Brain & Development 47 (2025) 104392

Contents lists available at ScienceDirect

Brain and Development

journal homepage: www.elsevier.com/locate/braindev

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

Review Article

Unraveling the connections between migraine and psychiatric comorbidities: A narrative review

Jungyon Yum [a], Min Kyung Chu [b,*]

[a] Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea
[b] Department of Neurology, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Anxiety
Attention deficit disorder with hyperactivity
Autism spectrum disorder
Depression
Migraine disorders
Mood disorders

ABSTRACT

The close association between migraine and psychiatric comorbidities is well documented. Migraine frequently co-occurs with mood disorders, particularly depression and anxiety, exhibiting a bidirectional relationship across various populations, including children and adolescents. Emerging research has also highlighted significant associations between migraine and bipolar disorder, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). Shared pathophysiological mechanisms, including genetic predisposition, neurotransmitter imbalances, hormonal influences, and environmental factors, contribute to these comorbidities. Diagnosing migraine in individuals with ASD and ADHD presents unique challenges due to overlapping symptoms and communication barriers. Furthermore, psychiatric medications may influence migraine symptoms, necessitating careful management. This review explores the relationship between migraine and psychiatric disorders, emphasizing shared mechanisms, diagnostic considerations, and treatment strategies to optimize patient care. This review highlights the necessity for integrated clinical approaches that address both migraine and psychiatric comorbidities, ultimately improving health outcomes for affected individuals.

1. Introduction

The close association between migraine and psychiatric comorbidities has long been recognized [1–3]. Both migraine and psychiatric comorbidities share several characteristics, including high prevalence, frequent underdiagnosis, significant impairment of daily functioning, and suboptimal treatment [4,5]. Moreover, when migraine and psychiatric disorders co-occur, their combined impact tends to be more severe [6]. Consequently, the identification and appropriate management of psychiatric comorbidities represent a crucial aspect of comprehensive migraine treatment. A thorough understanding of these comorbidities is therefore essential for optimizing migraine care.

Migraine and mood disorders, particularly depression and anxiety exhibit a significant comorbidity in pediatric population [7–9]. Among younger individuals, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are particularly noteworthy psychiatric conditions that frequently co-occur with mood disorders and with each other [10]. Recent research has further highlighted a significant association between migraine and both ASD and ADHD [11,12]. This review examines the relationship between migraine and mood disorders, ASD, and ADHD, with a focus on their shared mechanisms, diagnostic considerations, and treatment approaches.

2. Findings on the psychiatric comorbidities of migraine

2.1. Depression

The strong association between migraine and depression exists in pediatric populations. A meta-analysis of 51 studies demonstrated that children and adolescents with migraine faced a higher risk of developing depression, with an OR of 2.01 (95 % CI: 1.46–2.78) [13]. Conversely, adolescents with depression exhibited an increased prevalence of migraine, with an OR of 4.59 (95 % CI: 3.44–6.12) [9]. Although bidirectional comorbidity has not yet been confirmed through longitudinal follow-up in children and adolescents as it has in adults, the strong comorbid association observed in pediatric populations suggests a shared underlying pathogenesis [7,14].

2.1.1. Mechanism of comorbidity between depression and migraine

The comorbidity between depression and migraine has been

* Corresponding author at: Department of Neurology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
E-mail address: chumk@yonsei.ac.kr (M.K. Chu).

https://doi.org/10.1016/j.braindev.2025.104392
Received 18 March 2025; Received in revised form 27 June 2025; Accepted 29 June 2025
Available online 8 July 2025

attributed to genetic predisposition, neurotransmitter imbalances, hormonal influences, and shared environmental factors [15].

2.1.1.1. Genetic predisposition. Twin, family, and genetic studies have consistently demonstrated a strong relationship between migraine and depression, highlighting their shared genetic basis. Findings from twin and family studies indicate that both disorders exhibit significant heritability. Estimates for migraine heritability range from 0.33 to 0.53, suggesting that 33 % to 53 % of the phenotypic variance in migraine can be attributed to additive genetic effects [16,17]. Similarly, heritability estimates for depression range from 0.17 to 0.78 [18]. Notably, a heritability study that adjusted for depressive symptoms in individuals with migraine reported an estimate of 0.51 (95 % CI: 0.19–0.83), further reinforcing the genetic overlap between these conditions [14].

Genome-wide association studies (GWAS) have identified shared genetic variants between migraine and depression. A large GWAS involving 59,674 European individuals with migraine and 30,678 controls identified three novel single nucleotide polymorphisms (SNPs) (rs146377178, rs672931, and rs11858956) associated with both migraine and major depressive disorder (MDD) [19]. Additionally, gene-based association analyses identified two genes, *ANKDD1B* and *KCNK5*, that exceeded genome-wide significance thresholds [20]. Supporting this genetic link, the Brainstorm Consortium GWAS meta-analysis, which examined 25 brain disorders, found a significant correlation between migraine and MDD [21]. A replication study demonstrated that SNPs in previously identified migraine risk genes, including *REST, ADGRL2, HPSE2*, and the *1p31.1* locus, exhibited an association dependent on both disease status and lifetime history of depression [22]. These findings underscore the substantial genetic overlap between migraine and depression, suggesting shared biological mechanisms underlying their comorbidity.

2.1.1.2. Neurotransmitter imbalance. Serotonin imbalance is believed to play a critical role in the comorbidity between depression and migraine. Abnormalities in serotonin levels have been observed in both conditions, suggesting a shared pathophysiological mechanism. In migraine, plasma serotonin levels decrease between attacks and increase during acute episodes [23]. Similarly, a systematic review of 17 studies demonstrated a significant relationship between depressive symptoms and dysfunction in the serotonergic system [24].

From a therapeutic perspective, serotonin receptor agonists, such as triptans, as well as tricyclic antidepressants (TCA) and beta-blockers, have been shown to be effective in migraine management. Likewise, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly utilized in the treatment of depression [15]. Beyond serotonergic dysfunction, alterations in dopaminergic, glutamatergic, and neuropeptide Y systems have also been proposed as potential mechanisms contributing to the comorbidity between depression and migraine [25,26].

2.1.1.3. Hormonal factors. The prevalence of both migraine and depression is two to three times higher in women, suggesting that sex hormonal factors may play a role in their comorbidity [27,28]. Fluctuations in sex hormones, particularly declines in estrogen levels, have been implicated in the pathophysiology of both conditions [29]. A reduction in estrogen can lead to downregulation of the serotonergic system and upregulation of the sympathetic nervous system, contributing to the increased susceptibility to migraine and mood disorders. Conversely, progesterone has been shown to reduce the expression of the monoamine oxidase gene and decrease levels of monoamine oxidase, the primary enzyme responsible for serotonin degradation [29]. This mechanism can result in increased serotonin levels within the synaptic space, potentially alleviating symptoms of both depression and migraine.

2.1.1.4. Shared environmental factors. Family clustering of migraine and depression suggests the influence of shared environmental factors, in addition to genetic predisposition [30]. A twin study conducted in the United States provided evidence supporting the role of common environmental factors in the comorbidity of these conditions [31]. Chronic stress has been identified as a significant risk factor for both migraine and depression, thereby reinforcing the impact of environmental influences [32]. Additionally, studies reveal that women with both migraine and depression report a higher prevalence of childhood abuse compared to those without either condition, highlighting the potential contribution of early-life adversity to the development of these disorders [33].

2.1.1.5. Worsening depression in relation to migraine attacks. Recurrent migraine attacks can exacerbate depression primarily through shared neurobiological mechanisms, including dysregulation of serotonin neurotransmission, heightened release of neuropeptides such as calcitonin gene-related peptide (CGRP), and neuroinflammatory processes [3]. These alterations can induce structural and functional changes in brain regions responsible for both pain and mood regulation, particularly the medial prefrontal cortex and limbic system. Chronic migraine-related pain and stress may further disrupt emotional processing and resilience, creating a vicious cycle that intensifies depressive symptoms [15,26]. This relationship suggests that effective prophylactic treatment may improve both migraine and depressive symptoms in patients with comorbid migraine and depression. Indeed, clinical trials involving anti-CGRP monoclonal antibodies have demonstrated improvements in both conditions [34].

