Review

Sex/Gender Differences in Migraine: Exploring Pathophysiology, the Impact of Sex Hormones, and Tailored Therapeutic Approaches

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Review

Sex/Gender Differences in Migraine: Exploring Pathophysiology, the Impact of Sex Hormones, and Tailored Therapeutic Approaches

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Abstract: Migraine is a neurological disorder characterized by severe disabling headaches with a substantial global burden and elevated morbidity rates. Extensive research has established a clear association between migraine and sex/gender, with a notably higher incidence reported in females, reaching up to 18%, which is three times greater compared to males. Additionally, women commonly experience more intense pain and greater frequency of migraine symptoms, both with and without aura, highlighting the differential impact of sex/gender on migraine presentation. This review comprehensively examines the pathophysiology of migraine, with a particular focus on the effects of sex hormones in migraine pathophysiology and the central nervous system. Furthermore, we explore various treatment modalities tailored to gender differences, including pharmacological interventions and emerging therapeutic approaches. Furthermore, we explored alternative treatment strategies such as nutraceuticals and behavioural techniques, including mindfulness and cognitive behavioural therapy. This review aims to provide a comprehensive overview of the multifaceted nature of migraine and the diverse therapeutic approaches available for their management.

Keywords: migraine; sex hormones; pathology; treatment

Introduction

Migraine is an episodic neurological disorder, which can become chronic in later stages, characterized by severe disabling headaches with a strong genetic predisposition [1,2]. According to the Global Burden of Disease Study 2019, migraine ranked second in disability across all ages and genders, maintaining the highest rank among young women since 2019 [3]. Typical attacks involve unilateral moderate to severe headaches accompanied by nausea, vomiting, and sensitivity to light and sound [4,5]. Migraine is more prevalent in females, affecting them three times more than males, with an incidence rate as high as 18% [6–8]. The prevalence of migraine in women increases from puberty, affecting up to 55% during menstrual age, and varies with pregnancy and menopause [9–11]. This gender disparity is attributed to differences in sex hormone receptor binding, genetics, and environmental stressors [12–14]. While attack frequency is similar across genders, averaging 1 to 4 headache days per month, significant age-related differences are observed among women [15,16]. Studies suggest that women experience higher pain intensity due to longer attack durations and social constraints limiting men from expressing pain [17]. Additionally, women report higher frequencies of symptoms such as nausea, phonophobia, and photophobia [18]. Migraine recurrence is influenced by hormonal changes, including menarche, menstruation, pregnancy, menopause, and the use of contraceptives or hormone replacement therapy (HRT) [1–3].

The pathophysiology of migraine has advanced with functional neuroimaging and animal models yet remains incompletely defined. Migraine is characterized by recurrent unilateral throbbing headaches, often accompanied by nausea, photophobia, and phonophobia, leading to significant

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daily activity restriction [19] and pathophysiology is shown in Figure 1. Genetic, metabolic, environmental, and vascular factors contribute to migraine pathogenesis [20]. Historically, migraine has been recognized as a predominantly female condition. An episode of migraine may include four phases: premonitory, aura, headache, and postdrome, which can occur sequentially or overlap [21]. Initial theories by Thomas Willis in the 17th century proposed a neurovascular hypothesis, attributing migraine to carotid artery dilatation [22,23]. This shifted in the 18th century towards a neural hypothesis supported by neurologists like Edward Living and William Gowers [24]. The 20th century saw systematic research into migraine pathophysiology by neurologists such as Harold Wolff [24]. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), migraine with aura involves recurrent attacks of unilateral, fully reversible visual, sensory, or other CNS symptoms, usually followed by headache and other migraine symptoms [25–27]. The patterns of aura in migraine resemble cortical spreading depression (CSD), characterized by the progression of visual aura from the central visual field to the periphery, transient focal hyperemia followed by oligemia, and the effectiveness of ketamine in reducing aura intensity [28–32]. Moskowitz's hypothesis links the aura and headache phases, emphasizing the role of the ophthalmic division of the trigeminal ganglion, which surrounds large blood vessels and dural venous sinuses [33–36]. Stimulation of these fibres releases substance P and calcitonin gene-related peptide (CGRP), causing vasodilation and contributing to migraine pathogenesis [35,36]. Trigeminal ganglion stimulation also induces mast cell degranulation and release of inflammatory mediators, highlighting the interplay between vascular and neuronal factors in migraine [35,36].

In summary, vascular changes are not sufficient alone to explain migraine; instead, increased neuronal sensitization to sterile inflammatory stimuli appears to be responsible for clinical features. The exact neural mechanisms and genetic predispositions remain unclear [33–36]. This review aims to explore the relationship of migraine with female gender and gender-specific treatments, including non-pharmacological approaches.

