychiatric comorbidities in individuals with migraine. Across population-based and clinical studies, patients with migraine demonstrate a substantially higher prevalence of depressive symptoms and self-reported previous diagnoses of depression than individuals without migraine (Buse et al., 2020; Duan et al., 2023). Although the magnitude of this association varies according to the study population, diagnostic instruments, and migraine classification, the overall direction of the evidence remains consistent.

The likelihood of depressive symptoms or reported depression appears to increase in parallel with migraine severity. Higher headache frequency, greater pain intensity, and more pronounced migraine-related disability have repeatedly been associated with a greater burden of depressive symptoms (Buse et al., 2020; Duan et al., 2023). This relationship is particularly relevant in chronic migraine, where persistent pain, anticipatory fear of subsequent attacks, limitations in daily functioning, and reduced participation in occupational and social activities may contribute to psychological distress. At the same time, depression may intensify the subjective experience of pain, reduce treatment adherence, and impair the ability to adopt effective coping strategies.

Coexisting depressive symptoms are also associated with poorer sleep quality, lower health-related quality of life, and greater functional impairment than migraine alone (Duan et al., 2023). This pattern argues against viewing depression merely as an emotional reaction to recurrent headache. It may instead be part of a

broader clinical phenotype in which neurological, psychological, and behavioural disturbances reinforce one another.

Most evidence concerning depression in clinical migraine populations is nevertheless cross-sectional. These studies document a robust association but cannot determine whether depressive symptoms precede migraine progression, follow recurrent pain and disability, or arise from shared biological and environmental influences. Establishing temporal order requires prospective data.

3.1.2. Migraine in Patients with Depression

Migraine is a clinically significant comorbidity among individuals with depression. Population-based evidence demonstrates that migraine and depression coexist more frequently than would be expected by chance, supporting a clinically meaningful association between the two disorders (Lampl et al., 2016). In patients with major depressive disorder, the presence of migraine appears to identify a subgroup with a greater and more persistent burden of pain than that observed in patients without migraine (Hung et al., 2018).

The impact of this comorbidity is not limited to recurrent headache. Migraine in depressive populations has been associated with more severe bodily pain and poorer pain-related quality of life, including after adjustment for the concurrent severity of depressive and anxiety symptoms (Hung et al., 2018). These findings indicate that migraine represents an additional source of morbidity in patients with depression and should not be regarded solely as a nonspecific somatic manifestation of the psychiatric disorder.

These studies primarily document coexistence and increased clinical burden; they offer little evidence that depression precedes and directly promotes migraine. The population-based Eurolight data were cross-sectional, and the longitudinal study of patients with major depressive disorder examined the consequences of established migraine without assessing new-onset disease (Hung et al., 2018; Lampl et al., 2016). The next section considers more direct prospective and genetically informed evidence on directionality.

3.1.3. Prospective and Genetically Informed Evidence on Directionality

Prospective population-based evidence supports temporal associations in both directions. In the HUNT study, participants were followed for approximately 11 years. Among individuals without headache at baseline, an elevated depression score on the Hospital Anxiety and Depression Scale (HADS-D ≥8) was associated with a higher subsequent risk of definite migraine (RR 2.15, 95% CI 1.45–3.18). Conversely, among participants without elevated depression scores at baseline, definite migraine was associated with a higher subsequent risk of an elevated HADS-D score (RR 1.26, 95% CI 1.02–1.56) (Giri et al., 2022). These findings support a bidirectional temporal association, but the use of a screening scale and questionnaire-based headache diagnoses means that they should not be interpreted as evidence involving exclusively clinically diagnosed major depressive disorder and migraine.

Evidence for the migraine-to-affective-disorder direction is also provided by a nationwide Swedish register-based cohort of more than four million people. Migraine was associated with a higher subsequent rate of the composite outcome of depression or anxiety in the matched cohort (HR 1.78, 95% CI 1.75–1.81), and the association remained in a sibling analysis that partly accounted for shared genetic and childhood family factors (HR 1.63, 95% CI 1.58–1.68) (Johansson et al., 2026). Because the endpoint combined depression and anxiety, the study does not isolate an effect specific to depression.

Mendelian randomisation studies provide a different perspective by examining whether genetically predicted liability to one disorder is associated with the other. Lv et al. (2023) found that genetic liability to major depressive disorder was associated with a higher risk of migraine (OR 1.61, 95% CI 1.32–1.95), whereas the reverse analysis did not support an effect of genetic liability to migraine on major depressive disorder. W.-W. Li et al. (2024) similarly reported an association between genetic liability to major depressive disorder and migraine without aura (OR 1.93, 95% CI 1.22–3.04), without evidence for the reverse migraine-to-depression direction. Mendelian randomisation reduces some forms of confounding and reverse causation, but its validity depends on the strength and specificity of the genetic instruments and the assumptions of the analytical model.