2.1.2. Diagnosis of patients with migraine and comorbid depression

With the exception of individuals with severe depression, most patients with comorbid migraine and depression do not experience significant communication difficulties, and their migraine symptoms are generally comparable to those of individuals with migraine without depression [35–37]. However, patients with migraine and comorbid depression often exhibit more severe symptoms than those with migraine but no depression. Depression has been identified as a significant risk factor for the progression from episodic migraine (EM) to chronic migraine (CM), a condition associated with greater symptom severity and disability [38]. Given the high prevalence of depression among individuals with migraine, routine assessment of depressive symptoms should be an integral component of the diagnostic process in clinical and hospital settings.

2.1.3. Treatment of patients with migraine and comorbid depression

Non-pharmacological interventions may play a critical role in managing pediatric patients with comorbid migraine and depression, offering safe and effective strategies that target both conditions. Cognitive behavioral therapy (CBT) has demonstrated efficacy in reducing both headache frequency and depressive symptoms in children and adolescents, particularly when combined with education about headache triggers and stress management techniques [39]. Other approaches such as biofeedback, relaxation training, and mindfulness-based interventions have also shown promise in improving emotional regulation and reducing migraine-related disability [40,41]. These interventions are especially valuable in pediatric populations where pharmacologic options may be limited due to concerns about side effects and long-term safety.

From a pharmacological perspective, certain medications used for migraine management can influence depressive symptoms. Beta-blockers, topiramate, and flunarizine—commonly prescribed for oral migraine prophylaxis—have been associated with the potential exacerbation of depressive symptoms [42–44]. Conversely, venlafaxine and duloxetine, widely used antidepressants, have demonstrated efficacy in migraine prophylaxis [45,46]. Botulinum toxin A, which is administered

for both CM and depression, has shown therapeutic benefits for both conditions [47,48]. Amitriptyline, a TCA, is frequently utilized for migraine prevention; however, the dosage required for migraine prophylaxis differs from that required to achieve its antidepressant effects [49]. Additionally, anti-calcitonin gene-related peptide (CGRP) antibodies, an effective class of migraine prophylactic agents, have been reported to alleviate both migraine and comorbid depression [50]. Given these interactions, a comprehensive approach to diagnosing and managing depression in patients with migraine is essential for optimizing treatment outcomes and improving overall patient well-being.

2.2. Anxiety

Anxiety is prevalent as a comorbidity of migraine in pediatric populations. A meta-analysis of 15 pediatric studies found an increased OR of 1.93 (95 % CI: 1.49–2.50) for anxiety in children and adolescents with migraine [13]. Children and adolescents with migraine are at significantly higher risk for anxiety disorders, particularly generalized anxiety disorder (GAD), phobias, and panic disorder. These anxiety-related conditions not only co-occur more frequently in this population but also appear to contribute to increased migraine frequency, chronicity, and functional impairment. For example, children with chronic daily headache exhibit elevated rates of GAD and panic symptoms, which are associated with poorer treatment response and greater disability [13,51]. Additionally, phobic disorders, including social phobia and specific phobias, have been shown to be more prevalent among pediatric migraine sufferers and are linked to psychosocial difficulties [52]. These findings underscore the importance of early identification and integrated management of anxiety symptoms in young patients with migraine.

2.2.1. Mechanism underlying the comorbidity between anxiety and migraine

Similar to depression, the comorbidity between anxiety and migraine has been attributed to multiple underlying mechanisms, including genetic predisposition, neurotransmitter imbalances, hormonal influences, and environmental factors. These shared pathophysiological pathways suggest a complex interplay contributing to the frequent co-occurrence of both conditions.

2.2.1.1. Genetic factors. A twin study conducted in the Netherlands reported a significant genetic correlation between anxious depression and migraine ($r = 0.30$, 95 % CI: 0.18–0.43), suggesting shared genetic vulnerability between these conditions [53]. Although not specific to migraine, a recent GWAS meta-analysis on anxiety disorders identified 47 local genetic correlations with other psychiatric disorders, including MDD, which has been strongly associated with migraine [20,54]. Furthermore, the glutamate pathway has been implicated in the pathophysiology of both migraine and anxiety disorders. A GWAS study identified an association between migraine and a SNP (rs1835740); this SNP is located near genes that regulate glutamate homeostasis, further supporting the role of excitatory neurotransmission dysregulation in the comorbidity of these conditions [55].

2.2.1.2. Neurotransmitters. Dysfunction of serotonin, dopamine, and gamma aminobutyric acid (GABA) has been proposed as a key mechanism underlying the comorbidity of anxiety and migraine. Serotonin, a neurotransmitter involved in mood regulation and pain modulation, has been shown to be altered in both conditions, suggesting a shared pathophysiological pathway [56,57]. Dopamine also plays a crucial role in both anxiety and migraine, with evidence indicating that comorbid migraine and anxiety are associated with dopamine D2 receptor *NcoI* alleles [58,59]. Additionally, certain dopamine antagonists have been found to alleviate symptoms of both migraine and anxiety, further supporting the role of dopaminergic dysregulation in their co-occurrence [60].

2.2.1.3. Role of hormones. Sex hormones play a critical role in the comorbidity of anxiety and migraine, similar to their involvement in depression. Evidence suggests that anxiety symptoms often exacerbate during migraine attacks, particularly during estrogen withdrawal just before the onset of menstruation [61]. Additionally, perimenopause, a phase marked by significant hormonal fluctuations, has been associated with increased migraine activity and heightened vulnerability to mood disturbances, including anxiety [62]. These findings highlight the influence of hormonal regulation in the overlapping pathophysiology of migraine and anxiety disorders.

2.2.1.4. Worsening anxiety in relation to migraine attacks. Recurrent migraine attacks may worsen anxiety through several interconnected mechanisms, including heightened sensitization and hyperexcitability of limbic structures such as the amygdala, insula, and prefrontal cortex, dysregulation of serotonergic pathways, and maladaptive stress responses involving the hypothalamic–pituitary–adrenal axis [25,63]. These neurobiological alterations foster a persistent state of threat perception and emotional dysregulation. Moreover, repeated pain episodes may heighten anxiety sensitivity and promote catastrophic interpretations of bodily sensations, leading to avoidance behaviors and further amplification of anxiety.

2.2.2. Diagnosis of patients with migraine and comorbid anxiety

The diagnosis of migraine in patients with comorbid anxiety follows a similar approach to that of comorbid depression, another mood disorder. Most patients exhibit enough symptoms to confirm a diagnosis, though severe anxiety may complicate or influence this process. Notably, comorbid anxiety is more prevalent than comorbid depression, and migraine symptoms tend to be more severe in individuals with co-occurring anxiety [64]. Therefore, it is crucial to assess anxiety in patients with migraine who seek medical care, as they often present with more severe symptoms. Moreover, anxiety frequently coexists with depression, and the presence of both conditions further exacerbates migraine severity and associated distress [6,65] (See Fig. 1). These findings underscore the importance of comprehensive psychiatric evaluation in migraine management to improve patient outcomes.

2.2.3. Treatment of patients with migraine and comorbid anxiety

Non-pharmacological treatments such as CBT, biofeedback, relaxation training, and mindfulness-based interventions have demonstrated effectiveness in reducing headache frequency, improving anxiety symptoms, and enhancing quality of life in pediatric migraine [39,66,67]. Among these, CBT shows the most robust evidence, particularly when combined with medication, outperforming education or standard care alone. These interventions are increasingly recommended as first-line or adjunctive therapies for managing migraine in children and adolescents. Pharmacological interventions effective for both anxiety and migraine can be utilized in the management of migraine comorbid with anxiety. Although SSRIs have not demonstrated efficacy in migraine treatment through clinical trials, their use in panic disorder may alleviate comorbid migraine symptoms [68]. SNRIs, such as venlafaxine and duloxetine, have shown efficacy in treating both anxiety and depression, suggesting potential benefits for comorbid migraine [69]. Pregabalin, which is used for the treatment of GAD, has been suggested as a prophylactic option for CM based on findings from an open-label study [70]. Additionally, topiramate, a well-established prophylactic medication for migraine, has demonstrated effectiveness in treating social phobia [71].