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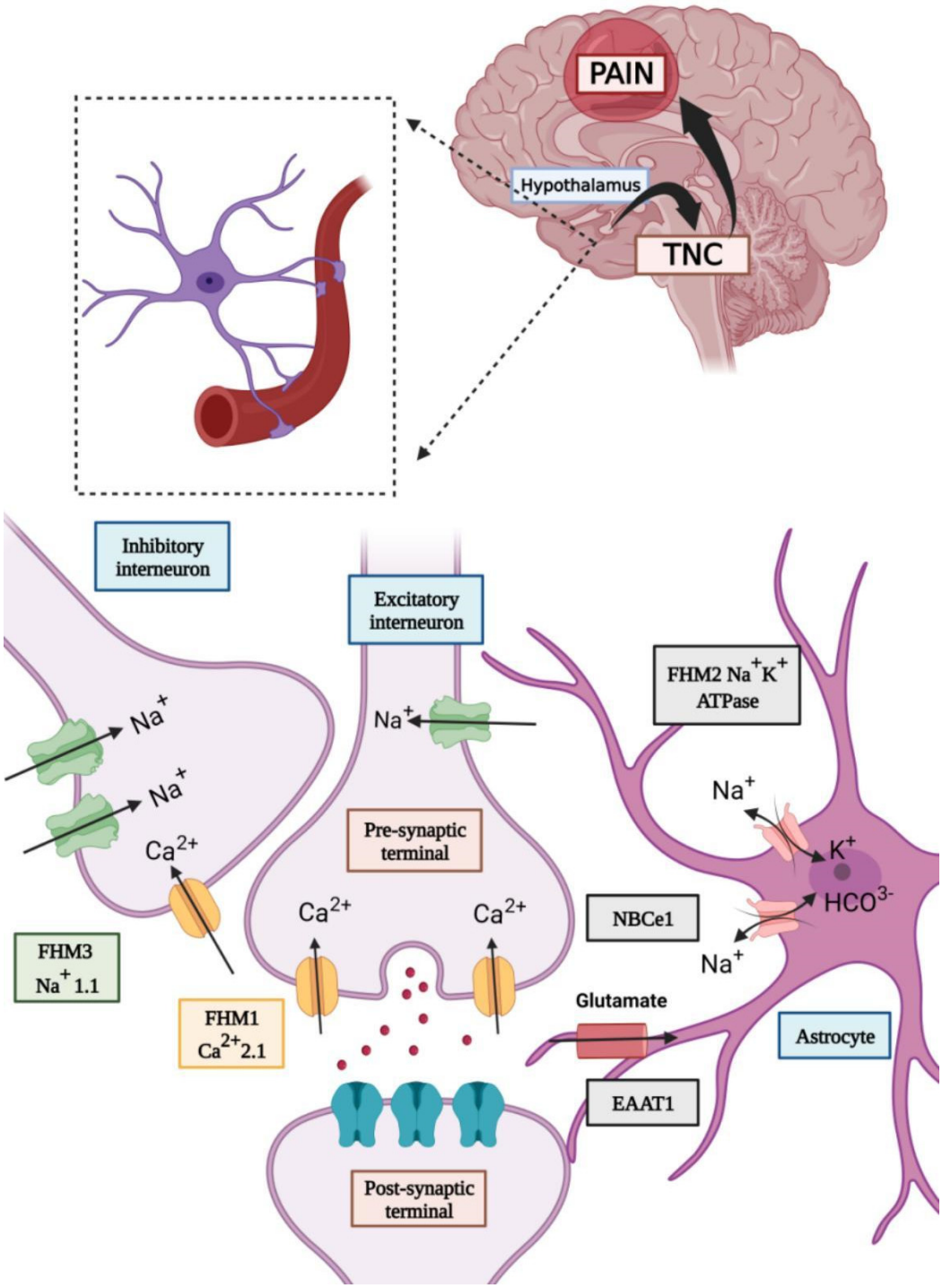

Figure 1. Pathophysiology of Migraine: Migraine begins with dysregulation in the hypothalamus, which activates the trigeminovascular system involving the trigeminal nucleus caudalis (TNC). The TNC becomes hyperactive, processing nociceptive signals from the meninges and cervical structures and transmitting pain signals to higher brain centres. Concurrently, overactive excitatory neurons utilizing glutamate lead to cortical spreading depression (CSD), a wave of neuronal depolarization followed by suppression. Genetic factors, such as mutations in CACNA1A (FHM1), SCN1A (FHM3), and dysfunctions in the Na+-HCO3- cotransporter 1 (NBCE1) and the excitatory amino acid transporter 1 (EAAT1), exacerbate this hyperexcitability by disrupting ion homeostasis and

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neurotransmitter regulation. This cascade results in the characteristic headache and sensory disturbances of a migraine.

Impact of Sex Hormones in the Pathophysiology of Migraine

Migraines are often triggered by sensory and environmental stimuli such as bright lights, loud sounds, stress, exertion, irregular sleep, alcohol, or hormonal fluctuations [37,38]. This sensory sensitivity is due to dysfunctions in monoaminergic sensory control systems in the brainstem and hypothalamus, amplified in women during hormonal fluctuations of the menstrual cycle [37,38]. Estrogen and progesterone significantly impact brain function. In female migraineurs, migraines often begin at menarche, improve during pregnancy, and worsen during perimenopausal years, but generally improve after natural menopause [37–39]. Sixty per cent of female migraineurs report increased frequency during the perimenstrual period, correlated with abrupt falls in estrogen and progesterone levels [38,39]. Pavlović et al. compared sex hormone levels and rates of change between females with and without a history of migraine and reported that females with a history of migraine demonstrated a faster late luteal phase estrogen decline compared to controls. Migraine attacks increase during the perimenstrual period in approximately half of females who experience migraine. There are notable differences in the pathogenesis and clinical features of menstrually-related migraines compared to non-menstrual migraines [40]. Güven et al. reported that menstrually-related migraines last longer, and accompanying symptoms reported nausea, vomiting, phonophobia, headache aggravation with physical activity, premonitory symptoms, and allodynia are more frequent and diverse in patients with menstrually related migraine without aura, suggesting increased brain excitability or susceptibility in these patients [41].

Estrogen and progesterone also exert widespread effects on various neurotransmitter systems. In the central serotonergic system, estrogen enhances serotonin synthesis and receptor sensitivity, potentially stabilizing mood and mitigating pain [42,43]. Estrogen's influence extends to the opioid system by increasing endogenous opioid activity, which helps modulate pain. It also impacts substance P receptor expression, a neuropeptide involved in pain pathways, potentially altering pain perception [44–46]. Estrogen boosts norepinephrine (NE) synthesis and release, which affects mood and alertness, while it enhances dopamine synthesis and receptor sensitivity, influencing mood and reward pathways [47,48].