A subsequent two-step Mendelian randomisation analysis examined potential sleep-related mediators. Y. Li et al. (2024) reported associations of genetically predicted depression with migraine (OR 1.32, 95% CI 1.18–1.47) and of genetically predicted insomnia with migraine (OR 1.77, 95% CI 1.12–2.78). Insomnia mediated 17.3% of the estimated total effect in the primary analysis and 19.3% in the validation analysis. These estimates are consistent with partial mediation, but they do not establish a clinical pathway in individual patients because both steps of the analysis share the assumptions and potential biases of Mendelian randomisation.

Prospective and genetically informed studies address different aspects of directionality. The former support temporal associations in both directions, whereas the latter more consistently indicate a potential contribution of major depressive disorder liability to migraine risk than the reverse pathway. Temporal bidirectionality is therefore distinct from causal bidirectionality, and neither body of evidence shows that treating one established disorder will necessarily prevent or resolve the other.

3.2. Shared Biological Mechanisms

3.2.1. Genetic Susceptibility

Migraine and major depressive disorder are polygenic conditions in which susceptibility results from the cumulative effects of numerous genetic variants. Cross-disorder analyses have demonstrated a positive genetic correlation between the two conditions, supporting the presence of partially shared inherited vulnerability (Brainstorm Consortium, 2018).

Large genome-wide association studies further indicate that migraine susceptibility involves genes related to neuronal excitability, vascular function, serotonergic signalling, and the CGRP pathway, including loci containing CACNA1A, HTR1F, and CALCA/CALCB (Hautakangas et al., 2022). Depression-associated loci include genes such as NEGR1, TCF4, and SORCS3, with broader enrichment of pathways involved in synaptic function and neurotransmission (Howard et al., 2019). These genes were identified mainly in disorder-specific analyses and do not constitute individually confirmed links between migraine and depression. The evidence is more consistent with a shared polygenic architecture than with a small set of common causative genes.

3.2.2. Neurotransmitter Dysregulation

Alterations in neurotransmitter signalling have been proposed as a potential biological link between migraine and depression, with particular attention given to serotonergic pathways. Serotonin participates in the regulation of nociceptive transmission, affective processing, sleep, and stress responses, making it biologically relevant to both conditions. The effectiveness of selective 5-HT$_1$F receptor agonism in the acute treatment of migraine confirms that serotonergic modulation can influence migraine-related pain pathways (Kuca et al., 2018).

Therapeutic responsiveness is not evidence that either disorder results from a simple serotonin deficiency. A systematic umbrella review found no consistent support for reduced serotonin concentrations or activity as a cause of depression; serotonergic findings are better considered within broader changes in receptor function, neuronal signalling, and neuroplasticity (Moncrieff et al., 2023). Glutamatergic and dopaminergic pathways could also affect cortical excitability, pain processing, and reward-related functions, but a common neurotransmitter abnormality has not been demonstrated directly in patients with both disorders. Neurotransmitter dysregulation remains one possible contributor to a multifactorial pathophysiology, not a unifying explanation.

3.2.3. Calcitonin Gene-Related Peptide (CGRP) and the Trigeminovascular System

Calcitonin gene-related peptide (CGRP) is a key mediator of trigeminovascular pain transmission in migraine. Its clinical relevance is supported by randomised trials showing that CGRP-targeted therapies reduce migraine frequency and disability (Dodick et al., 2018; Goadsby et al., 2017).

CGRP-targeted treatment studies have raised the possibility that the pathway may also be relevant to depressive symptoms. In a prospective one-year cohort of 577 patients treated with anti-CGRP monoclonal antibodies, 46.1% had depressive symptoms at baseline; among those patients, 63.5% achieved a clinically significant improvement, with changes observed across groups defined by headache-frequency response (Torres-Ferrús et al., 2024). In the placebo-controlled UNITE trial, fremanezumab improved depressive symptom scores in patients with migraine, a DSM-5-defined history of major depressive disorder, and active depressive symptoms (Lipton et al., 2025).

These findings justify further investigation of CGRP as a candidate contributor to the interaction between migraine and depression, but they do not establish it as a shared causal mechanism. The cohort study lacked a control group, while clinical response to CGRP blockade may reflect reduced pain, disability, attack severity, or other indirect effects. Even a placebo-controlled treatment effect cannot by itself determine the biological pathway through which depressive symptoms improve.