2.3. Bipolar disorder

The association between bipolar disorder (BD) and migraine in

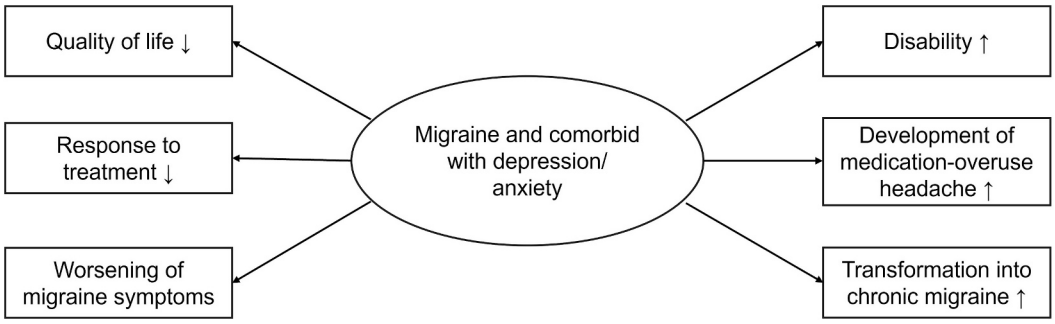

Fig. 1. The impact of comorbid depression/anxiety and migraine on migraine outcomes.

children and adolescents has been increasingly recognized, although empirical evidence remains limited compared to adult populations. Epidemiological data indicate that the prevalence of migraine is markedly higher in youth with BD compared to healthy controls, with some studies reporting an adjusted odds ratio as high as 14.76 [72]. This comorbidity is particularly notable in bipolar II and bipolar NOS subtypes, and is often associated with greater affective lability, higher severity of depressive symptoms, and increased functional impairment. Familial studies further support this relationship, showing that parental history of migraine increases the risk of BD in offspring, independent of parental BD status [73].

2.3.1. *Mechanisms underlying the comorbidity of BD and migraine*

BD shares high heritability with other mood disorders. In addition, a family history of BD has been reported to be associated with an increased risk of developing migraines [74,75]. These results suggest that genetic factors contribute not only to the development of BD and migraines individually but also to their co-occurrence. Similar to other mood disorders discussed above, serotonergic, dopaminergic, and glutaminergic dysfunction are implicated in the pathogenesis of BD; therefore, abnormalities in these neurotransmitter systems in individuals with migraine may contribute to the observed comorbidity [76–78].

2.3.1.1. Worsening BD in relation to migraine attacks. Recurrent migraine in children and adolescents is significantly associated with increased risk and severity of BD, with comorbidity linked to worse psychiatric outcomes, including more frequent depressive episodes, affective lability, and functional impairment [72]. Shared pathophysiological mechanisms include dysregulated serotonergic, dopaminergic, and glutamatergic signaling, genetic vulnerability, chronic neuroinflammation, and mitochondrial dysfunction [79]. Elevated proinflammatory cytokines (e.g., TNF-α, IL-1β, IFN-γ), oxidative stress, and sleep disturbances may further contribute to mood instability. These findings underscore the need for early recognition and integrated treatment approaches to prevent illness progression in affected youth.

2.3.2. *Diagnosis of patients with migraine and comorbid BD*

BD is less prevalent than other mood disorders such as anxiety and depression; however, it still affects a significant proportion of the population. Like other mood disorders, BD frequently co-occurs with migraine [80]. It is crucial to distinguish BD from depression or anxiety when diagnosing mood disorders, as these conditions may manifest at different times. Moreover, BD is often associated with greater symptom severity and functional impairment compared to unipolar mood disorders, underscoring the importance of accurate diagnosis and appropriate clinical management [81].

2.3.3. *Treatment of patients with migraine and comorbid BD*

In children and adolescents with comorbid BD and migraine, non-pharmacological treatment should be comprehensive and individualized. Effective strategies include family-based psychoeducation, cognitive-behavioral therapy, and social rhythm therapy for mood stabilization, along with behavioral interventions such as biofeedback, relaxation, mindfulness, and lifestyle modifications for migraine [82]. Non-invasive neuromodulation and nutraceuticals may also be considered when medication is limited, supporting an integrated approach to managing both conditions.

Among the pharmacological treatments with established mood-stabilizing properties in BD, valproate and topiramate have also demonstrated efficacy in managing migraine [83]. Additionally, some evidence supports the effectiveness of lamotrigine in preventing migraine, particularly in cases of migraine with aura [84]. The shared mechanisms of action of these medications suggest a potential overlap in the pathophysiological processes underlying both BD and migraine. Conversely, the use of SSRIs and, to an even greater extent, SNRIs has been associated with an increased risk of exacerbating manic episodes or inducing a more rapid cycling course in BD [85]. Given that migraine frequently precedes the diagnosis of BD, the use of antidepressants to manage migraine or early depressive symptoms may inadvertently trigger manic episodes [86]. This highlights the potential risk of misdiagnosis and inappropriate treatment in patients with comorbid BD and migraine, underscoring the need for careful clinical evaluation and therapeutic decision-making.

2.4. *ASD*

ASD is a complex neurobehavioral disorder characterized by difficulties in social interaction and communication, distinctive behaviors, and altered sensory processing [87]. ASD is postulated to result from various pathological processes that lead to characteristic behaviors, and it is seen in conjunction with a wide range of conditions [88,89]. Migraine has been reported as one of the various comorbidities of ASD. To date, three studies have reported the co-occurrence of ASD and migraine, documenting a high prevalence of migraines in individuals with ASD [90–92]. A summarization of the noteworthy findings from studies on the comorbidity between ASD and migraine is presented in Table 1. Moreover, individuals with ASD who have migraines also have other psychiatric conditions, such as depression and anxiety [90].

2.4.1. *Mechanism behind the comorbidity of ASD and migraine*

Both ASD and migraine exhibit sensory hypersensitivity, with research indicating partially overlapping neurobiological mechanisms, such as altered thalamocortical connectivity and neurotransmitter dysregulation (GABA, serotonin, et al.), as well as shared genetic risk in ion channel genes (e.g., *CACNA1A, SCN1A*) [93]. However, while ASD-related hypersensitivity is pervasive and interacts with social-emotional regulation, migraine hypersensitivity is episodic and closely linked to trigeminothalamic pathway sensitization, highlighting both shared and distinct mechanisms. This shared hypersensitivity may be the mechanism for the coexistence of the two conditions [94,95]. Serotonin has been implicated in both pain sensitivity and abnormal

Table 1
A brief overview of the studies on the comorbidity between autism spectrum disorder and migraine.

Studies	Setting	Participants	Frequency of migraine	Other findings
Underwood et al., 2019 [91]	Data was obtained from the National Centre for Mental Health, UK	105 adults with ASD having intellectual disability; 76 matched controls	42.7 % in adults with ASD and 20.5 % in controls	High rate of comorbid psychiatric disorders, including depression (62.9 %) and anxiety (55.2 %), in adults with ASD.
Sullivan et al., 2014 [90]	Online survey, USA	81 children with ASD; no control participants	28.4 %	High sensory hyperactivity in children with ASD having migraine.
Victorio, 2014 [92]	Retrospective chart review, Denmark	18 patients with ASD	11 (61 %) patients; 8 had migraine without aura and 3 had migraine with aura	

ASD, autism spectrum disorder.

behavior in individuals with ASD [96]. Dysregulation of serotonin in the central nervous system has been respectively reported in children with ASD [97], and altered serotonin levels in the brain and blood were also observed [98]. Changes in regional activity in ASD correlate spatially with several key neurotransmitter systems, including dopaminergic, glutamatergic, GABA, and cholinergic systems, where changes are also observed in migraine [99]. Neuroinflammation plays significant roles in migraine, while mast cell-mediated neuroinflammation is hypothesized to play a role in ASD [100,101]. A wide range of gastrointestinal signs and symptoms are present in both migraine and ASD [102]. Such gastrointestinal symptomatology is attributed to a dysfunctional gut–brain axis in both migraine and ASD [103,104]. Genes such as *CACNA1A* and their homologs have been implicated in both migraine and ASD [105,106].

2.4.2. Diagnosis of migraine in children and adolescents with ASD

Diagnosing migraine in children and adolescents with ASD is challenging due to communication difficulties, atypical symptom expression, and the limitations of adult-oriented diagnostic criteria. Unlike adults, these children may be unable to describe headache characteristics, instead expressing pain through behavioral changes such as irritability, withdrawal, or aggression. Sensory abnormalities common in ASD, such as baseline light or sound sensitivity, can mask migraine-associated symptoms. Additionally, comorbid conditions (e.g., ADHD, epilepsy) and medications may confound the clinical picture. The current migraine criteria, the third edition of International Classification of Headache Disorders, reliant on verbal self-report and typical symptom profiles, may not capture the full spectrum of migraine presentations in this population, often leading to underdiagnosis or misdiagnosis. Clinical judgment based on behavioral cues and caregiver observations is essential [107].