Additionally, estrogen promotes endorphin release, contributing to pain relief and mood improvement [49]. It increases prolactin release, particularly during pregnancy and postpartum [49]. Estrogen also plays a crucial role in modulating calcitonin gene-related peptide (CGRP), a key player in migraine pathophysiology, by influencing its expression and release, which can promote vasodilation and neurogenic inflammation, potentially triggering migraines [50]. The International Classification of Headache Disorders, 2nd edition (ICHD-II), defines menstrual-related migraines as those occurring between -2 to +3 days of the menstrual cycle, whereas pure menstrual migraines occur only during these days [35]. Menstrual migraines are associated with estrogen withdrawal during the late luteal phase. Early studies demonstrated that estradiol supplementation delayed migraines until estrogen levels dropped to pretreatment levels [32]. Progesterone supplementation delayed bleeding but did not affect migraines, indicating that sudden estrogen withdrawal precipitates migraines [32]. Recent studies have shown faster declines in conjugated urinary estrogens (E1c) in female migraineurs compared to controls during the late luteal phase, supporting the role of estrogen withdrawal in migraine in the luteal phase [15,36]. During pregnancy, sustained high levels of estrogen and progesterone are maintained by the corpus luteum and placenta, leading to decreased migraine frequency [37,38]. However, most women report a return of migraines post-delivery. Conditions associated with declining estrogen levels, such as the late luteal phase, post-delivery, and hormone-free periods in contraceptive or HRT users, correlate with worsening migraines [50,51]. Conversely, natural menopause with gradual estrogen declines or sustained high estrogen levels during pregnancy significantly improves migraine attacks. Perimenopause, characterized by fluctuating ovarian hormones, often worsens migraine patterns [52–54].

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The variability in migraine patterns due to hormonal changes remains unexplained for some women. Ovarian hormones influence migraine pathophysiology through activational effects on brain neurotransmitters [55–57]. Estrogen affects the brainstem and hypothalamus monoaminergic sensory control system, impacting serotonin and norepinephrine and impairing antinociceptive regulation. Estrogen also affects vasculature via increased nitric oxide activity, enhances neuronal excitability through glutaminergic system facilitation, and suppresses the GABAergic system. Cortical spreading depression (CSD), implicated in aura, relies heavily on glutaminergic transmission [58–60]. Combined oral contraceptives (COCs) stabilize hormonal fluctuations by providing consistent levels of estrogen and progestin. However, COCs have only demonstrated minor changes in the course of perimenstrual migraine in menstruating women with migraine [61]. Estro-progestin drugs in patients who use them may induce hyperinsulinism and hypoglycemia, thereby increasing the severity of migraines [62]. A systematic review reported that COC users with a history of migraine were 2-4 times more prone to an ischemic stroke than nonusers with a history of migraine [63]. Hormonal imbalances, including elevated androgens and irregular estrogen and progesterone levels, characterize polycystic ovary syndrome (PCOS). Hyperandrogenemia associated with PCOS may have a protective effect on migraine headaches; however, other manifestations and complications can exacerbate hormonal imbalances, thus inducing migraines. The association between PCOS and migraines may be partly explained by poor sleep quality in women with PCOS due to reduced REM sleep time [64]. There is conflicting evidence regarding the frequency of migraines after menopause. A meta-analysis reported that there may be an improvement in migraine after menopause, although there may be an increase in migraine frequency during perimenopause. Conversely, studies conducted on patients at headache centres often report no improvement or even worsening of migraines after menopause. The aetiology of menopause appears to influence the evolution of migraines during this period, with spontaneous menopause more likely to result in migraine improvement compared to surgical menopause [65]. Perimenopause is always marked by an increased prevalence of migraines in women, many of whom also experience vasomotor symptoms. Fluctuating estrogen levels influence migraines during this time, as estrogen withdrawal can trigger menstrual attacks of migraine without aura, and high estrogen levels can trigger migraine with aura [65]. Maintaining a stable estrogen environment through hormone replacement therapy can benefit women suffering from estrogen-withdrawal migraines and provide relief from vasomotor symptoms. For women with migraines, whether with or without aura, using the lowest effective doses of transdermal estrogen to control vasomotor symptoms helps minimize the risk of side effects. Cyclical progestogens can adversely affect migraines, so continuous progestogens, as provided by the levonorgestrel intrauterine system or continuous combined transdermal preparations, are preferred [66]. Vascular and neuronal effect is shown in Figure 2.

