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Review Article

Sex-Based Differences in Migraine: Bridging Hormonal Mechanisms and Individualised Therapy

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Abstract:

Migraine stands as one of the most consequential disabling neurological disorders confronting modern medicine, characterized by recurrent episodes of severe head pain with neurological manifestations that substantially diminish quality of life and impose considerable socioeconomic burden. Contemporary epidemiological investigations consistently document a striking disparity in disease prevalence between biological sexes, with women experiencing migraine attacks at rates exceeding those in men by approximately threefold, with documented prevalence reaching 18 percent among adult female populations. The female migraine phenotype characteristically includes amplified pain intensity, elevated attack frequency, and more diverse symptomatological presentations. This comprehensive review synthesizes accumulated evidence illuminating the complicated relationship between biological sex, hormonal steroid signaling pathways, central nervous system function, and the spectrum of therapeutic modalities available for migraine management. The overarching conclusion emphasizes that truly effective, patient-centered migraine management necessarily incorporates biological sex and individual hormonal circumstances as core organizing principles influencing both disease manifestation and therapeutic response patterns.

Keywords: Sexual dimorphism in migraine, ovarian steroid signaling, hormonal influences on pain processing, gender-informed treatment, neuroendocrine mechanisms, women's headache disorders

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Introduction:

The Burden of Migraine and the Imperative for Sex-Informed Understanding

Migraine disease represents far more than occasional headache inconvenience—it constitutes a significant public health challenge impacting hundreds of millions of individuals worldwide and generating enormous direct medical costs alongside incalculable indirect expenses through lost productivity, diminished earning capacity, and compromised personal relationships [1-5]. According to the most recent Global Burden of Disease assessments, migraine ranks among the leading causes of disability across all ages, with particularly pronounced burden among working-age adults and specifically among women of reproductive potential [6-9]. The condition characteristically manifests as recurrent episodes of moderate to severe unilateral headache, frequently accompanied by nausea, vomiting, heightened sensitivity to light and sound, and for some individuals, visual or sensory disturbances preceding the headache phase [10-15].

The epidemiological data regarding sex differences in migraine prevalence presents a compellingly consistent pattern across diverse populations and geographic regions: women experience migraine approximately three times more frequently than men [1,5]. This ratio persists across age groups, though magnitude varies somewhat depending on age and reproductive status [6]. Additionally, women report qualitatively different migraine experiences, including longer attack durations, more profound functional impairment, greater difficulty managing responsibilities during attacks, and more frequent accompanying symptoms including gastrointestinal distress and sensory hypersensitivity [1,9]. The public health implications of this sex disparity prove substantial—migraine represents the leading cause of disability specifically among women under age 50, exceeding even musculoskeletal conditions and effective disorders in disability burden [4].

The temporal relationship between migraine occurrence and reproductive events in women provides perhaps the most convincing clinical evidence for hormonal involvement [10,11]. Careful epidemiological studies consistently document that migraine onset or substantial exacerbation frequently coincides with menarche, when ovarian hormone production begins [12]. Throughout reproductive years, many women report menstrual association with their migraines—approximately 60 percent of female migraineurs describe increased attack frequency during the perimenstrual window, typically occurring between two days before through three days after menstrual bleeding [10]. During pregnancy, when ovarian hormone levels rise substantially and remain stable throughout gestation, many women experience partial or complete remission of migraine attacks [16].

Contemporary Understanding of Migraine Pathophysiology: Moving Beyond Outdated Vascular Paradigms

Historical conceptualizations of migraine stemmed from observations of vascular changes accompanying migraine attacks, but contemporary neuroscience has substantially revised this understanding through systematic investigation employing advanced neuroimaging, electrophysiological recording, and animal models [14]. Current evidence compellingly demonstrates that migraine fundamentally represents a neurobiological disorder involving dysregulation of complex, interconnected neural systems rather than a primary vascular condition [15].

The modern conceptualization recognizes migraine as involving exaggerated responsivity and hyperexcitability within neural circuits specialized for pain processing, sensory integration, and autonomic regulation [2,14]. The hypothalamus, involved in numerous homeostatic functions, appears to undergo dysregulation that triggers the initiation cascade leading to migraine attacks [15]. This trigeminovascular system, when activated inappropriately, releases numerous neuroactive substances including neuropeptides and neurotransmitters that induce both pains signaling and accompanying vascular and inflammatory responses (Figure -1) [16,17]. The neuropeptides released from activated trigeminal nerves, particularly calcitonin gene-related peptide (CGRP), exert powerful effects on nearby blood vessels, causing vasodilation and increased vascular permeability [16,18].