When obtaining a medical history from children and adolescents with ASD, clinicians should collect a comprehensive medical and psychiatric history, family history, potential headache triggers, and sleep patterns from both the child and their parents or caregivers. If the history reveals any "red flags" suggestive of an alternative underlying cause for headaches, appropriate diagnostic testing should be conducted to assess for secondary etiologies.

2.4.3. Treatment of migraine in patients with ASD

In children and adolescents with both migraine and ASD, non-pharmacological treatments must be tailored to address sensory sensitivities, communication difficulties, and behavioral rigidity. Strategies such as structured routines, visual supports, sensory modulation tools (e.g., noise-canceling headphones), and simplified relaxation techniques can be effective when individualized [67,108,109]. Parental involvement and school-based accommodations are also essential.

In principle, the treatment of migraine in children with ASD follows the same approach as in children without ASD. Acute treatment is essential for most children with ASD, and if acute therapy proves inadequate or headache frequency is high, prophylactic treatment should be considered. The selection of prophylactic medication should account for its potential effects on ASD-related symptoms. For instance, if comorbid depression is present, medications that address both depression and migraine, such as SNRIs, may be preferred. Although topiramate is commonly used for migraine prophylaxis, it is associated with cognitive decline. If behavioral deterioration occurs following the use of topiramate, transitioning to an alternative prophylactic medication should be considered.

2.5. Attention-deficit/hyperactivity disorder

The association between primary headaches and ADHD has been long recognized. Furthermore, headaches are frequently reported as side effects of stimulant medications, which remain the most effective treatment for ADHD. Both migraine and ADHD exhibit high comorbidity with anxiety, depression, and sleep disorders and are strongly influenced by genetic factors [55,110]. Despite these commonalities, both conditions can significantly impact an individual's functioning, including academic and occupational performance [111,112]. A systematic review of 14 studies identified a positive association between ADHD and migraine, with an odds ratio of 1.322 (95 % confidence interval: 1.018–1.717). However, this significant association was not observed in individuals with tension-type headaches [113]. A summarization of the noteworthy findings from studies on the comorbidity between ADHD and migraine is presented in Table 2.

2.5.1. Mechanisms underlying comorbidity of ADHD and migraine

The comorbidity between ADHD and migraine has been attributed to shared neurobiological pathways, genetic factors, autonomic nervous system dysfunction, and inflammatory processes. Dysregulation of the dopaminergic system is implicated in both conditions, as dopamine plays a critical role in attention regulation and pain modulation. Abnormalities in dopamine transmission may therefore contribute to the pathophysiology of both ADHD and migraine [114,115]. Genetic studies further support this association, demonstrating that individuals with ADHD are more likely to have relatives with a history of migraine, suggesting a hereditary component [116]. Both migraine and ADHD are associated with abnormal ANS function. ANS dysfunction is evident through symptoms like alterations in heart rate and blood pressure, gastrointestinal disturbances, and other autonomic manifestations during migraine attacks [117]. Similarly, individuals with ADHD may exhibit signs of ANS dysregulation, including irregular heart rate and blood pressure, which could be linked to the characteristic hyperactivity and impulsivity associated with the disorder [118]. Chronic inflammation has been proposed as a potential link between the two conditions, as elevated levels of pro-inflammatory cytokines have been observed in both ADHD and migraine, indicating a possible role of systemic inflammation in their comorbidity [119,120].

2.5.2. Diagnosis of migraine in patients with ADHD

Diagnosing migraine in patients with ADHD is challenging due to overlapping symptoms, medication effects, and comorbidities. Clinical

Table 2
A brief overview of the studies on the comorbidity between attention-deficit/hyperactivity disorder and migraine or headache.

Studies	Setting	Participants	Findings
Fasmer et al., 2012 [139]	Norwegian prescription database	18,481 anti-ADHD drug users	Odds ratio for anti-migraine drugs among ant-ADHD drug users: 1.76–2.81. 2.4 % of men and 8.5 % of women who were prescribed anti-ADHD drugs also received prescriptions for antimigraine drugs.
Fasmer et al., 2011 [110]	Cross-sectional and case-control study, Norway	572 adults with ADHD; 675 controls	The prevalence of migraine was 28.3 % (OR = 1.67; 95 % CI: 1.28–2.17). High depression, anxiety, and bipolar disorder in ADHD group
Arruda et al., 2014 [140]	Cross-sectional population study, Brazil	846 children	Children with migraine had a higher risk of adjustment
Genizi et al., 2013 [141]	Retrospective chart review, Israel	243 children and adolescents with primary headaches	28 % of children and adolescents with primary headaches had ADHD.
Pavone et al., 2012 [142]	Retrospective case-control, Italy	560 children in a university hospital	No significant difference in the frequency of ADHD between headache and control groups.
Riva et al., 2011 [143]	Prospective case-control, Italy	43 and 19 children with migraine and tension-type headache; 52 controls	No significant difference in the frequency of ADHD among the three groups
Genizi et al., 2016 [144]	Prospective cohort, Israel	230 10th grade students	No significant difference in the frequency of ADHD between headache (27 %) and control (23 %) groups.
Strine et al., 2006 [145]	Population-based study, USA	9264 children	Children with headache were 3.2 times more likely to have difficulties compared those without headache
Lateef et al., 2009 [146]	Cross-sectional, USA	10,918 children	17.1 % had migraine. Children with headache had more learning disabilities (14.62 %, OR = 1.59; 95 % CI: 1.26–2.02)
Pitrou et al., 2010 [147]	Cross-sectional, France	2324 children	Children with headache had a higher risk of ADHD, Odds ratio: 2.02 (95 % CI: 1.16–3.51)
Jameson et al., 2016 [148]	Cross-sectional, USA	550 adolescents with ADHD; 5933 controls	Adolescent with ADHD had a higher risk of migraine (37.3 %) than controls (31.6 %, OR: 1.46; 95 % CI: 1.07–1.98)
Arruda et al., 2012 [149]	Cross-sectional, Brazil	5671 children	Children with migraine showed poor school performance.
Arruda et al., 2010 [150]	Population study, Brazil	1856 children	Children with migraine (23.7 %, RR: 2.6; 95 % CI: 1.6–4.2) and tension-type headache (18.4 %, RR: 2.1; 95 % CI: 1.4–3.2) had a higher risk of ADHD than those without headache (8.1 %).
Mazzone et al., 2006 [151]	Cross-sectional, Italy	67 and 47 children with migraine and tension-type headache; 36 controls	Hypersensitivity symptoms were elevated in migraine and tension-type headache groups compared to controls

ADHD, attention-deficit/hyperactivity disorder; OR, odds ratio; CI, confidence interval; RR, relative risk.

features such as difficulties in concentration and heightened sensitivity to external stimuli, common to both conditions, may lead to diagnostic ambiguity [110]. Both conditions share cognitive impairments, such as difficulty concentrating and sensitivity to stimuli, increasing the risk of symptom misattribution [121]. Additionally, ADHD medications, particularly stimulants, may induce headaches, complicating the distinction between medication side effects and migraine episodes [122]. The frequent coexistence of ADHD with mood disorders, which are also linked to migraine, further obscures the diagnostic process. Moreover, attention and memory deficits in ADHD can lead to inconsistent symptom reporting, hindering accurate diagnosis and management [121]. A comprehensive, multidisciplinary approach is essential for effectively assessing and treating migraine in individuals with ADHD.

2.5.3. *Treatment of migraine in patients with ADHD*

In children and adolescents with migraine and comorbid ADHD, non-pharmacological treatments include behavioral therapy, CBT, neurofeedback, biofeedback, mindfulness-based interventions, executive function training, and lifestyle modifications such as regular exercise, healthy diet, and sleep hygiene [66,123]. These approaches aim to improve both headache and ADHD symptoms by enhancing emotional regulation, attention, and coping skills, while avoiding the potential side effects of medication. Neurofeedback and biofeedback have shown promise in reducing behavioral problems, anxiety, and hyperactivity, while behavioral interventions and mindfulness can further support self-regulation and functional outcomes [124].