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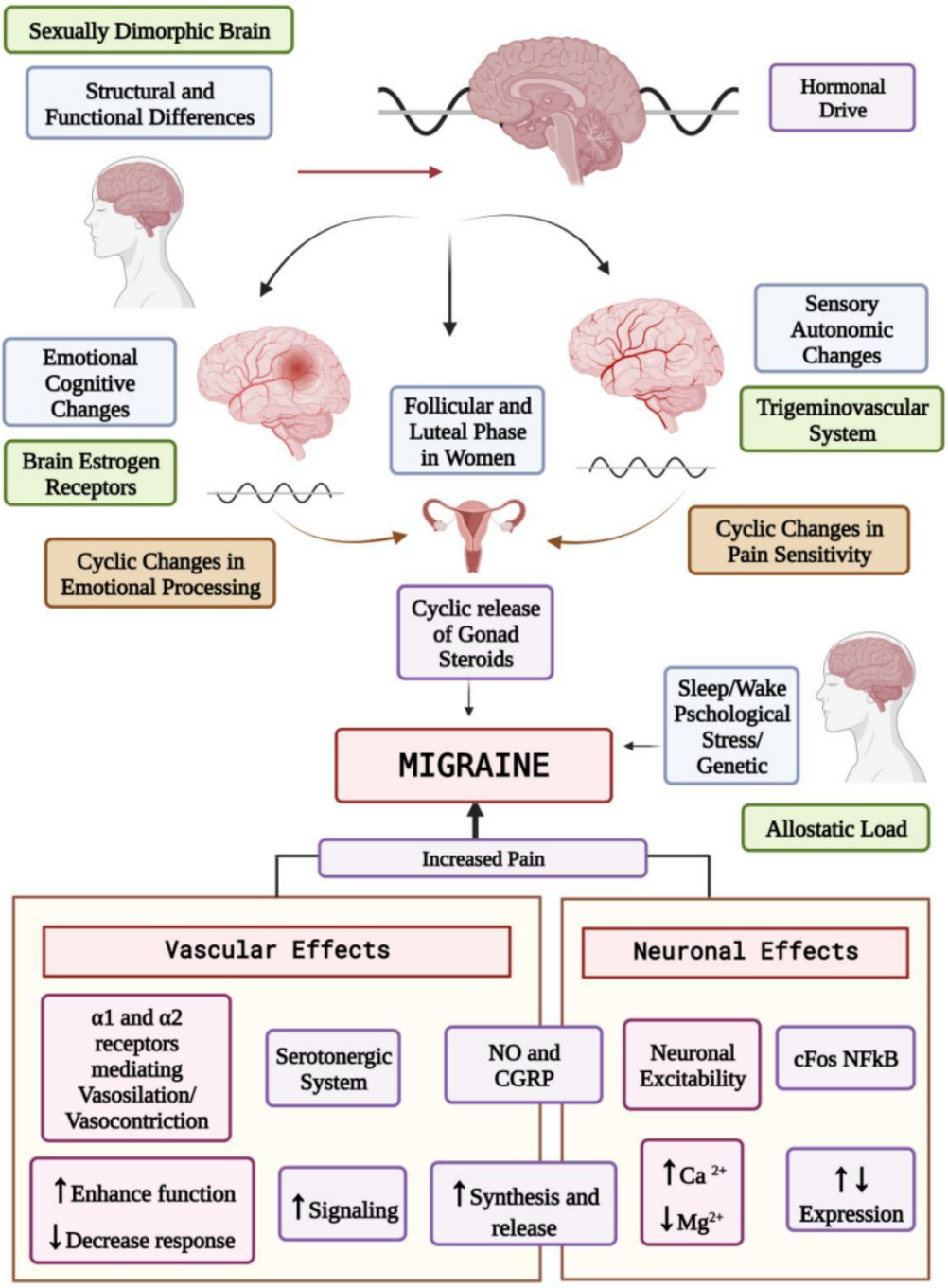

Figure 2. Estrogen-mediated activation of alpha-1 receptors promotes vasoconstriction, while activation of alpha-2 receptors induces vasodilation. Additionally, estrogen enhances the serotonergic system, increasing serotonin levels, which can affect vascular tone and pain perception. These conflicting effects can lead to fluctuations in blood vessel diameter, contributing to the vascular component of migraines. Estrogen also stimulates the synthesis and release of nitric oxide (NO) and calcitonin gene-related peptide (CGRP), both potent vasodilators that play critical roles in migraine pathogenesis by promoting neurogenic inflammation and vasodilation, exacerbating pain. Furthermore, estrogen increases intracellular calcium levels and decreases magnesium levels, which heightens neuronal excitability and susceptibility to cortical spreading depression (CSD) associated with migraine aura and headache. Elevated estrogen levels also upregulate the expression of immediate early genes like cFos and pro-inflammatory transcription factors like NF-κB, which are

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involved in pain signalling pathways. The increased neuronal activity and inflammation due to these factors amplify pain perception during a migraine attack.

Physiology of the Female Hormonal Life Cycle

Estrogen and progesterone are crucial hormones for female health, influencing various organ systems, including the brain, throughout a woman's life, from menarche to menopause [67]. They regulate the menstrual cycle, support pregnancy, and contribute to the development of secondary sexual characteristics. While estrogen and progesterone levels are high at birth, they decrease within months and remain low until puberty [68]. Puberty marks a significant increase in circulating sex hormones, primarily estrogen, which drives physical changes such as breast, vagina, uterus, and ovary development, as well as the onset of menstruation [69]. During the reproductive period, hormone levels fluctuate in a cyclical pattern over an average 28-day menstrual cycle, comprising the follicular and luteal phases, with each cycle starting on the first day of menstrual bleeding [70]. During menstruation, estrogen and progesterone levels are low. Estrogen gradually rises, peaking at the end of the follicular phase before a rapid decline just before ovulation due to luteinizing hormone (LH) surge. In the luteal phase, progesterone levels rise and plateau due to corpus luteum secretion, accompanied by a second rise in estrogen levels. In the absence of pregnancy, the corpus luteum degenerates, leading to decreased hormone levels and menstrual initiation [71]. This cycle repeats throughout the fertile period.

During pregnancy, estrogen and progesterone levels remain high and increase significantly, with the placenta maintaining their levels. They peak during the third trimester, around 32 weeks of gestation [72]. Postpartum delivery of the placenta reduces the levels of all placenta-produced hormones, leading to extremely low sex hormone levels comparable to menopause [73]. Perimenopause typically starts in the late forties, during which menstrual cycles become irregular due to a gradual decline in sex hormone levels [74]. Menopause is reached when a year passes after a woman's last menstrual period, with low hormone levels causing physical, mental, and emotional issues [75]. These hormonal fluctuations throughout a woman's life lead to significant physical and mental changes, increasing susceptibility to certain conditions, particularly affecting the brain and nervous system [76].