3.2.4. Inflammatory Signalling

Inflammatory signalling has been proposed as a potential disease-modifying pathway in both migraine and depression, but the evidence is largely indirect and derives from separate patient populations. In a randomised dietary trial involving adults with migraine, alteration of n-3 and n-6 fatty acid intake changed circulating lipid mediators and was accompanied by reductions in headache days and moderate-to-severe headache hours (Ramsden et al., 2021). Dietary fatty acid modification therefore affected both biochemical and clinical outcomes, but the trial did not isolate inflammation as the mechanism of benefit, directly measure neuroinflammation, or establish a pathway shared with depression.

In depression, meta-analytic evidence indicates higher mean peripheral concentrations of several inflammatory markers, including C-reactive protein, interleukin-6, and tumour necrosis factor-α (Osimo et al.,

2020). Evidence for increased between-participant variability was marker-dependent and should not be generalised across all inflammatory measures. Moreover, peripheral marker concentrations do not directly demonstrate inflammation within the central nervous system and are not specific to depression.

The available findings identify inflammatory signalling as a candidate modifier, not a confirmed mechanism shared by migraine and depression. Before an inflammatory subtype can guide assessment or treatment, longitudinal studies need to examine patients with both clinically diagnosed conditions and use clearly specified central or peripheral biomarkers.

3.2.5. Hypothalamic–Pituitary–Adrenal (HPA) Axis and Cortisol

The hypothalamic–pituitary–adrenal (HPA) axis has been proposed as a potential stress-related link between migraine and depression. A systematic review and meta-analysis reported small average increases in morning and evening salivary cortisol among patients with depression compared with controls. Interpretation was constrained by substantial heterogeneity, overlap between groups, and sensitivity to analytical assumptions, leaving no firm evidence of a clinically discriminating cortisol abnormality (Knorr et al., 2010). In migraine, a systematic review found increased, decreased, and unchanged cortisol concentrations across generally small studies (Lippi & Mattiuzzi, 2017). The cortisol literature thus provides a testable hypothesis for migraine–depression comorbidity, but not an established mechanism.

3.2.6. Structural and Functional Brain Alterations

Neuroimaging findings suggest that migraine and major depressive disorder may involve partially overlapping brain regions responsible for pain processing, salience detection, and emotional regulation. A large multicentre MRI study found subtle cortical thinning in adults with major depressive disorder, particularly in the orbitofrontal cortex, anterior and posterior cingulate cortex, insula, and temporal regions (Schmaal et al., 2017). These regions contribute to the integration of emotional, cognitive, and bodily information.

In migraine, structural imaging findings, including white matter hyperintensities, are generally nonspecific, and their clinical and pathophysiological significance remains uncertain (Evans et al., 2020). Cortical–limbic involvement in both conditions may indicate overlapping disturbances in pain and emotion processing, but most imaging studies have examined migraine and depression separately. At present, structural and functional brain alterations are better interpreted as potential correlates; direct evidence for a common mechanism is lacking.

3.3. Psychological, Behavioural, and Functional Interactions

Psychological and behavioural factors may influence the clinical relationship between migraine and depression. Pain-related distress, sleep disturbances, and anxiety are associated with greater disability and poorer quality of life in patients affected by these conditions (Buse et al., 2020; Duan et al., 2023).

3.3.1. Chronic Pain and Emotional Distress

Migraine-related pain and emotional distress appear to be closely interconnected. In a large population-based survey, a self-reported history of healthcare-provider-diagnosed depression was substantially more common among individuals meeting migraine criteria than among controls. Within the migraine group, greater headache frequency and moderate-to-severe pain intensity were also associated with higher odds of reported depression (Buse et al., 2020). Similarly, a clinical study found that depressive symptoms measured with a self-report scale were independently associated with migraine frequency, pain severity, disability, headache impact, and poorer quality of life (Duan et al., 2023).

Frequent or severe migraine pain may increase emotional distress, while depression may magnify the perceived burden and functional consequences of migraine. Because the underlying studies are predominantly cross-sectional, their temporal order remains unknown. Pain and depressive symptoms are best interpreted as potentially interacting components of the clinical burden, not as a demonstrated causal sequence.

3.3.2. Sleep Disturbances

Sleep disturbances may contribute to the clinical interaction between migraine and depression. A systematic review found that migraine is associated with poor sleep quality and several sleep disorders, particularly insomnia, while nocturnal or early-morning migraine attacks may further disrupt sleep (Tiseo et al., 2020). Among patients with migraine, depressive symptoms have also been associated with poorer sleep quality and greater headache-related burden (Duan et al., 2023).