In principle, the treatment of migraine in individuals with ADHD follows a similar approach to that used in individuals without ADHD, encompassing acute therapy for headache relief and preventive measures when necessary [125]. However, certain ADHD medications may exacerbate migraine symptoms, requiring careful assessment to determine whether symptom worsening is attributable to pharmacological treatment [110]. In addition to medication, non-pharmacological interventions such as trigger avoidance, regular physical activity, and stress management are commonly recommended [126]. Individuals with ADHD, are, however, more susceptible to lifestyle factors that may aggravate migraine, including irregular sleep patterns, inconsistent dietary habits, and heightened stress levels. Consequently, addressing these factors is an integral component of the treatment plan. Moreover, comorbid mood disorders, such as depression and anxiety, frequently coexist with both migraine and ADHD, potentially exacerbating symptom severity. Therefore, effective management of these conditions is essential to optimize treatment outcomes and enhance overall patient well-being.

3. Additional psychiatric conditions comorbid with migraine

Post-traumatic stress disorder (PTSD), substance use, somatoform disorders, and eating disorders have been identified as having significant associations with migraine in pediatric population. Pediatric migraine is increasingly recognized to co-occur with PTSD in children and adolescents, with trauma exposure contributing to migraine severity and frequency. Studies focusing specifically on pediatric populations

report that PTSD symptoms exacerbate migraine-related disability and psychological distress [127,128]. Early identification and trauma-informed care are critical in managing these comorbidities in children [129].

The relationship between pediatric migraine and substance use disorders is complex and somewhat inconsistent across studies. While some research in adolescents suggests an increased risk of substance use, such as alcohol and drug abuse among migraineurs, other studies have not confirmed a direct association [130,131]. The high comorbidity between bipolar disorder and substance use may partly explain these discrepancies. In clinical populations, substance use disorders often co-occur with a variety of psychiatric conditions, including migraine, and may complicate both diagnosis and management in pediatric patients [132].

Somatoform disorders, particularly in the form of somatoform headaches, are frequently observed in children and adolescents with migraine. Approximately 10 % of pediatric patients presenting with headache in neurology settings may exhibit somatoform features. These children often have additional biological and psychosocial risk factors, such as coexisting psychological disorders, chronic illness, or dysfunctional family environments [133]. The overlap between migraine and somatoform symptoms, including vertigo and dizziness, is particularly prominent in adolescent girls, highlighting the need for comprehensive psychological assessment in pediatric headache management [134].

There is growing evidence of a significant association between migraine and eating disorders in pediatric populations, including anorexia nervosa, bulimia nervosa, and binge eating disorder. Studies have shown that symptoms of eating disorders are more prevalent among teenagers with migraine, especially in females, with bulimia nervosa symptoms being 1.5 times more likely in migraineurs [135,136]. Furthermore, migraine severity and disability scores positively correlate with disordered eating attitudes, anxiety, and depression, suggesting shared neurobiological and psychosocial risk factors [136]. A Finnish study of adolescents reported that the prevalence of migraine was nearly twice as high in women with anorexia nervosa or bulimia nervosa compared to those without an eating disorder (22 % vs. 11 %) [137]. However, further analysis revealed that this association was mediated by depression, suggesting that eating disorders may increase migraine risk in certain subgroups through comorbid psychiatric conditions, such as anxiety and depression. Given the established link between eating disorders and depression, clinicians should remain vigilant for depressive symptoms in individuals with migraine who are underweight or experiencing rapid weight changes. Additionally, specific behaviors associated with eating disorders, such as dieting, fasting, or skipping meals, are commonly reported migraine triggers [138].

4. Conclusions

This review examines the relationship between migraine and various psychiatric comorbidities focusing pediatric populations. Psychiatric comorbidity is more common in severe forms of migraine or CM and medication-overuse headache, with depression identified as a significant factor in the transformation of CM from EM. Individuals with migraine have an increased risk of depression and anxiety, and vice versa. Recently, BD and substance abuse have also been reported to have a significant relationship with migraine. The close relationship between migraine and mood disorders suggests a shared pathogenesis and contributes to our understanding of the pathogenesis of migraine and mood disorders. To date, reports of ASD and ADHD comorbidity with migraine are scarce; however, most studies have reported a significant association. Unlike mood disorders, diagnosing migraines in patients with ASD and ADHD can be particularly challenging, owing to the overlapping symptoms and a tendency for under-reporting. In addition, medications for ASD and ADHD may affect migraine symptoms. Therefore, evaluating psychiatric comorbidities is a crucial aspect of migraine management. If such psychiatric comorbidities are identified, they should be carefully addressed and appropriately treated. Nevertheless, it remains essential to conduct thorough migraine evaluations and provide appropriate treatment, even when a psychiatric disorder is diagnosed.

Ethics approval and consent to participate

Not applicable.

Author contributions

JY: study design; acquisition, analysis, and interpretation of data; and drafting and revising the manuscript. MKC: study conception and design, data analysis and interpretation, and manuscript drafting and revision. All authors have read approved the final version of the manuscript.

Funding

This study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant No.: HV22C0106), and a National Research Foundation of Korea (NRF) grant from the Korean government (MSIT) (Grant No.: 2022R1A2C1091767). The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Declaration of generative AI in scientific writing

During the preparation of this work, the authors used ChatGPT 4.0 to improve language and readability. After using this tool/service, the authors carefully reviewed and edited the content as needed, thereby taking full responsibility for the final publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MKC was the site investigator for a multicenter trial sponsored by Abbvie Inc., Pfizer Inc., and SK Biopharm; he has received lecture honoraria from Abbvie Inc., Handok-Teva, Organon Korea, and the SK Chemical Company over the past 24 months. Additionally, he has received grants from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant No.: HV22C0106), and National Research Foundation of Korea (2022R1A2C1091767). JY declares no conflicts of interest.

Acknowledgments

None.

References

[1] Radat F, Swendsen J. Psychiatric comorbidity in migraine: a review. Cephalalgia 2005;25:165–78.
[2] Dresler T, Caratozzolo S, Guldolf K, Huhn JI, Loiacono C, Niiberg-Pikksoot T, et al. Understanding the nature of psychiatric comorbidity in migraine: a systematic review focused on interactions and treatment implications. J Headache Pain 2019;20:51.
[3] Minen MT, Begasse De Dhaem O, Kroon Van Diest A, Powers S, Schwedt TJ, Lipton R, et al. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 2016;87:741–9.
[4] Miller S, Matharu MS. Migraine is underdiagnosed and undertreated. Practitioner 2014;258(19–24):2–3.
[5] Davidson JR, Meltzer-Brody SE. The underrecognition and undertreatment of depression: what is the breadth and depth of the problem? J Clin Psychiatry 1999;60(Suppl. 7):4–9.
[6] Lipton RB, Seng EK, Chu MK, Reed ML, Fanning KM, Adams AM, et al. The effect of psychiatric comorbidities on headache-related disability in migraine: results