Effects of Sex Hormones on the Central Nervous System

In the brain, the effects of female sex hormones are broadly classified into organizational and activational categories. Organizational effects are long-lasting changes in brain structure, such as myelination and synapse strengthening, that permanently alter the brain's architecture. Activational effects involve temporary changes in brain activity through modulation of neurotransmitters, significantly impacting brain function on a short-term basis. [36,39]. Estrogen and progesterone improve the brain's resilience by upregulating enzymes that reduce free radicals, thereby minimizing oxidative stress. They also activate anti-apoptotic pathways that prevent cell death and promote the proliferation of neural cells, contributing to brain health and function. Progesterone specifically plays a crucial role in regulating neuronal myelination and glial cell activity, which is essential for maintaining the integrity and efficiency of neural networks. While estrogen and progesterone do not work synergistically, their combined effects are achieved during the natural hormonal fluctuations of the menstrual cycle. These fluctuations ensure that the protective and regulatory actions of these hormones are balanced, thus supporting both the structural and functional health of the brain throughout a woman's reproductive years [36]

Effects on Neurotransmitter Systems

1. **Effect on Nitric Oxide**: Disturbances in nitric oxide (NO) signaling have been implicated in the initiation and progression of migraine attacks. Abnormalities in NO levels have been observed in various stages of migraine, including during the prodromal phase, aura, and headache phase. The vasodilatory effects of NO can lead to cerebral blood flow dysregulation, potentially contributing to migraine aura and headache [77]. Endogenous estrogen enhances NO production and bioavailability

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within the vasculature via upregulation and increased activity of endothelial Nitric Oxide Synthase (eNOS), an enzyme critical for NO synthesis. When combined with estrogen, progesterone or synthetic progestins help maintain high levels of eNOS. NO plays an important role in regulating the neuroplasticity of synapses, which contributes significantly to the neuroprotective functions of estrogen. By promoting NO production, estrogen supports vascular health and facilitates the adaptability and resilience of neural connections in the brain. [38,52].

2. **Effect on Norepinephrine and Alpha Receptors**: Estrogen's influence on norepinephrine synthesis and breakdown is not fully defined. Estrogen infusion in ovariectomized rhesus macaques increased norepinephrine activity in the hypothalamus. The mechanism may involve estrogen's influence on genes, enhancing norepinephrine activity. Estrogen treatment in rats upregulated alpha one receptors in the nucleus tractus solitaries (NTS), but mestranol treatment decreased alpha two receptors in the NTS and frontal cortex and both alpha one and alpha two receptors in the locus coeruleus. NE is involved in pain processing and modulation, and alterations in NE levels or receptor expression can influence migraine susceptibility and severity. Estrogen's ability to increase NE activity in certain brain regions, such as the hypothalamus, may contribute to the onset or exacerbation of migraine. [40,51]

3. **Effect on GABA:** Estrogen and progesterone have complementary roles in modulating neurotransmission. Estrogen decreases GABA neurotransmission by inhibiting L-type calcium channels, leading to increased synaptic activity of glutamate and dopamine. This promotes excitatory neurotransmission, which can contribute to the onset and severity of migraines by enhancing neuronal excitability and cortical spreading depression, a wave of neuronal and glial depolarization associated with migraine aura. In contrast, progesterone promotes GABA activity by enhancing the activation of GABA-A receptors and increasing the function of GABA-mediated chloride channels, hyperpolarizing the cell membrane and inhibiting synaptic impulse transmission. The inhibitory effects of progesterone help stabilize neural activity, counterbalancing the excitatory effects of estrogen. During the menstrual cycle, the drop in estrogen levels just before menstruation can reduce its inhibitory effect on GABA neurotransmission, leading to increased neuronal excitability and the potential for migraine attacks. Conversely, the stabilizing effects of progesterone on GABA neurotransmission may offer some protective benefits against migraine triggers. [52,53].

4. **Effect on Glutamate**: Migraine pain-relay centres, such as the trigeminal ganglion, trigeminal nucleus caudalis, and thalamus, contain neurons that express glutamate that plays a key role in activating the trigeminal nucleus caudalis, a critical relay station involved in pain processing. Furthermore, glutamate is implicated in several migraine-related processes, including cortical spreading depression, trigeminovascular activation, and central sensitization, all of which contribute to the generation and propagation of migraine pain [78]. Estrogen increases glutamate release, upregulates NMDA receptor expression, and enhances receptor sensitivity, promoting neuron excitability, learning and memory. Progesterone inhibits glutamate transmission, release, and receptor sensitivity. Allopregnanolone inhibits glutamate release via L-type calcium channel inhibition on presynaptic neurons [52–54].

5. **Effect on Dopamine:** Estrogen upregulates dopaminergic receptors, increases dopamine synthesis, and reduces its breakdown and reuptake in synapses, influencing addiction, pleasure, rewards, motivation, and learning. Dopamine also plays a role in migraine pathophysiology, with most migraine features being inducible by dopaminergic stimulation. Migraineurs exhibit hypersensitivity to dopamine receptor agonists, experiencing migraine symptoms at doses ineffective in non-migraineurs. Dopamine receptor antagonists are effective in migraine treatment, particularly when combined with other anti-migraine agents [58,59].