Two-step Mendelian randomisation provides additional, although still indirect, support for a role of sleep. Y. Li et al. (2024) estimated that insomnia mediated 17.3% of the association between genetically predicted depression and migraine in the primary analysis and 19.3% in the validation analysis. This design is less susceptible to some forms of confounding and reverse causation than conventional observational analysis,

but the estimates still depend on instrument validity, the absence of influential horizontal pleiotropy, and comparability of the source populations. The result supports insomnia as a possible and potentially modifiable partial mediator, but does not confirm it as a mechanism in individual patients.

3.3.3. Stress and Anxiety

Stress and anxiety may contribute to the interaction between migraine and depressive symptoms. In a case-control study, patients with chronic migraine reported higher perceived stress than healthy controls even after adjustment for depression and anxiety. Within the migraine group, anxiety and depressive symptom severity were among the strongest independent predictors of perceived stress, which was also associated with poorer migraine-specific quality of life (Moon et al., 2017). Similarly, Duan et al. (2023) found that self-reported anxiety and depressive symptoms were independently associated with greater migraine frequency, pain severity, disability, headache impact, poorer sleep quality, and reduced quality of life.

Stress, anxiety, and depressive symptoms may jointly amplify the clinical burden of migraine. Recurrent and unpredictable attacks can also increase psychological distress. Since both studies were cross-sectional, causal direction cannot be inferred; the findings identify interrelated clinical modifiers rather than established causes of migraine–depression comorbidity.

3.3.4. Functional Impairment and Quality of Life

The coexistence of migraine and depressive symptoms is associated with greater functional impairment and poorer quality of life. In a study of 170 patients with migraine, depressive symptoms were associated with more than threefold higher odds of severe migraine-related disability after adjustment for demographic and clinical factors (OR 3.48, 95% CI 1.55–7.80) (Duan et al., 2023). The outcome concerned symptoms defined by the Self-Rating Depression Scale, not a diagnosis established by structured psychiatric assessment.

Longitudinal evidence also indicates that migraine contributes additional burden among patients with major depressive disorder. In a cohort of 290 patients followed for up to 10 years, comorbid migraine was independently associated with an 8.93-point reduction in the bodily pain domain of the SF-36 and a 1.33-point increase in pain severity after adjustment for depression, anxiety, pharmacotherapy, and demographic factors (Hung et al., 2018). Attrition was substantial: only 137 participants attended the ten-year assessment, creating a risk of selection bias in the long-term estimates. The study documents a greater and potentially sustained burden when both disorders coexist, but functional impairment and reduced quality of life do not establish a causal relationship between them.

3.4. Clinical Implications

The substantial clinical burden associated with coexisting migraine and depression highlights the need to consider both conditions within an integrated management approach (Buse et al., 2020; Duan et al., 2023).

3.4.1. Screening and Early Diagnosis

The high prevalence and clinical burden of migraine–depression comorbidity make active assessment of depressive symptoms clinically reasonable, particularly in patients with frequent or severe headaches and substantial disability. In the cross-sectional analysis of baseline MAST survey data, which included 15,133 respondents meeting modified migraine criteria and 77,453 controls, migraine was associated with more than threefold higher odds of a self-reported history of healthcare-provider-diagnosed depression after adjustment for sociodemographic factors (OR 3.18, 95% CI 3.0–3.3). Within the migraine group, the likelihood of reported depression also increased with headache frequency and pain intensity (Buse et al., 2020).

Recognition should also be reciprocal. Among 290 patients with major depressive disorder diagnosed using a structured interview, migraine diagnosed by a headache specialist was present in 46.9% at baseline and was associated with greater pain burden across follow-up independently of depression and anxiety severity (Hung et al., 2018). This finding supports evaluating recurrent headache in patients with depression for migraine rather than automatically interpreting it as a nonspecific somatic symptom, although the substantial loss to ten-year follow-up limits the precision of the longest-term estimates.

Brief self-report questionnaires may help identify patients requiring further evaluation, but their results are not equivalent to a psychiatric diagnosis. For example, Duan et al. (2023) identified depressive symptoms in 25.9% of patients with migraine compared with 9.4% of controls using the Self-Rating Depression Scale. A positive screening result warrants further clinical assessment of symptom duration, severity, and functional impact.

3.4.2. Pharmacological Management

Pharmacological management in patients with migraine and depressive symptoms should address both conditions as related but distinct treatment targets. Available evidence suggests that effective migraine

prevention may also reduce depressive symptom burden. In a subgroup analysis of the randomised, placebo-controlled HALO CM trial, fremanezumab reduced headache frequency and improved depressive symptom scores in patients with chronic migraine and moderate-to-severe depressive symptoms (Lipton et al., 2021). Similarly, during the 108-week COMPEL study, onabotulinumtoxinA treatment was associated with sustained improvements in headache frequency, migraine-related disability, and symptoms of depression and anxiety (Blumenfeld et al., 2019).