from the chronic migraine epidemiology and outcomes (CaMEO) study. Headache 2020;60:1683–96.
[7] Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology 2003;60:1308–12.
[8] Giri S, Tronvik EA, Hagen K. The bidirectional temporal relationship between headache and affective disorders: longitudinal data from the HUNT studies. J Headache Pain 2022;23:14.
[9] Orr SL, Potter BK, Ma J, Colman I. Migraine and mental health in a population-based sample of adolescents. Can J Neurol Sci 2017;44:44–50.
[10] Hours C, Recasens C, Baleyte JM. ASD and ADHD comorbidity: what are we talking about? Front Psych 2022;13:837424.
[11] Hansen TF, Hoeffding LK, Kogelman L, Haspang TM, Ullum H, Sørensen E, et al. Comorbidity of migraine with ADHD in adults. BMC Neurol 2018;18:147.
[12] Vetri L. Autism and migraine: an unexplored association? Brain Sci 2020;10:615.
[13] Falla K, Kuziek J, Mahnaz SR, Noel M, Ronksley PE, Orr SL. Anxiety and depressive symptoms and disorders in children and adolescents with migraine: a systematic review and Meta-analysis. JAMA Pediatr 2022;176:1176–87.
[14] Stam AH, de Vries B, Janssens AC, Vanmolkot KR, Aulchenko YS, Henneman P, et al. Shared genetic factors in migraine and depression: evidence from a genetic isolate. Neurology 2010;74:288–94.
[15] Zhang Q, Shao A, Jiang Z, Tsai H, Liu W. The exploration of mechanisms of comorbidity between migraine and depression. J Cell Mol Med 2019;23:4505–13.
[16] Gervil M, Ulrich V, Kaprio J, Olesen J, Russell MB. The relative role of genetic and environmental factors in migraine without aura. Neurology 1999;53:995–9.
[17] Ulrich V, Gervil M, Kyvik KO, Olesen J, Russell MB. The inheritance of migraine with aura estimated by means of structural equation modelling. J Med Genet 1999;36:225–7.
[18] Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157:1552–62.
[19] Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 2016;48:856–66.
[20] Yang Y, Zhao H, Boomsma DI, Ligthart L, Belin AC, Smith GD, et al. Molecular genetic overlap between migraine and major depressive disorder. Eur J Hum Genet 2018;26:1202–16.
[21] Consortium TB, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al. Analysis of shared heritability in common disorders of the brain. Science 2018;360.
[22] Petschner P, Baksa D, Hullam G, Torok D, Millinghoffer A, Deakin JFW, et al. A replication study separates polymorphisms behind migraine with and without depression. PLoS One 2021;16:e0261477.
[23] Ferrari MD, Saxena PR. On serotonin and migraine: a clinical and pharmacological review. Cephalalgia 1993;13:151–65.
[24] Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Mol Psychiatry 2023;28:3243–56.
[25] Altamura C, Corbelli I, de Tommaso M, Di Lorenzo C, Di Lorenzo G, Di Renzo A, et al. Pathophysiological bases of comorbidity in migraine. Front Hum Neurosci 2021;15:640574.
[26] Viudez-Martínez A, Torregrosa AB, Navarrete F, García-Gutiérrez MS. Understanding the biological relationship between migraine and depression. Biomolecules 2024;14:163.
[27] Holsen LM, Spaeth SB, Lee JH, Ogden LA, Klibanski A, Whitfield-Gabrieli S, et al. Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. J Affect Disord 2011;131:379–87.
[28] Cohen F, Brooks CV, Sun D, Buse DC, Reed ML, Fanning KM, et al. Prevalence and burden of migraine in the United States: a systematic review. Headache 2024;64:516–32.
[29] Martin VT, Behbehani M. Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis–part 2. Headache 2006;46:365–86.
[30] Yang Y, Zhao H, Heath AC, Madden PA, Martin NG, Nyholt DR. Familial aggregation of migraine and depression: insights from a large Australian twin sample. Twin Res Hum Genet 2016;19:312–21.
[31] Schur EA, Noonan C, Buchwald D, Goldberg J, Afari N. A twin study of depression and migraine: evidence for a shared genetic vulnerability. Headache 2009;49:1493–502.
[32] Blackburn-Munro G, Blackburn-Munro RE. Chronic pain, chronic stress and depression: coincidence or consequence? J Neuroendocrinol 2001;13:1009–23.
[33] Tietjen GE, Brandes JL, Digre KB, Baggaley S, Martin VT, Recober A, et al. History of childhood maltreatment is associated with comorbid depression in women with migraine. Neurology 2007;69:959–68.
[34] Lipton RB, Ramirez Campos V, Roth-Ben Arie Z, Galic M, Mitsikostas D, Tassorelli C, et al. Fremanezumab for the treatment of patients with migraine and comorbid major depressive disorder: the UNITE randomized clinical trial. JAMA Neurol 2025;82(6):560–9.
[35] Alwhaibi M, Balkhi B, AlRuthia Y. Anxiety and depression and health-related quality of life among adults with migraine: a National Population-Based Study. Front Public Health 2023;11:1241800.
[36] Saunders K, Merikangas K, Low NC, Von Korff M, Kessler RC. Impact of comorbidity on headache-related disability. Neurology 2008;70:538–47.
[37] Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric disorders–a national population-based study. Headache 2008;48:501–16.
[38] Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC, et al. Depression and risk of transformation of episodic to chronic migraine. J Headache Pain 2012;13:615–24.
[39] Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. JAMA 2013;310:2622–30.
[40] Stokes DA, Lappin MS. Neurofeedback and biofeedback with 37 migraineurs: a clinical outcome study. Behav Brain Funct 2010;6:9.
[41] Seng EK, Singer AB, Metts C, Grinberg AS, Patel ZS, Marzouk M, et al. Does mindfulness-based cognitive therapy for migraine reduce migraine-related disability in people with episodic and chronic migraine? A phase 2b pilot randomized clinical trial. Headache 2019;59:1448–67.
[42] Celano CM, Freudenreich O, Fernandez-Robles C, Stern TA, Caro MA, Huffman JC. Depressogenic effects of medications: a review. Dialogues Clin Neurosci 2011;13:109–25.
[43] Micheli FE, Pardal MM, Giannaula R, Gatto M, Parera I, Paradiso G, et al. Movement disorders and depression due to flunarizine and cinnarizine. Mov Disord 1989;4:139–46.
[44] Bornand D, Reinau D, Jick SS, Meier CR. β-Blockers and the risk of depression: a matched case-control study. Drug Saf 2022;45:181–9.
[45] Hedayat M, Nazarbaghi S, Heidari M, Sharifi H. Venlafaxine can reduce the migraine attacks as well as amitriptyline: a noninferiority randomized trial. Clin Neurol Neurosurg 2022;214:107151.
[46] Young WB, Bradley KC, Anjum MW, Gebeline-Myers C. Duloxetine prophylaxis for episodic migraine in persons without depression: a prospective study. Headache 2013;53:1430–7.
[47] Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives NJ, et al. Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine. BMJ Open 2019;9:e027953.
[48] Parsaik AK, Mascarenhas SS, Hashmi A, Prokop LJ, John V, Okusaga O, et al. Role of botulinum toxin in depression. J Psychiatr Pract 2016;22:99–110.
[49] Doyle Strauss L, Weizenbaum E, Loder EW, Rizzoli PB. Amitriptyline dose and treatment outcomes in specialty headache practice: a retrospective cohort study. Headache 2016;56:1626–34.
[50] de Vries Lentsch S, van der Arend BWH, de Boer I, van Zwet EW, MaassenVanDenBrink A, Terwindt GM. Depression and treatment with anti-calcitonin gene related peptide (CGRP) (ligand or receptor) antibodies for migraine. Eur J Neurol 2024;31:e16106.
[51] Slater SK, Kashikar-Zuck SM, Allen JR, LeCates SL, Kabbouche MA, O'Brien HL, et al. Psychiatric comorbidity in pediatric chronic daily headache. Cephalalgia 2012;32:1116–22.
[52] Vulić-Prtorić A, Galić S, Renata C, Marina G, Lopižić J, Patricija P. Anxiety in children with headaches. Psihologijske teme 2007;16:201–24.
[53] Ligthart L, Nyholt DR, Penninx BW, Boomsma DI. The shared genetics of migraine and anxious depression. Headache 2010;50:1549–60.
[54] Friligkou E, Løkhammer S, Cabrera-Mendoza B, Shen J, He J, Deiana G, et al. Gene discovery and biological insights into anxiety disorders from a large-scale multi-ancestry genome-wide association study. Nat Genet 2024;56:2036–45.
[55] Anttila V, Stefansson H, Kallela M, Todt U, Terwindt GM, Calafato MS, et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet 2010;42:869–73.
[56] Raudenská J, Macko T, Vodičková Š, Buse DC, Javůrková A. Anxiety disorders, anxious symptomology and related Behaviors associated with migraine: a narrative review of prevalence and impact. Curr Pain Headache Rep 2025;29:40.
[57] Gasparini CF, Smith RA, Griffiths LR. Genetic and biochemical changes of the serotonergic system in migraine pathobiology. J Headache Pain 2017;18:20.
[58] Mascia A, Afra J, Schoenen J. Dopamine and migraine: a review of pharmacological, biochemical, neurophysiological, and therapeutic data. Cephalalgia 1998;18:174–82.
[59] Dong MX, Chen GH, Hu L. Dopaminergic system alteration in anxiety and compulsive disorders: a systematic review of neuroimaging studies. Front Neurosci 2020;14:608520.
[60] Kluge M, Schüssler P, Steiger A. Persistent generalized anxiety after brief exposure to the dopamine antagonist metoclopramide. Psychiatry Clin Neurosci 2007;61:193–5.
[61] Kundakovic M, Rocks D. Sex hormone fluctuation and increased female risk for depression and anxiety disorders: from clinical evidence to molecular mechanisms. Front Neuroendocrinol 2022;66:101010.
[62] Peterlin BL, Katsnelson MJ, Calhoun AH. The associations between migraine, unipolar psychiatric comorbidities, and stress-related disorders and the role of estrogen. Curr Pain Headache Rep 2009;13:404–12.
[63] Kumar R, Asif S, Bali A, Dang AK, Gonzalez DA. The development and impact of anxiety with migraines: a narrative review. Cureus 2022;14:e26419.
[64] Oh K, Cho SJ, Chung YK, Kim JM, Chu MK. Combination of anxiety and depression is associated with an increased headache frequency in migraineurs: a population-based study. BMC Neurol 2014;14:238.
[65] Song TJ, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Anxiety and depression in probable migraine: a population-based study. Cephalalgia 2017;37:845–54.
[66] Baglioni V, Bozza F, Beatrice A, Cameli N, Colacino Cinnante EM, Lentini G, et al. Non-pharmacological treatments in paediatric migraine. J Clin Med 2024:13.
[67] Andrasik F, Grazzi L, Sansone E, D'Amico D, Raggi A, Grignani E. Non-pharmacological approaches for headaches in Young age: an updated review. Front Neurol 2018;9:1009.
[68] Yamada K, Moriwaki K, Oiso H, Ishigooka J. High prevalence of comorbidity of migraine in outpatients with panic disorder and effectiveness of