6. **Effect on Serotonin:** Serotonin regulates mood, sleep, sexual behaviour, and cognitive functions, playing a role in psychiatric and neurological disorders, including migraine. Estrogen activates estrogen receptors in the trigeminovascular system, upregulating enzymes in serotonin production pathways like Tryptophan hydroxylase and downregulating enzymes in serotonin breakdown like Monoamine oxidase (MAO). Estrogen also increases the expression of 5HT1A, 1B, and 2A receptors and inhibits serotonin reuptake by presynaptic neurons. This leads to increased

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serotonin levels and activity in the trigeminovascular system, contributing to migraine pathogenesis. Serotonin and its receptors decrease following a fall in serum estrogen levels, leading to sensory control system dysfunction in the hypothalamus and brainstem (including the trigeminal nucleus), predisposing females to migraines [79].

7. **Effect on CGRP:** Calcitonin Gene-Related Peptide (CGRP) is a potent vasodilator primarily stored and secreted in sensory neurons, contributing to the pain pathway, particularly in migraine pathophysiology. Studies show that women in estrogen-deprived states (perimenopausal/post-late luteal estrogen peak) have higher plasma and urine CGRP concentrations. Conversely, replenishing estrogen in ovariectomized animals reduces plasma CGRP levels and CGRP receptor expression in the trigeminovascular system. The exact mechanism by which estrogen modulates CGRP levels remains unclear, but it is a basis for increased susceptibility to migraines and hot flashes, especially during perimenopause and the late luteal period. Notably, while many migraine patients experience reduced attacks post-menopause, those who have undergone surgical ovariectomy, often experience worsened migraine attacks due to the sudden fall in serum estradiol levels, unlike the gradual decline post-physiological menopause [34–36]. These activational effects of sex hormones on the central nervous system demonstrate the intricate modulation of neurotransmitter systems, highlighting the significant influence of estrogen and progesterone on brain function and behavior throughout a woman's life cycle.

Management of Migraine

Migraine is characterized by sudden, severe headaches that occur recurrently, significantly impacting an individual's quality of life and imposing a substantial socioeconomic burden on society [80]. Diagnosis relies heavily on the accuracy of history taking, which is subjective. Therefore, research focuses on identifying biological markers or specific changes in brain structure or function to improve diagnosis and treatment [81]. Migraine is three times more common in women than in men, leading to a negligible representation of men in migraine studies [82].

Migraine management is typically categorized into two types: episodic (less than 15 headache days per month) and chronic (15 or more headache days per month) [83]. Treatment usually involves a two-pronged approach: abortive therapy, which aims to relieve symptoms during an attack, and preventative therapy, which aims to reduce the frequency and severity of attacks [84–88]. Approximately 30-50% of cases find relief with abortive therapy, while around 40% require both approaches for effective management of severe, recurring episodes. Preventative measures are especially important for chronic cases and about a third of acute migraine patients [89]. Chronic migraine significantly impairs quality of life and is associated with increased incidence of comorbidities such as mood disorders, medication overuse, and obesity [87,88]. However, minimal compliance with treatment remains a major challenge, often due to issues of tolerance and safety [90,91]. The primary goal of migraine management is to avoid the overuse of over-the-counter headache medications, ensure timely and effective abortive medication during acute attacks, minimize headache intensity and frequency, and ensure an economical approach to management [92–94]. Pharmacological options for migraine management include calcium channel blockers, beta-blockers, tricyclic antidepressants, and anticonvulsants, with varying evidence regarding tolerance and efficacy [95,96]. Understanding gender-based differences in response to migraine medication can lead to more effective and targeted treatment strategies. Pharmacokinetics and pharmacodynamics differences between males and females is shown in Figure 3.

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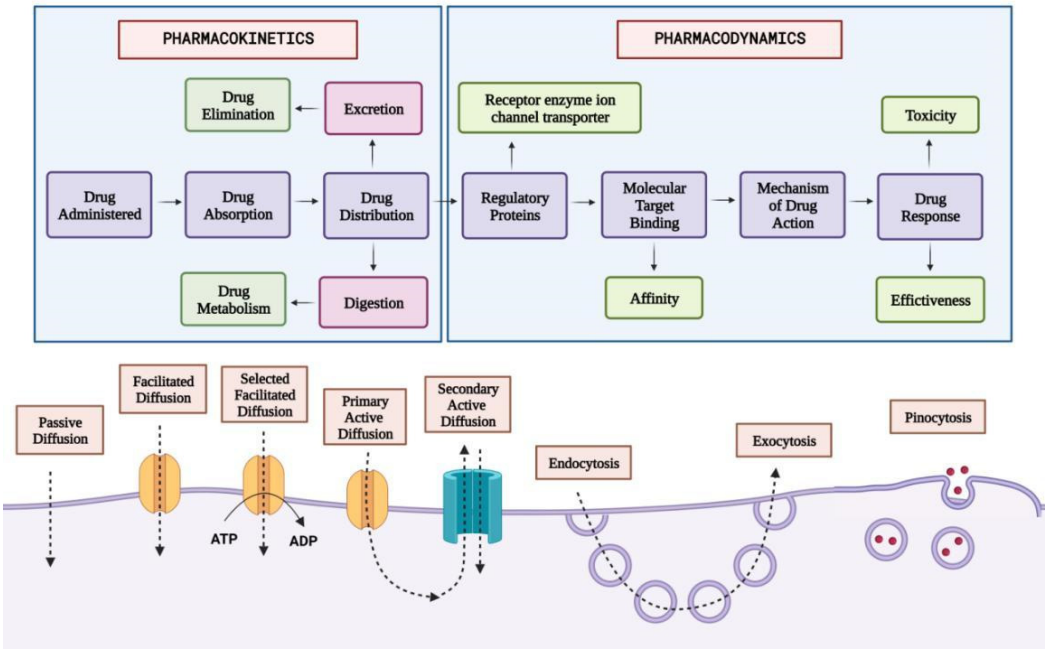

Figure 3. Pharmacokinetic and pharmacodynamic differences between males and females. This figure illustrates the processes involved in pharmacokinetics and pharmacodynamics, emphasizing the differences between males and females in drug absorption, distribution, metabolism, excretion, and response. The figure emphasizes that males and females may differ in these pharmacokinetic and pharmacodynamic processes due to variations in physiology, enzyme activity, hormonal levels, and body composition, impacting drug effectiveness and safety.