In individuals experiencing migraine with aura, waves of intense neuronal depolarization known as cortical spreading depression propagate slowly across the cerebral cortex, generating patterns of electrical activity corresponding to visual and sensory symptoms [19]. Genetic investigations have identified several rare forms of familial

hemiplegic migraine resulting from mutations in genes encoding ion channels or ion pumps essential for maintaining proper cellular electrolyte balance [20].

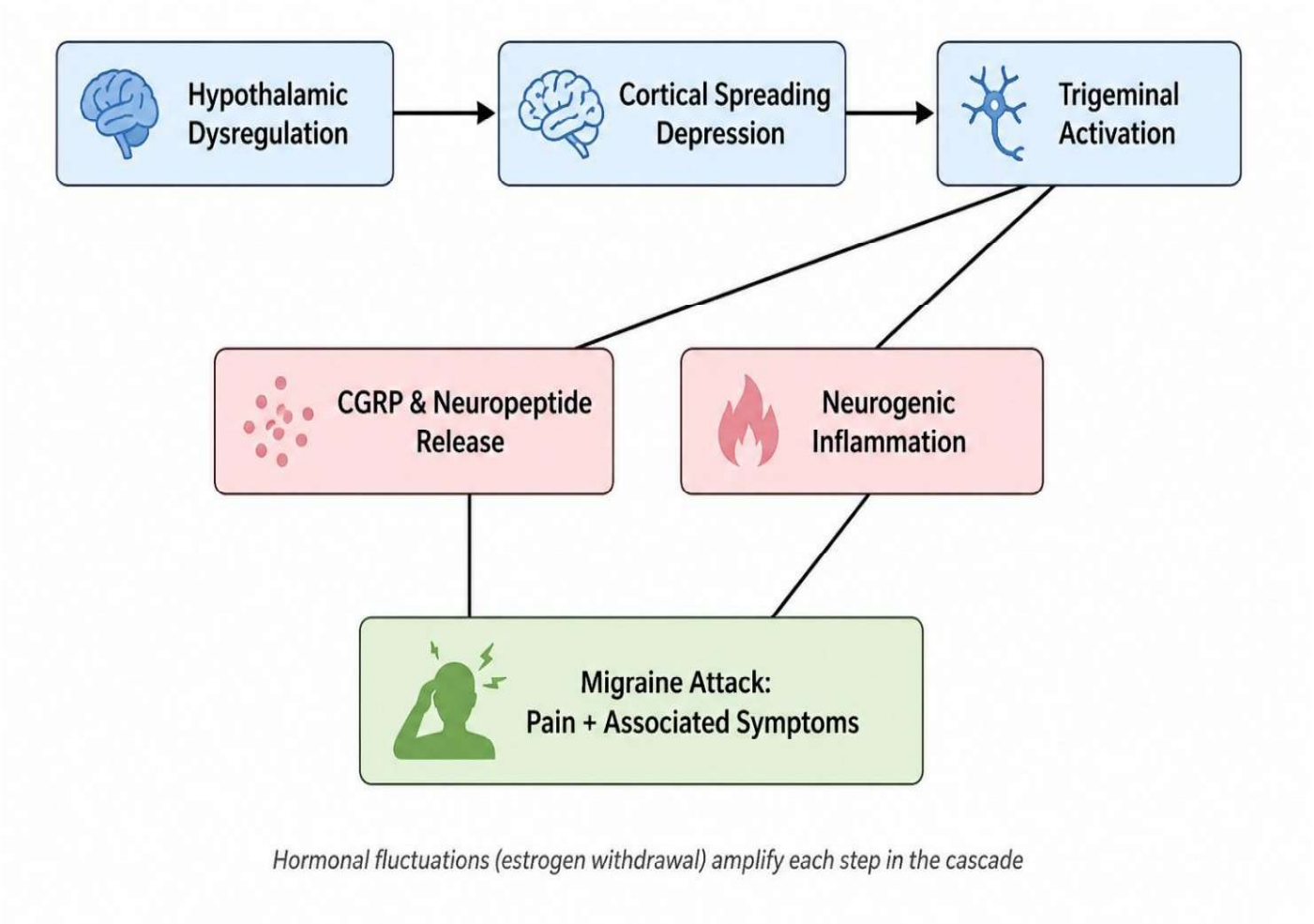

Figure 1: Schematic representation of the trigeminovascular pathway in migraine pathophysiology, illustrating the cascade from hypothalamic dysregulation through CGRP release to neurogenic inflammation and pain generation. Estrogen withdrawal amplifies each step, increasing migraine vulnerability in women during perimenstrual, postpartum, and perimenopausal phases.