More direct evidence comes from the 28-week, multicentre UNITE randomised clinical trial. The study randomised 353 adults with episodic or chronic migraine, a DSM-5 history of major depressive disorder for at least 12 months, and active depressive symptoms to monthly fremanezumab 225 mg or placebo for 12 weeks. Mean monthly migraine days decreased by 5.1 days with fremanezumab and 2.9 days with placebo ($p < 0.001$). At week 8, the mean Hamilton Depression Rating Scale–17 score decreased by 6.0 and 4.6 points, respectively, with a least-squares mean between-group difference of −1.4 points (95% CI −2.61 to −0.22; $p = 0.02$) (Lipton et al., 2025).

Complementary real-world evidence was provided by Torres-Ferrús et al. (2024). Among 577 patients starting anti-CGRP monoclonal antibodies, 266 had depressive symptoms at baseline and 63.5% of this subgroup achieved a clinically significant improvement after one year. Beck Depression Inventory–II scores decreased across headache-frequency response categories. Interpretation is limited by the single-centre observational design and the absence of a control group. Only 50.8% of the cohort completed 12 months of follow-up, 35.0% discontinued treatment, and 47.1% were using antidepressants at baseline. Together with the use of a symptom scale instead of a structured diagnosis of major depressive disorder, these features preclude attributing the improvement to a direct antidepressant effect of CGRP blockade.

These newer data extend the evidence beyond earlier subgroup and open-label analyses. UNITE shows that fremanezumab can improve migraine outcomes and depressive symptom scores in selected patients with a DSM-5-defined history of major depressive disorder and active depressive symptoms. The between-group effect on the depression scale was modest, both trial groups improved, 64% of participants used concomitant antidepressant medication, and the timing of change in migraine and depression did not establish mediation. It remains unclear whether depressive symptoms improved independently of the reduction in migraine burden or through a direct antidepressant action of CGRP blockade. These symptom changes do not replace appropriate assessment and treatment of depression.

Treatment response should be monitored separately for each condition. If clinically significant depressive symptoms persist despite adequate migraine control, targeted depression management is indicated; further escalation of migraine therapy alone is unlikely to address the remaining psychiatric burden.

3.4.3. Non-Pharmacological Interventions

Evidence for non-pharmacological interventions specifically designed for patients with both migraine and clinically diagnosed depression is sparse. In a randomised clinical trial of 89 adults with migraine, an eight-week mindfulness-based stress reduction programme did not reduce migraine-day frequency more than headache education. The intervention did, however, produce greater improvements in migraine-related disability, quality of life, pain self-efficacy, pain catastrophising, and depressive symptoms, with several benefits maintained during follow-up (Wells et al., 2021).

Mindfulness-based interventions may lessen the functional and psychological burden of migraine even when headache frequency changes little. Depressive symptoms were secondary outcomes, and participants were not required to have major depressive disorder. The intervention is therefore best viewed as an adjunct to care, not as treatment for confirmed depression. Trials designed specifically for patients with clinically diagnosed migraine–depression comorbidity are still needed.

3.4.4. Multidisciplinary Care

The interaction between migraine and depression supports a coordinated approach to clinical management. A systematic review of psychiatric comorbidity in migraine emphasised the need for comprehensive psychiatric assessment and an integrated model of care. The authors also indicated that an interdisciplinary approach combining pharmacological and non-pharmacological strategies may help reduce the combined burden of migraine and psychiatric comorbidity (Dresler et al., 2019).

Within such an approach, migraine and depression should be assessed as distinct but interacting clinical problems. Professionals responsible for headache care and mental-health care should coordinate treatment goals and monitor the response of both conditions. Assessment may include headache frequency and severity, migraine-related disability, depressive symptom severity, sleep quality, and health-related quality of life. This is supported by an observational study in which depressive symptoms were independently associated with

migraine frequency, pain severity, disability, headache impact, poorer sleep quality, and reduced quality of life (Duan et al., 2023).

The Duan et al. (2023) findings came from a cross-sectional study that measured depressive symptoms with a self-report scale, not a structured psychiatric interview. The study consequently cannot show that depression causes greater migraine burden or that multidisciplinary care improves outcomes. Its clinical value lies in supporting parallel assessment of psychological and neurological burden when both conditions are present.

The present narrative search identified no trials demonstrating that multidisciplinary care is superior to standard care in patients clinically diagnosed with migraine and major depressive disorder. Coordinated management is clinically reasonable on the basis of the available synthesis, but its comparative effectiveness remains untested. Prospective randomised studies should assess headache frequency, depressive symptoms, disability, quality of life, treatment adherence, and long-term clinical outcomes.