Abortive Therapy For the Management of Migraine

Abortive therapy for managing migraines involves a range of medications such as triptans, ergot derivatives, NSAIDs, paracetamol, opioids, and other derivatives. However, studies focusing on understanding gender-based differences in the response to therapy are very limited [97]. An overall pattern of compliance to prescribed medications is observed in women with triptans or ergot derivatives, while men mainly use over-the-counter medications for such acute attacks (NSAIDs, ibuprofen, acetylsalicylic acid, etc.) [98,99]. Moreover, women have a higher report of remission at 2 hours and 24 hours after medication and show higher relapse rates [99].

1. **Triptans:** Triptans comprise a class of medications approved by the US Food and Drug Administration (FDA) as the first-line agent for treating acute migraine episodes with or without aura [101,102]. In the United States, seven triptans are available in diverse dosage formulations, including Sumatriptan, Naratriptan, Zolmitriptan, Rizatriptan, Almotriptan, frovatriptan, and Eletriptan [103]. Triptans bind to the vascular 5-HT1B receptors, leading to vasoconstriction of the cranial arteries, which dilate during a migraine attack. Triptans bind to the neurogenic and central 5-HT1D receptors and prevent the release of vasoactive neuropeptides by inhibiting trigeminal nerve activation and blocking the transmission of pain signals to the central nervous system [104]. Triptans are available in multiple dosage forms, including oral tablets, orally disintegrating tablets, nasal sprays, and SQ injections to accommodate patient preferences [103]. Patients are instructed to administer triptans at the first onset of the headache phase of a migraine attack, as their efficacy diminishes if taken during the aura phase before the onset of the headache [104]. If a patient has no response to one of the triptans after III trials, increasing the dose, switching to a different dosage of the same agent, or another triptan should be considered [105]. Triptans may cause nausea, dizziness, coronary vasoconstriction, flushing and paresthesia [106].

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2. **Sumatriptan:** Sumatriptan acts as an agonist on 5-HT1B/1D receptors by inducing vasoconstriction in the basilar artery and blood vessels within the dura mater. The drug reduces peripheral nociception either by selective cranial vasoconstriction or by affecting trigeminovascular nerves [107].
3. **Frovatriptan:** It is the most potent triptan for its selective action on the 5HT1B receptor. It has a high affinity for 5HT1B and 5HT1D, like other triptans, and also a moderate affinity for 5HT1A and 5HT1F [108,109]. Studies have revealed the role of estrogen in mediating serotonin levels in the raphe nucleus by regulating the function of the tyrosine hydroxylase enzyme involved in the synthesis of 5HT and reducing the reuptake of this neurotransmitter. Estrogen also lowers the vasoconstriction effect of 5HT [110,111]. Frovatriptan attains twice the higher plasma levels in females as compared to males due to higher bioavailability in females [111–113]. It has a longer half-life and also a lower recurrence rate in the next 24 hours [114]. Naratriptan, Rizatriptan, and Zolmitriptan also exhibit similar efficacy in migraine management; however, they do not exhibit a sexually dimorphic response [115]. Frovatriptan is chiefly metabolized by CYP1A2 and is cleared by the kidney and liver making moderate failure of either organ not a limiting factor in treatment. Frovatriptan has a low risk of interactions with other drugs [116].
4. **Lasmiditan**—Lasmiditan is a high-affinity, highly selective 5-HT1F receptor agonist that acts on the trigeminal system, where it hyperpolarizes nerve endings and reduces the release of CGRP to provide pain relief [117]. Because it is selective to 5-HT1F receptors, lasmiditan has no action on 5-HT1B/1D receptors located on cerebral blood vessels and does not involve vasoconstrictive mechanisms [118]. Lasmiditan can be used as an acute therapy for migraine in patients for whom triptans may be ineffective or contraindicated [119]. It is less likely to produce other side effects common to triptans, such as chest, neck, and throat tightness, and, therefore, may be a useful option for patients who experience these undesired phenomena [120]. The most common adverse effects associated with Lasmiditan use include dizziness, nausea, fatigue and paresthesias, which are dose-dependent [121].
5. **NSAIDs:** Non-steroidal anti-inflammatory Drugs (NSAIDs) function by inhibiting the enzyme cyclooxygenase, which is responsible for the conversion of arachidonic acid into prostaglandins, especially E1, F2α, I (prostacyclin). These prostaglandins alter the excitability of afferent neurons and the sensitivity of the trigeminal nerve [122].
6. **CGRP Antagonist**: CGRP antagonists reduce neuronal inflammation and thereby provide relief from migraine headaches [123]. Some of the CGRP antagonists that have the potential for abortive management of migraine episodes are Rimegepant, Olcegepant, and Telcagepant. Studies in healthy human beings have revealed that CGRP levels are higher in plasma in females than in males [123]. Animal experiments have revealed that in ovariectomized rats, administration of estrogen increases the level of CGRP in the arterioles. This establishes the fact that CGRP levels are higher in males than females and are particularly raised at higher levels by the intake of estrogen-containing birth control pills [124]
7. **Hormone Therapy:** Fluctuating levels of sex steroids, both estrogen and androgen, have been found to be associated with frequent attacks of migraine. Menstrual migraine is one such condition where the fluctuation of plasma estrogen level is more drastic than in non-migraineurs [125]. This was proved in a study where intramuscular administration of estrogen during the perimenstrual period led to the postponement of migraine attacks. However, the same effect was not seen in the administration of progesterone during migraine attacks [126,127]. HRT, which is used for the management of postmenopausal symptoms, can also lead to the onset of migraine de novo or worsening of the preexisting condition. These conditions can be managed by minimizing the degree of fluctuation of the level of estrogen. This can be done by administration of gels and patch forms of sex steroids rather than their oral variants [128,129]. The association of migraine attacks is higher in surgically induced menopause than in naturally induced conditions. Furthermore, studies have shown that in male-to-female transsexuals, the use of anti-androgens to suppress male characteristics has led to an increased frequency of migraine attacks [130].
8. **GnRH Agonist:** Recent studies have shown the role of GnRH agonists in the management of severe treatment-resistant menstrual migraine. Administration of GnRH agonists with a specific