Ovarian Steroid Signaling in Migraine Biology: Mechanistic Pathways

Estrogen and progesterone exert profound influences on migraine susceptibility through multiple interconnected mechanisms operating at cellular, circuit, and systems levels [9,11]. The 'estrogen withdrawal hypothesis,' extensively investigated through both clinical observations and experimental investigations, proposes that rapidly falling estrogen concentrations rather than absolute hormone levels constitute the critical trigger for migraine attacks in hormonally-sensitive individuals [10,12]. Supporting evidence comes from multiple lines of investigation: women experiencing menstrually-related migraines demonstrate steeper estrogen decline trajectories during the late luteal menstrual phase compared to women without menstrual migraine associations [6,10]. The mechanisms underlying estrogen withdrawal-induced migraine susceptibility involve alterations in multiple neurotransmitter systems and receptor expression patterns [9,11]. Specifically, estrogen enhances serotonin synthesis by increasing expression and activity of tryptophan hydroxylase, the rate-limiting enzyme in serotonin production, while simultaneously decreasing activity of monoamine oxidase [12]. When estrogen levels precipitously decline, these protective neuromodulatory effects diminish, and the combination of reduced inhibition with reduced monoaminergic tone creates a neurobiological milieu characterized by excessive neuronal excitability and reduced pain

suppression [9,11,12]. CGRP, the neuropeptide implicated throughout migraine pathophysiology, undergoes substantial hormonal modulation [8,16]. Women in hypoestrogenic states demonstrate significantly elevated plasma and urinary CGRP concentrations compared to estrogen-replete women, and experimental studies in ovariectomized animals demonstrate that estrogen supplementation reduces CGRP levels and CGRP receptor expression within the trigeminovascular system [8,17].

Migraine Evolution Across the Female Reproductive Life Continuum: From Menarche Through Menopause

The trajectory of migraine across a woman's reproductive lifespan reflects the profound influence of changing hormonal circumstances and age-related changes in neural function [7,11]. The onset or substantial worsening of migraine frequently occurs around menarche, coinciding with establishment of regular ovulatory cycles and initiation of substantial menstrual-phase estrogen decline [12].

Pregnancy represents a distinctive hormonally-dependent life event substantially affecting migraine for many women, with sustained elevated hormone levels producing migraine remission in approximately two-thirds of women with established migraines [11,12]. The postpartum period, conversely, represents a particularly challenging time due to precipitous estrogen collapse within hours of delivery, triggering substantial worsening or recurrence of migraines in many previously remitted women [7,9].

The perimenopause, typically lasting 5–10 years and characterized by gradually reducing ovarian hormone production coupled with increasingly erratic hormonal fluctuations, represents another crucial transitional period during which many women report their most severe migraine episodes ever [7,21-22]. Paradoxically, completion of menopause with establishment of stable, persistently low estrogen levels frequently produces migraine improvement, reflecting the stabilization of hormone levels rather than the low absolute levels per se [7]. The distinction between natural menopause and surgical menopause (oophorectomy) provides illuminating insight into the primacy of hormone withdrawal velocity over absolute hormone levels, effectively demonstrating that the rate of hormone change determines migraine susceptibility (Figure 2 & Table – 1) [7,22].