psychopharmacotherapy for both disorders: a retrospective open label study. Psychiatry Res 2011;185:145–8.
[69] Jakubovski E, Johnson JA, Nasir M, Müller-Vahl K, Bloch MH. Systematic review and meta-analysis: dose-response curve of SSRIs and SNRIs in anxiety disorders. Depress Anxiety 2019;36:198–212.
[70] Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, Rodriguez-Lopez CM. Pregabalin in the treatment of chronic migraine: an open-label study. Clin Neuropharmacol 2010;33:35–9.
[71] Van Ameringen M, Mancini C, Pipe B, Oakman J, Bennett M. An open trial of topiramate in the treatment of generalized social phobia. J Clin Psychiatry 2004; 65:1674–8.
[72] Mehrhof SZ, Fiksenbaum LM, Bettridge AM, Goldstein BI. Markedly increased prevalence of migraine headaches in adolescents with bipolar disorder. Bipolar Disord 2021;23:255–62.
[73] Sucksdorff D, Brown AS, Chudal R, Heinimaa M, Suominen A, Sourander A. Parental and comorbid migraine in individuals with bipolar disorder: a nationwide register study. J Affect Disord 2016;206:109–14.
[74] Fasmer OB. The prevalence of migraine in patients with bipolar and unipolar affective disorders. Cephalalgia 2001;21:894–9.
[75] Saunders EF, Nazir R, Kamali M, Ryan KA, Evans S, Langenecker S, et al. Gender differences, clinical correlates, and longitudinal outcome of bipolar disorder with comorbid migraine. J Clin Psychiatry 2014;75:512–9.
[76] Mahmood T, Silverstone T. Serotonin and bipolar disorder. J Affect Disord 2001; 66:1–11.
[77] Ashok AH, Marques TR, Jauhar S, Nour MM, Goodwin GM, Young AH, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol Psychiatry 2017;22:666–79.
[78] Chen G, Henter ID, Manji HK. Presynaptic glutamatergic dysfunction in bipolar disorder. Biol Psychiatry 2010;67:1007.
[79] Duan J, Yang R, Lu W, Zhao L, Hu S, Hu C. Comorbid bipolar disorder and migraine: from mechanisms to treatment. Front Psych 2020;11:560138.
[80] Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543–52.
[81] Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005;62:1322–30.
[82] Brickman HM, Fristad MA. Psychosocial treatments for bipolar disorder in children and adolescents. Annu Rev Clin Psychol 2022;18:291–327.
[83] Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry 2011;72: 156–67.
[84] Lampl C, Katsarava Z, Diener HC, Limmroth V. Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry 2005;76:1730–2.
[85] Frye MA. Bipolar disorder — a focus on depression. N Engl J Med 2011;364:51–9.
[86] Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PK, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry 2014;171:1067–73.
[87] Diagnostic and statistical manual of mental disorders: DSM-5™. 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.; 2013.
[88] Smirni D, Carotenuto M, Precenzano F, Smirni P, Operto FF, Marotta R, et al. Memory performances and personality traits in mothers of children with obstructive sleep apnea syndrome. Psychol Res Behav Manag 2019;12:481–7.
[89] Carotenuto M, Ruberto M, Fontana ML, Catania A, Misuraca E, Precenzano F, et al. Executive functioning in autism spectrum disorders: a case-control study in preschool children. Curr Pediatr Res 2019;23:112–6.
[90] Sullivan JC, Miller LJ, Nielsen DM, Schoen SA. The presence of migraines and its association with sensory hyperreactivity and anxiety symptomatology in children with autism spectrum disorder. Autism 2014;18:743–7.
[91] Underwood JF, Kendall KM, Berrett J, Lewis C, Anney R, Van den Bree MB, et al. Autism spectrum disorder diagnosis in adults: phenotype and genotype findings from a clinically derived cohort. Br J Psychiatry 2019;215:647–53.
[92] Victorio M, EHMTI-0290.. Headaches in patients with autism spectrum disorder. J Headache Pain 2014;15:B37.
[93] Scheerer N, Curcin K, Stojanoski B, Anagnostou E, Nicolson R, Kelley E, et al. Exploring sensory phenotypes in autism spectrum disorder. Mol Autism 2021;12: 67.
[94] Ashina S, Lipton RB, Bendtsen L, Hajiyeva N, Buse DC, Lyngberg AC, et al. Increased pain sensitivity in migraine and tension-type headache coexistent with low back pain: a cross-sectional population study. Eur J Pain 2018;22:904–14.
[95] Failla MD, Gerdes MB, Williams ZJ, Moore DJ, Cascio CJ. Increased pain sensitivity and pain-related anxiety in individuals with autism. Pain Rep 2020;5: e861.
[96] Tordjman S, Anderson GM, Botbol M, Brailly-Tabard S, Perez-Diaz F, Graignic R, et al. Pain reactivity and plasma beta-endorphin in children and adolescents with autistic disorder. PLoS One 2009;4:e5289.
[97] Yang C-J, Tan H-P, Du Y-J. The developmental disruptions of serotonin signaling may involved in autism during early brain development. Neuroscience 2014;267: 1–10.
[98] Deen M, Christensen CE, Hougaard A, Hansen HD, Knudsen GM, Ashina M. Serotonergic mechanisms in the migraine brain - a systematic review. Cephalalgia 2017;37:251–64.
[99] Grumbach P, Kasper J, Hipp JF, Forsyth A, Valk SL, Muthukumaraswamy S, et al. Local activity alterations in autism spectrum disorder correlate with neurotransmitter properties and ketamine induced brain changes. medRxiv [Preprint]. 2024. [cited 2024 Oct 21] :2024.10.20.24315801. doi:10.1101/2024.10.20.24315801.
[100] Theoharides TC, Stewart JM, Panagiotidou S, Melamed I. Mast cells, brain inflammation and autism. Eur J Pharmacol 2016;778:96–102.
[101] Xanthos DN, Sandkühler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci 2014;15:43–53.
[102] Fulceri F, Morelli M, Santocchi E, Cena H, Del Bianco T, Narzisi A, et al. Gastrointestinal symptoms and behavioral problems in preschoolers with autism Spectrum disorder. Dig Liver Dis 2016;48:248–54.
[103] Aurora SK, Shrewsbury SB, Ray S, Hindiyeh N, Nguyen L. A link between gastrointestinal disorders and migraine: insights into the gut-brain connection. Headache 2021;61:576–89.
[104] Ristori MV, Quagliariello A, Reddel S, Ianiro G, Vicari S, Gasbarrini A, et al. Autism, gastrointestinal symptoms and modulation of gut microbiota by nutritional interventions. Nutrients 2019;11:2812.
[105] Damaj L, Lupien-Meilleur A, Lortie A, Riou É, Ospina LH, Gagnon L, et al. CACNA1A haploinsufficiency causes cognitive impairment, autism and epileptic encephalopathy with mild cerebellar symptoms. Eur J Hum Genet 2015;23: 1505–12.
[106] Gargus JJ. Genetic calcium signaling abnormalities in the central nervous system: seizures, migraine, and autism. Ann N Y Acad Sci 2009;1151:133–56.
[107] Kang BS, Lee J, Choi JH, Kwon HH, Kang JW. Clinical manifestations of headache in children younger than 7 years. Korean J Pediatr 2018;61:355–61.
[108] Mazefsky CA, Herrington J, Siegel M, Scarpa A, Maddox BB, Scahill L, et al. The role of emotion regulation in autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2013;52:679–88.
[109] Hershey AD. Pediatric headache: update on recent research. Headache 2012;52: 327–32.
[110] Fasmer OB, Halmøy A, Oedegaard KJ, Haavik J. Adult attention deficit hyperactivity disorder is associated with migraine headaches. Eur Arch Psychiatry Clin Neurosci 2011;261:595–602.
[111] Mangrum R, Bryant AL, Gerstein MT, McCarrier KP, Houts CR, McGinley JS, et al. The impacts of migraine on functioning: results from two qualitative studies of people living with migraine. Headache 2024;64:156–71.
[112] French B, Nalbant G, Wright H, Sayal K, Daley D, Groom MJ, et al. The impacts associated with having ADHD: an umbrella review. Front Psych 2024;15: 1343314.
[113] Salem H, Vivas D, Cao F, Kazimi IF, Teixeira AL, Zeni CP. ADHD is associated with migraine: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2018;27:267–77.
[114] da Silva BS, Grevet EH, Silva LCF, Ramos JKN, Rovaris DL, Bau CHD. An overview on neurobiology and therapeutics of attention-deficit/hyperactivity disorder. Discover Mental Health 2023;3:2.
[115] Akerman S, Goadsby PJ. Dopamine and migraine: biology and clinical implications. Cephalalgia 2007;27:1308–14.
[116] Kutuk MO, Tufan AE, Guler G, Yalin OO, Altintas E, Bag HG, et al. Migraine and associated comorbidities are three times more frequent in children with ADHD and their mothers. Brain Dev 2018;40:857–64.
[117] Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function. Neurology 2002;58:422–7.
[118] Bellato A, Arora I, Hollis C, Groom MJ. Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence. Neurosci Biobehav Rev 2020;108:182–206.
[119] Ha W-S, Chu MK. Altered immunity in migraine: a comprehensive scoping review. J Headache Pain 2024;25:95.
[120] Misiak B, Wójta-Kempa M, Samochowiec J, Schiweck C, Aichholzer M, Reif A, et al. Peripheral blood inflammatory markers in patients with attention deficit/hyperactivity disorder (ADHD): a systematic review and meta-analysis. Prog Neuropsychopharmacol Bio Psychiatry 2022;118:110581.
[121] Kofler MJ, Singh LJ, Soto EF, Chan ESM, Miller CE, Harmon SL, et al. Working memory and short-term memory deficits in ADHD: a bifactor modeling approach. Neuropsychology 2020;34:686–98.
[122] Pan PY, Jonsson U, Şahpazoğlu Çakmak SS, Häge A, Hohmann S, Nobel Norrman H, et al. Headache in ADHD as comorbidity and a side effect of medications: a systematic review and meta-analysis. Psychol Med 2022;52:14–25.
[123] Sibley MH, Bruton AM, Zhao X, Johnstone JM, Mitchell J, Hatsu I, et al. Non-pharmacological interventions for attention-deficit hyperactivity disorder in children and adolescents. Lancet Child Adolesc Health 2023;7:415–28.
[124] Santamaría-Vázquez E, Estudillo-Guerra A, Ali L, Martinez D, Hornero R, Morales-Quezada L. Effects of a novel non-pharmacological intervention based on respiratory biofeedback, neurofeedback and median nerve stimulation to treat children with ADHD. Front Hum Neurosci 2025;19:1478501.
[125] Ailani J, Burch RC, Robbins MS. Board of Directors of the American headache S. The American headache society consensus statement: update on integrating new migraine treatments into clinical practice. Headache 2021;61:1021–39.
[126] Puledda F, Shields K. Non-pharmacological approaches for migraine. Neurotherapeutics 2018;15:336–45.
[127] Kucukgoncu S, Yildirim Ornek F, Cabalar M, Bestepe E, Yayla V. Childhood trauma and dissociation in tertiary care patients with migraine and tension type headache: a controlled study. J Psychosom Res 2014;77:40–4.
[128] Özdil Demiryürek E, Demiryürek BE, Tekin A, Güzey Aras Y, Doğan Güngen B, Erdoğan S. The association between childhood traumatic events and headache-related parameters in patients with migraine: a cross-sectional study in Turkish population. Noro Psikiyatr Ars 2017;54:291–4.