4. Conclusions

Current evidence demonstrates a robust and clinically meaningful association between migraine and depression. Individuals with migraine, particularly those experiencing frequent, severe, or disabling attacks, have a greater burden of depressive symptoms and depressive disorders. Conversely, migraine contributes additional and potentially persistent pain, disability, and deterioration in quality of life among individuals with depression. Prospective evidence supports temporal associations in both directions, but causal bidirectionality has not been established. Mendelian randomisation findings are currently more consistent with a potential effect of genetic liability to major depressive disorder on migraine risk than with the reverse direction, suggesting that the two pathways may be aetiologically asymmetric.

Multiple mechanisms probably contribute to the association between migraine and depression. Partially shared polygenic susceptibility, changes in neural systems involved in pain and emotional processing, neurotransmitter signalling, inflammatory regulation, stress-related pathways, sleep disturbance, anxiety, and functional impairment could all participate in the coexistence and mutual amplification of the two conditions. Most of these pathways, however, have been studied separately in migraine and depression, and direct mechanistic research in patients with verified comorbidity is scarce. They remain biologically credible contributors, but none is a confirmed common mechanism.

From a clinical perspective, the findings support reciprocal assessment. Patients with frequent or disabling migraine should be screened for depressive symptoms, while recurrent headache in individuals with depression warrants evaluation for migraine and should not be automatically classified as a nonspecific somatic symptom. Screening questionnaires may facilitate early recognition but cannot replace structured clinical assessment. Migraine and depression are distinct but interacting conditions, and response to treatment should be monitored separately for each disorder. UNITE provides controlled evidence that fremanezumab may improve both migraine and depressive symptoms in patients with a DSM-5-defined history of major depressive disorder and active depressive symptoms. Prospective real-world data likewise indicate that depressive improvement during anti-CGRP treatment can occur without a strong headache-frequency response. Neither finding establishes an independent antidepressant mechanism or supports replacing targeted depression treatment with migraine prevention alone.

Future research should prioritise prospective longitudinal cohorts with clinically verified diagnoses, replication of genetically informed analyses across populations, and mechanistic studies conducted specifically in patients with coexisting migraine and major depressive disorder. Studies should distinguish depression from anxiety outcomes and test the direction of association separately for migraine with and without aura. Further randomised trials should compare CGRP-targeted treatment with active migraine preventives and depression-focused treatments, establish the temporal sequence of changes in headache and mood, and determine whether coordinated multidisciplinary management provides additional benefits over standard care. Although the causal structure of the association remains unresolved, recognition and appropriate management of this comorbidity may facilitate earlier diagnosis, improve quality of life, and reduce the combined neurological and psychological burden experienced by affected patients.