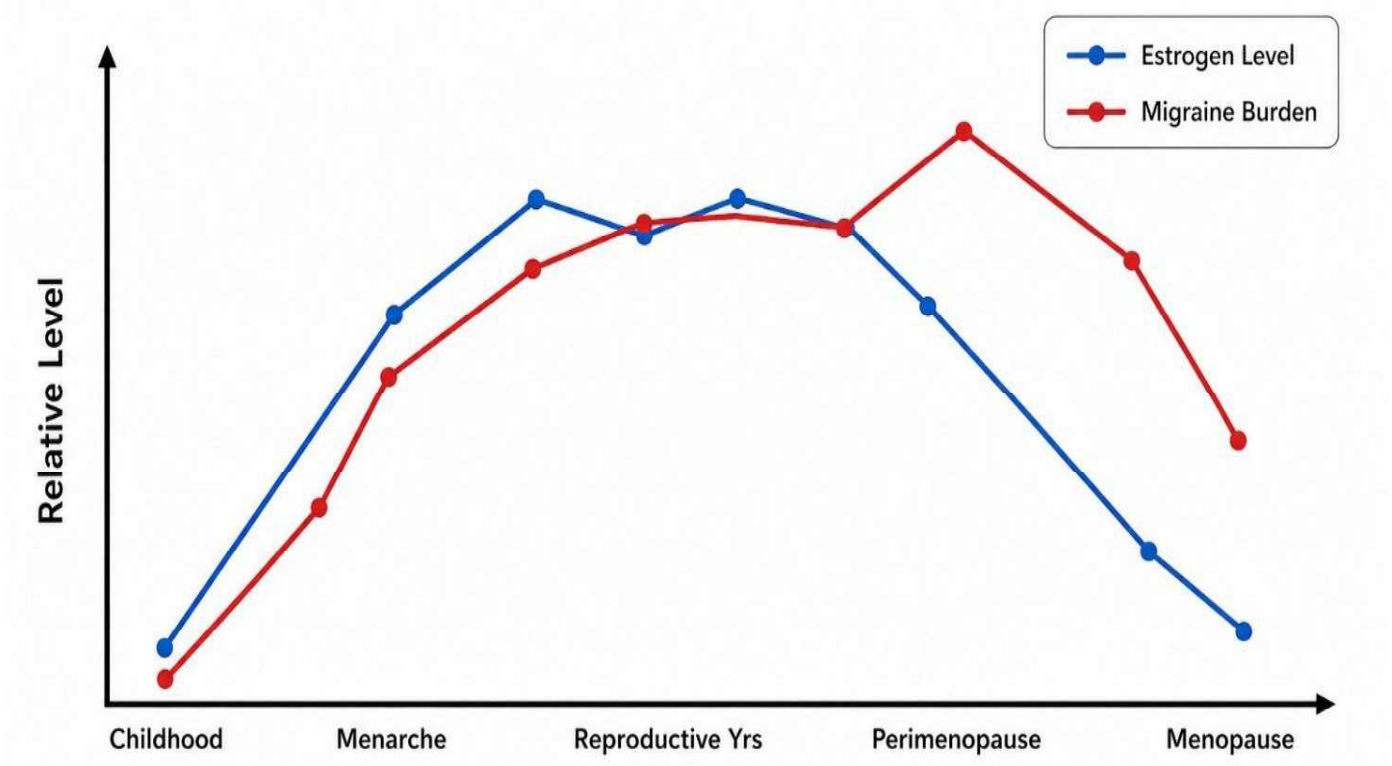

Figure 2: Schematic illustration of relative estrogen levels (blue) and migraine burden (red) across the female reproductive lifespan. Note parallel increases in migraine burden at menarche, perimenopausal instability, and improvement following menopause stabilization. Adapted from Vetvik & MacGregor, 2017 [1].

Table 1: Sex Differences in Migraine Characteristics

Characteristic	Women	Men	Clinical Significance
Prevalence	18%	6%	3:1 Female predominance
Attack Duration	Longer (24–72 hrs)	Shorter (4–24 hrs)	Women: prolonged attacks
Pain Intensity	Moderate–Severe	Moderate	Higher VAS scores in women
Nausea/Vomiting	More frequent	Less frequent	70% vs. 50% in men
Photophobia	More pronounced	Less pronounced	Estrogen-mediated sensitivity
Menstrual Trigger	60% of women affected	N/A	Perimenstrual window
Medication Overuse	Higher rates	Lower rates	Women: 2.5× higher risk
CGRP Levels	Elevated, hormonally linked	Lower baseline	Hormonal modulation
Triptan Response	Higher remission (2h)	Lower remission (2h)	Sex-differential PK
Disability (MIDAS)	Higher scores	Lower scores	Greater functional impact

Table 1: Comparative summary of migraine epidemiology, clinical features, and biological markers between women and men. PK = pharmacokinetics; VAS = Visual Analogue Scale; CGRP = calcitonin gene-related peptide; MIDAS = Migraine Disability Assessment Scale.