[129] Patterson Gentile C, Shah R, Irwin SL, Greene K, Szperka CL. Acute and chronic management of posttraumatic headache in children: a systematic review. Headache 2021;61:1475–92.
[130] Thomasius R, Paschke K, Arnaud N. Substance-use disorders in children and adolescents. Dtsch Arztebl Int 2022;119:440–50.
[131] Ziplow J. The psychiatric comorbidities of migraine in children and adolescents. Curr Pain Headache Rep 2021;25:69.
[132] Goldstein BI, Strober MA, Birmaher B, Axelson DA, Esposito-Smythers C, Goldstein TR, et al. Substance use disorders among adolescents with bipolar spectrum disorders. Bipolar Disord 2008;10:469–78.
[133] Dell ML, Campo JV. Somatoform disorders in children and adolescents. Psychiatr Clin North Am 2011;34:643–60.
[134] Emich-Widera E, Kazek B, Szwed-Bialozyt B, Kopyta I, Kostorz A. Headaches as somatoform disorders in children and adolescents. Ment Illn 2012;4:e9.
[135] Łangowska-Grodzka B, Grodzka O, Czarnecki D, Domitrz I. Is there a correlation between migraine and eating disorders? A systematic literature review. Neurol Neurochir Pol 2023;57:457–64.
[136] de Oliveira-Souza AIS, da Silva Freitas D, Ximenes RCC, Raposo MCF, de Oliveira DA. The presence of migraine symptoms was associated with a higher likelihood to present eating disorders symptoms among teenage students. Eat Weight Disord 2022;27:1661–7.
[137] Mustelin L, Raevuori A, Kaprio J, Keski-Rahkonen A. Association between eating disorders and migraine may be explained by major depression. Int J Eat Disord 2014;47:884–7.
[138] Pellegrino ABW, Davis-Martin RE, Houle TT, Turner DP, Smitherman TA. Perceived triggers of primary headache disorders: a meta-analysis. Cephalalgia 2018;38:1188–98.
[139] Fasmer OB, Riise T, Lund A, Dilsaver SC, Hundal O, Oedegaard KJ. Comorbidity of migraine with ADHD. J Atten Disord 2012;16:339–45.
[140] Arruda MA, Arruda R. Psychological adjustment in children with episodic migraine: a population-based study. Psychol Neurosci 2014;7:33–41.
[141] Genizi J, Gordon S, Kerem NC, Srugo I, Shahar E, Ravid S. Primary headaches, attention deficit disorder and learning disabilities in children and adolescents. J Headache Pain 2013;14:54.
[142] Pavone P, Rizzo R, Conti I, Verrotti A, Mistretta A, Falsaperla R, et al. Primary headaches in children: clinical findings on the association with other conditions. Int J Immunopathol Pharmacol 2012;25:1083–91.
[143] Riva D, Usilla A, Aggio F, Vago C, Treccani C, Bulgheroni S. Attention in children and adolescents with headache. Headache 2012;52:374–84.
[144] Genizi JMD, Srugo I, Kerem NC. The relations between attention deficit hyperactivity disorder and headaches in a non-clinical sample of adolescents. Acad J Ped Neonatol 2016;2:555583.
[145] Strine TW, Okoro CA, McGuire LC, Balluz LS. The associations among childhood headaches, emotional and behavioral difficulties, and health care use. Pediatrics 2006;117:1728–35.
[146] Lateef TM, Merikangas KR, He J, Kalaydjian A, Khoromi S, Knight E, et al. Headache in a national sample of American children: prevalence and comorbidity. J Child Neurol 2009;24:536–43.
[147] Pitrou I, Shojaei T, Chan-Chee C, Wazana A, Boyd A, Kovess-Masféty V. The associations between headaches and psychopathology: a survey in school children. Headache: the journal of head and face. Pain 2010;50:1537–48.
[148] Jameson ND, Sheppard BK, Lateef TM, Vande Voort JL, He JP, Merikangas KR. Medical comorbidity of attention-deficit/hyperactivity disorder in US adolescents. J Child Neurol 2016;31:1282–9.
[149] Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: association with school performance. Neurology 2012;79:1881–8.
[150] Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Migraine, tension-type headache, and attention-deficit/hyperactivity disorder in childhood: a population-based study. Postgrad Med 2010;122:18–26.
[151] Mazzone L, Vitiello B, Incorpora G, Mazzone D. Behavioural and temperamental characteristics of children and adolescents suffering from primary headache. Cephalalgia 2006;26:194–201.