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REFERENCES

1. Blumenfeld, A. M., Tepper, S. J., Robbins, L. D., Manack Adams, A., Buse, D. C., Orejudos, A., & Silberstein, S. D. (2019). Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. *Journal of Neurology, Neurosurgery & Psychiatry, 90*(3), 353–360. https://doi.org/10.1136/jnnp-2018-319290
2. Brainstorm Consortium. (2018). Analysis of shared heritability in common disorders of the brain. *Science, 360*(6395), eaap8757. https://doi.org/10.1126/science.aap8757
3. Buse, D. C., Reed, M. L., Fanning, K. M., Bostic, R., Dodick, D. W., Schwedt, T. J., Munjal, S., Singh, P., & Lipton, R. B. (2020). Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: Results of the Migraine in America Symptoms and Treatment (MAST) study. *The Journal of Headache and Pain, 21*(1), 23. https://doi.org/10.1186/s10194-020-1084-y
4. Dodick, D. W., Silberstein, S. D., Bigal, M. E., Yeung, P. P., Goadsby, P. J., Blankenbiller, T., Grozinski-Wolff, M., Yang, R., Ma, Y., & Aycardi, E. (2018). Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized clinical trial. *JAMA, 319*(19), 1999–2008. https://doi.org/10.1001/jama.2018.4853
5. Dresler, T., Caratozzolo, S., Guldolf, K., Huhn, J.-I., Loiacono, C., Niiberg-Pikksööt, T., Puma, M., Sforza, G., Tobia, A., Ornello, R., & Serafini, G. (2019). Understanding the nature of psychiatric comorbidity in migraine: A systematic review focused on interactions and treatment implications. *The Journal of Headache and Pain, 20*(1), 51. https://doi.org/10.1186/s10194-019-0988-x
6. Duan, S., Ren, Z., Xia, H., Wang, Z., Zheng, T., Li, G., Liu, L., & Liu, Z. (2023). Associations between anxiety, depression with migraine, and migraine-related burdens. *Frontiers in Neurology, 14*, 1090878. https://doi.org/10.3389/fneur.2023.1090878
7. Evans, R. W., Burch, R. C., Frishberg, B. M., Marmura, M. J., Mechtler, L. L., Silberstein, S. D., & Turner, D. P. (2020). Neuroimaging for migraine: The American Headache Society systematic review and evidence-based guideline. *Headache: The Journal of Head and Face Pain, 60*(2), 318–336. https://doi.org/10.1111/head.13720
8. Giri, S., Tronvik, E. A., & Hagen, K. (2022). The bidirectional temporal relationship between headache and affective disorders: Longitudinal data from the HUNT studies. *The Journal of Headache and Pain, 23*(1), 14. https://doi.org/10.1186/s10194-022-01388-x
9. Goadsby, P. J., Reuter, U., Hallström, Y., Broessner, G., Bonner, J. H., Zhang, F., Sapra, S., Picard, H., Mikol, D. D., & Lenz, R. A. (2017). A controlled trial of erenumab for episodic migraine. *New England Journal of Medicine, 377*(22), 2123–2132. https://doi.org/10.1056/NEJMoa1705848
10. Hautakangas, H., Winsvold, B. S., Ruotsalainen, S. E., Bjornsdottir, G., Harder, A. V. E., Kogelman, L. J. A., Thomas, L. F., Noordam, R., Benner, C., Gormley, P., Artto, V., Banasik, K., Bjornsdottir, A., Boomsma, D. I., Brumpton, B. M., Burgdorf, K. S., Buring, J. E., Chalmer, M. A., de Boer, I., . . . Pirinen, M. (2022). Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. *Nature Genetics, 54*(2), 152–160. https://doi.org/10.1038/s41588-021-00990-0
11. Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., Coleman, J. R. I., Hagenaars, S. P., Ward, J., Wigmore, E. M., Alloza, C., Shen, X., Barbu, M. C., Xu, E. Y., Whalley, H. C., Marioni, R. E., Porteous, D. J., Davies, G., Deary, I. J., . . . McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience, 22*(3), 343–352. https://doi.org/10.1038/s41593-018-0326-7
12. Hung, C.-I., Liu, C.-Y., Yang, C.-H., & Wang, S.-J. (2018). Migraine and greater pain symptoms at 10-year follow-up among patients with major depressive disorder. *The Journal of Headache and Pain, 19*(1), 56. https://doi.org/10.1186/s10194-018-0884-9