Pharmacological Management of Acute Migraine: Sex-Informed Treatment Approaches

Triptan medications, first introduced in the 1990s, revolutionized migraine treatment through their selective targeting of serotonin 5-HT1B and 5-HT1D receptors [21-25]. These medications exert dual antinociceptive mechanisms: peripheral actions on vascular 5-HT1B receptors induce cranial arterial vasoconstriction, counteracting the vasodilation characterizing migraine; and central actions on trigeminal nuclei and ganglia directly inhibit pain transmission and neuropeptide release [21,26]. Notably, frovatriptan demonstrates substantially higher bioavailability in women compared to men, achieving plasma concentrations roughly twice as high following equivalent doses, likely reflecting estrogen-mediated effects on drug-metabolizing enzymes [21]. The recent development of calcitonin gene-related peptide (CGRP) antagonists and small-molecule CGRP receptor antagonists (gepants) represents a paradigm shift in acute migraine management, with these agents directly interrupting CGRP signaling and blocking the neuropeptide's contribution to pain generation and neurogenic inflammation [16,17]. Women demonstrate higher baseline CGRP concentrations compared to men, and estrogen deprivation further elevates CGRP levels, suggesting that women—particularly those experiencing hormonally-triggered migraines—may benefit most from CGRP-targeting therapeutics [8,17].

For women experiencing exclusively menstrually-associated migraines, short-term prevention through perimenstrual estrogen supplementation via transdermal patches offers a targeted approach, preventing the estrogen withdrawal that triggers menstrual attacks, [22,23]. Non-steroidal anti-inflammatory drugs (NSAIDs) demonstrate particular efficacy for menstrually-related migraines, suggesting that anti-inflammatory mechanisms prove especially relevant for hormonally-triggered attacks [26].

Preventive Pharmacotherapy: Sex-Informed Prophylactic Approaches

Beta-adrenergic blockers, including propranolol and atenolol, remain foundational preventive agents despite development of newer alternatives, with women demonstrating substantially lower drug clearance rates compared to men, resulting in approximately 30–50 percent higher steady-state plasma concentrations following identical doses [25,26].

Antiepileptic medications, particularly topiramate and sodium valproate, demonstrate migraine preventive effects through mechanisms including cortical spreading depression suppression, sodium channel blockade, and enhancement of GABAergic function [25]. Notably, estrogen-containing oral contraceptives and hormone replacement therapy substantially induce hepatic enzyme activity, accelerating antiepileptic drug metabolism and reducing steady-state concentrations, necessitating higher doses in women using hormonal contraceptives [23,25]. Recent investigations into greater occipital nerve (GON) blocks suggest this minimally invasive intervention provides substantial pain relief in chronic migraine, with meta-analyses indicating superior pain outcomes compared to control interventions through interruption of nociceptive input from the greater occipital nerve distribution [26,27]. For women experiencing treatment-resistant menstrually-associated migraines refractory to conventional approaches, gonadotropin-releasing hormone (GnRH) agonists combined with low-dose estrogen and progesterone add-back represent an option, effectively converting hormonally-sensitive migraine to a more stable hormonal state (Table -2) [22,23].

Table 2: Pharmacological Agents with Sex-Specific Pharmacokinetics and Dosing Considerations

Agent	Type	Standard Dose	Sex-Specific PK	Clinical Note
Frovatriptan	Acute	Standard	Higher (2×) in women	Reduce dose in women; COX interaction
Propranolol	Preventive	80–240 mg/day	30–50% higher in women	Start low: 60–160 mg/day women
Verapamil	Preventive	120–480 mg/day	Higher bioavailability (F)	Monitor for hypotension in women
Topiramate	Preventive	50–200 mg/day	OCP lowers levels	Dose ↑ if using OCP
Sodium Valproate	Preventive	500–1500 mg/day	Enzyme-induced by OCP	Monitor serum levels; teratogenic
Amitriptyline	Preventive	10–75 mg/day	Higher bioavailability (F)	Lower starting dose in women
Sumatriptan	Acute	25–100 mg	Similar PK	Standard dosing; first-line
Erenumab (CGRP mAb)	Preventive	70–140 mg/month	Women: superior response	Preferred in hormonal migraine
Rimegepant (gepant)	Acute/Prevent	75 mg PRN	Women: higher responders	CYP3A4 interactions
Magnesium glycinate	Preventive	360–400 mg/day	Similar	Especially effective perimenstrual

Table 2: Summary of key pharmacological agents used in migraine management with sex-specific pharmacokinetic profiles and clinical dosing recommendations. PK = pharmacokinetics; OCP = oral contraceptive pill; CGRP mAb = calcitonin gene-related peptide monoclonal antibody.

Complementary and Integrative Management Approaches: Nutritional and Behavioral Interventions

Riboflavin (vitamin B2) supplementation targets potential mitochondrial dysfunction implicated in migraine pathophysiology, with high-dose supplementation (400 mg daily) demonstrating modest but statistically significant prophylactic effects in randomized controlled trials [28]. A landmark Belgian study demonstrated that 400 mg daily riboflavin, sustained for at least three months, reduces migraine attack frequency by approximately 30 percent in responsive individuals, with minimal adverse effects primarily involving minor gastrointestinal disturbance and yellow discoloration of urine [28]. Coenzyme Q10 (ubiquinone), another mitochondrial energy metabolism cofactor, shows promise in migraine prevention with recommended dosing of 1–3 mg/kg daily demonstrating modest

efficacy in some investigations through enhanced mitochondrial energy generation and reduced oxidative stress [29-30]. Magnesium deficiency has been documented in migraine populations relative to healthy controls, and supplementation with 360–400 mg magnesium daily demonstrates efficacy particularly for perimenstrual migraine, with minimal adverse effect risk aside from dose-dependent gastrointestinal side effects [30]. Herbal supplements including butterbur root extract (*Petasites hybridus*) at doses of 50–75 mg twice daily show efficacy in reducing migraine frequency comparably to certain preventive medications, with favorable safety profiles in appropriately selected preparations avoiding hepatotoxic pyrrolizidine alkaloids [31]. Feverfew (*Tanacetum parthenium*) shows less consistent efficacy across trials, with some studies demonstrating benefit while others show negative results [32]. Cognitive-behavioral therapy (CBT) helps individuals identify and modify maladaptive thoughts, beliefs, and behaviors perpetuating migraine vulnerability, with studies comparing CBT combined with preventive pharmacotherapy versus pharmacotherapy alone demonstrating superior outcomes with combination approaches [33]. Mindfulness-based stress reduction (MBSR) demonstrates efficacy in reducing migraine frequency by approximately 30–40 percent in responsive individuals through decreased physiological stress reactivity, enhanced parasympathetic tone, and improved emotion regulation [34]. Relaxation training encompassing progressive muscle relaxation, autogenic training, and guided imagery produces migraine frequency reductions of 30–40 percent in some studies, facilitating parasympathetic activation and muscular tension reduction [35]. Acupuncture, though mechanisms remain incompletely understood from a Western neurobiological perspective, demonstrates efficacy with meta-analyses suggesting frequency reductions of approximately 5–15 percent with typical treatment courses (Table-3) [36].

Table 3: Summary of Complementary Interventions for Migraine — Evidence, Efficacy, and Safety

Intervention	Dose/ Protocol	Evidence Level	Efficacy	Safety Profile
Riboflavin (B2)	400 mg/day	Moderate (RCT)	~30% frequency reduction	Excellent; yellow urine
Coenzyme Q10	1–3 mg/kg/day	Moderate (RCT)	~31% reduction	Good; expensive
Magnesium	360–400 mg/day	Moderate (RCT)	~41% perimenstrual	Good; GI upset possible
Butterbur (PA-free)	75 mg BID	Moderate (RCT)	~48% reduction	Good; avoid PA forms
Feverfew	50–100 mg/day	Low (inconsistent)	Modest, variable	Low GI effects
Cognitive-Behavioral Therapy	8–12 sessions	High (multiple RCTs)	30–50% reduction	Excellent; durable
MBSR	8-week program	Moderate (RCTs)	30–40% reduction	Good; high adherence
Acupuncture	6–8 sessions	Moderate (meta-analysis)	5–15% reduction	Good; minimal risk
Progressive Muscle Relaxation	Daily practice	Moderate (RCT)	30–40% reduction	Excellent; self-administered
Omega-3 Fatty Acids	2–4 g/day	Low–Moderate	Modest benefit	Good; anti-inflammatory

Table 3: Evidence-based summary of complementary and integrative interventions for migraine management. RCT = randomized controlled trial; PRN = as needed; GI = gastrointestinal; PA = pyrrolizidine alkaloids; MBSR = Mindfulness-Based Stress Reduction.