13. Johansson, E. W., Linde, M., Ohlis, A., Mattsson, M., Shaaban, A. N., Gustafsson, S., Holm, J., Dalman, C., & Agardh, E. E. (2026). Association of migraine with subsequent risk of depression or anxiety by small-area deprivation: National cohort study with sibling analysis. *The Journal of Headache and Pain, 27*(1), 57. https://doi.org/10.1186/s10194-026-02280-8
14. Knorr, U., Vinberg, M., Kessing, L. V., & Wetterslev, J. (2010). Salivary cortisol in depressed patients versus control persons: A systematic review and meta-analysis. *Psychoneuroendocrinology, 35*(9), 1275–1286. https://doi.org/10.1016/j.psyneuen.2010.04.001
15. Kuca, B., Silberstein, S. D., Wietecha, L., Berg, P. H., Dozier, G., & Lipton, R. B. (2018). Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology, 91*(24), e2222–e2232. https://doi.org/10.1212/WNL.0000000000006641
16. Lampl, C., Thomas, H., Tassorelli, C., Katsarava, Z., Laínez, J. M., Lantéri-Minet, M., Rastenyte, D., Ruiz de la Torre, E., Stovner, L. J., Andrée, C., & Steiner, T. J. (2016). Headache, depression and anxiety: Associations in the Eurolight project. *The Journal of Headache and Pain, 17*(1), 59. https://doi.org/10.1186/s10194-016-0649-2
17. Li, W.-W., Zhang, J.-X., Wang, J., Chen, Y.-Q., Lai, S., & Qiu, Z.-K. (2024). Bidirectional two-sample Mendelian randomization analysis identifies causal associations between migraine and five psychiatric disorders. *Frontiers in Neurology, 15*, 1432966. https://doi.org/10.3389/fneur.2024.1432966
18. Li, Y., Luo, G., Zhou, L., Wang, X., Liu, H., Zhang, Y., & Yan, M. (2024). Mediators of the association between depression and migraine: A Mendelian randomization study. *Frontiers in Genetics, 15*, 1326817. https://doi.org/10.3389/fgene.2024.1326817
19. Lippi, G., & Mattiuzzi, C. (2017). Cortisol and migraine: A systematic literature review. *Ağrı, 29*(3), 95–99. https://doi.org/10.5505/agri.2017.25348
20. Lipton, R. B., Cohen, J. M., Galic, M., Seminerio, M. J., Yeung, P. P., Aycardi, E., Bigal, M. E., Bibeau, K., & Buse, D. C. (2021). Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized HALO CM study. *Headache: The Journal of Head and Face Pain, 61*(4), 662–672. https://doi.org/10.1111/head.14097
21. Lipton, R. B., Ramirez Campos, V., Roth-Ben Arie, Z., Galic, M., Mitsikostas, D., Tassorelli, C., Denysenko, L., & Cohen, J. M. (2025). Fremanezumab for the treatment of patients with migraine and comorbid major depressive disorder: The UNITE randomized clinical trial. *JAMA Neurology, 82*(6), 560–569. https://doi.org/10.1001/jamaneurol.2025.0806
22. Lv, X., Xu, B., Tang, X., Liu, S., Qian, J.-H., Guo, J., & Luo, J. (2023). The relationship between major depression and migraine: A bidirectional two-sample Mendelian randomization study. *Frontiers in Neurology, 14*, 1143060. https://doi.org/10.3389/fneur.2023.1143060
23. Moncrieff, J., Cooper, R. E., Stockmann, T., Amendola, S., Hengartner, M. P., & Horowitz, M. A. (2023). The serotonin theory of depression: A systematic umbrella review of the evidence. *Molecular Psychiatry, 28*(8), 3243–3256. https://doi.org/10.1038/s41380-022-01661-0
24. Moon, H.-J., Seo, J.-G., & Park, S.-P. (2017). Perceived stress in patients with migraine: A case-control study. *The Journal of Headache and Pain, 18*(1), 73. https://doi.org/10.1186/s10194-017-0780-8
25. Osimo, E. F., Pillinger, T., Rodriguez, I. M., Khandaker, G. M., Pariante, C. M., & Howes, O. D. (2020). Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain, Behavior, and Immunity, 87*, 901–909. https://doi.org/10.1016/j.bbi.2020.02.010
26. Ramsden, C. E., Zamora, D., Faurot, K. R., MacIntosh, B., Horowitz, M., Keyes, G. S., Yuan, Z.-X., Miller, V., Lynch, C., Honvoh, G., Park, J., Levy, R., Domenichiello, A. F., Johnston, A., Majchrzak-Hong, S., Hibbeln, J. R., Barrow, D. A., Loewke, J., Davis, J. M., . . . Mann, J. D. (2021). Dietary alteration of n-3 and n-6 fatty acids for headache reduction in adults with migraine: Randomized controlled trial. *BMJ, 374*, n1448. https://doi.org/10.1136/bmj.n1448
27. Schmaal, L., Hibar, D. P., Sämann, P. G., Hall, G. B., Baune, B. T., Jahanshad, N., Cheung, J. W., van Erp, T. G. M., Bos, D., Ikram, M. A., Vernooij, M. W., Niessen, W. J., Tiemeier, H., Hofman, A., Wittfeld, K., Grabe, H. J., Janowitz, D., Bülow, R., Selonke, M., . . . Veltman, D. J. (2017). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. *Molecular Psychiatry, 22*(6), 900–909. https://doi.org/10.1038/mp.2016.60
28. Tiseo, C., Vacca, A., Felbush, A., Filimonova, T., Gai, A., Glazyrina, T., Hubalek, I. A., Marchenko, Y., Overeem, L. H., Piroso, S., Tkachev, A., Martelletti, P., & Sacco, S. (2020). Migraine and sleep disorders: A systematic review. *The Journal of Headache and Pain, 21*(1), 126. https://doi.org/10.1186/s10194-020-01192-5
29. Torres-Ferrús, M., Gallardo, V. J., Alpuente, A., Caronna, E., Giné-Ciprés, E., & Pozo-Rosich, P. (2024). Improvement of migraine depressive symptoms is not related to headache frequency: Exploring the impact of anti-CGRP therapies. *Cephalalgia, 44*(2), 03331024231222923. https://doi.org/10.1177/03331024231222923
30. Wells, R. E., O'Connell, N., Pierce, C. R., Estave, P., Penzien, D. B., Loder, E., Zeidan, F., & Houle, T. T. (2021). Effectiveness of mindfulness meditation vs headache education for adults with migraine: A randomized clinical trial. *JAMA Internal Medicine, 181*(3), 317–328. https://doi.org/10.1001/jamainternmed.2020.7090