Emerging Research Directions: Toward Precision Medicine in Migraine Management

Contemporary migraine research increasingly recognizes that migraine likely represents not a single disease entity but rather a heterogeneous collection of related conditions with potentially distinct mechanistic underpinnings, necessitating progressive movement toward precision medicine approaches [15,37-38]. Iron deficiency represents an emerging micronutrient deficiency gaining recognition in migraine populations, with surprisingly high prevalence of iron deficiency anemia in women with chronic recurrent migraines, particularly those with menstrually-related patterns [30].

The dopaminergic hypothesis of migraine, increasingly compelling given clinical observations and genetic findings, suggests dopamine signaling disturbances underlie some migraine pathophysiology, with migraineurs demonstrating hypersensitivity to dopamine receptor agonist medications [2,14]. The observation that dopamine signaling undergoes substantial estrogen modulation—estrogen increases dopamine synthesis, reduces dopamine reuptake, and upregulates dopamine receptor expression—suggests dopaminergic pathways represent another critical neuroendocrine interface relevant to sex-based migraine disparities [9,12].

Pharmacogenomic approaches incorporating genetic variation in drug-metabolizing enzymes, drug transporters, and therapeutic targets promise improved medication selection and dosing optimization, with cytochrome P450 enzyme polymorphisms producing rapid, normal, and slow metabolizers substantially affecting achievable drug concentrations and therapeutic and adverse effects [21,26,39]. Advanced computational approaches including connectomics and network analysis may identify disease-relevant alterations in brain organization distinguishing migraine subtypes, while machine learning approaches promise improved patient stratification and prediction of treatment response [14,15].

Conclusion:

Integrating Biological Sex as a Fundamental Organizing Principle in Migraine Management

This comprehensive review has illuminated the profoundly intricate nature of migraine as a neurobiological condition substantially shaped by sexual dimorphism in neural organization and by fluctuating ovarian steroid signaling throughout the female reproductive years. Rather than representing a primary vascular disorder or a simple neurological condition characterized by uniform pathophysiology across sexes, evidence demonstrates that migraine emerges from dysregulation of interconnected neural systems involved in nociceptive transmission, neuroendocrine signaling, vascular function, and emotional processing—systems that all exhibit important sex-based differences. The accumulated evidence reviewed throughout this manuscript effectively demonstrates that effective, patient-centered migraine management must necessarily account for biological sex as a fundamental organizing principle shaping both disease manifestation and treatment response patterns. Contemporary therapeutic options have expanded substantially to span a widening spectrum from rapidly-acting acute medications through long-term preventive pharmacotherapy, from conventional pharmacological interventions through behavioral and nutritional modalities, and from traditional established approaches through novel cutting-edge mechanisms of action. Future progress in migraine management requires sustained investment in mechanistic research illuminating the neural and hormonal foundations of sex-based migraine differences, clinical implementation science identifying optimal strategies for translating mechanistic knowledge into improved outcomes, and comparative effectiveness research in diverse patient subpopulations with adequate sex-disaggregated analysis. The convergence of advances in basic neuroscience, endocrinology, pharmacology, and clinical epidemiology, combined with novel technologies including neuroimaging, connectomics, and machine learning, promises continued advancement in our collective capacity to reduce the burden of migraine through truly individualized, evidence-based management benefiting all affected individuals.

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Authors' contributions

Conceptualization: AA & RG; Data Curation: AA, HM, KC & RG; Formal Analysis: AA, HM, KC & RG; Investigation: AA, HM, KC & RG; Methodology: AA, HM, KC & RG; Project Administration: AA, & RG; Resources: AA, HM, KC & RG; Supervision: AA, & RG; Validation: HM, & KC ; Visualization: AA, & RG; Writing – Original Draft Preparation: AA, & RG; Writing – Review & Editing: HM, & KC.

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares no competing int

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