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dose of estrogen and progesterone has shown relief in menstrual migraine. The role of GnRH agonists in migraine of males has not been studied yet [131].

9. **Prophylactic Therapy for Migraine:** The main aim of prophylactic therapy is to reduce the frequency and severity of the episodes in chronic cases. There is a wide range of therapeutic options available like calcium channel blockers, antiepileptic drugs, botulinum neurotoxin, and antibodies against CGRP. Sexually dimorphic response to prophylactic management has not been identified yet. However, it is noted that women are more likely to use prescribed medications for prophylactic therapy than males [132].

Drugs commonly used for prophylactic management: Focused on Sex-based differences

1. **Propranolol:** Propranolol is a non-selective beta-blocker often used in the prophylactic treatment of migraine. The clearance of propranolol from plasma is lower in females compared to males. Thus, women may have higher plasma concentrations of the drug for a longer period, potentially increasing both its efficacy and the risk of side effects [133].

2. **Atenolol**: Atenolol, another beta-blocker, is also used for migraine prevention. Females exhibit lower clearance and a lower volume of distribution for atenolol, leading to higher plasma concentrations compared to males. This higher concentration could enhance the drug's effectiveness in preventing migraines in women but might also increase the likelihood of side effects. Therefore, careful monitoring and possible dose adjustments are important when prescribing atenolol to females [133].

3. **Verapamil**: Verapamil is a calcium channel blocker used for migraine prevention. The bioavailability of verapamil is higher in females than in males, resulting in increased plasma concentrations of the drug. Thus, women may experience more pronounced effects, both therapeutic and adverse [133].

4. **CYP45A**—The cytochrome P450 enzyme system (CYP450) and P-glycoprotein play crucial roles in drug metabolism and clearance. There are various sex-based differences in the activity of these enzymes, making the pharmacokinetics of many drugs, including those used for migraine prevention, more complex in males and females. These differences can affect the metabolism and clearance rates of various medications, necessitating sex-specific considerations in drug dosing and management [133].

5. **SSRIs:** SSRIs are sometimes used off-label for migraine prevention. Females tend to have increased bioavailability of SSRIs due to reduced hepatic metabolism, thus more likely to achieve therapeutic plasma concentrations at lower doses than men [133].

6. **Anti-epileptics**: The primary role of antiepileptics in migraine prevention is to suppress the CSD (cortical spreading depression) and thus prevent neural inflammation and trigeminal sensitization [134]. They act by stabilizing the voltage-gated ion channels and preventing neuronal stimulation [135]. Topiramate and sodium valproate are the only two AEDs that are FDA-approved for the prevention of migraine. The most striking sex-based pharmacokinetic difference in antiepileptics is the increased rate of elimination and hepatic clearance associated with increased activity of CYP enzymes and increased protein binding capacity during pregnancy and intake of OC pills [136].

Alternative treatment approach for migraine

Alternative treatment approaches for migraine encompass a range of methods, including nutraceuticals, behavioral techniques, and surgical interventions. These approaches provide potential alternatives or complements to traditional migraine treatments, especially for cases resistant to pharmacologic interventions.

Nutraceuticals

1.1 **Riboflavin (Vitamin B12)**—Riboflavin is a precursor of flavin mononucleotide and flavin adenine dinucleotide. All these coenzymes are important for energy production inside mitochondria and energy-related cellular functions. During magnetic resonance spectroscopy

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use of Riboflavin in migraine emerged, and studies suggest that there can be mitochondrial dysfunction in the migraine brain. In Belgium the first randomized controlled trial to assess the use of Riboflavin was done in which 400 mg of the daily dose was tested in 55 adult migraine patients (with or without aura). Riboflavin showed positive results by reducing headache and attack frequency with only minor or rare adverse effects compared to placebo. AAN/AHS guidelines have given evidence B for the treatment of migraine. The recommended dose is 400 mg daily for at least three months, during which adverse effects like diarrhoea, polyuria and yellowish discolouration of urine are noticed. Still, research is needed on Riboflavin. Riboflavin Coenzyme Q10 plays a vital role in energy metabolism. In one randomized control trial, 50 migraine children and adolescents were given a dose of CoQ10 100 mg per day and compared to a placebo, and no difference or effect was seen. Further studies are needed to support the use of CoQ10 for migraine. CoQ10 is available in the market in the US, and AAN/AHS guidelines consider CoQ10 for the prevention of migraine. The recommended dose is 1-3mg/kg/day [137,138].

1.2 **Oral Magnesium**—The first study on oral magnesium was conducted by Faachine Hi et al.; 360mg of oral magnesium was given to 20 menstrual migraine patients compared to a placebo. Both groups reduced the frequency of migraine attacks and the pain [139,140].

1.3 **Petasites hybridus or butterbur**—Butterbur root is an herbal extract. Petadolex is a tablet made of butterbur root extract manufactured in Germany, and safety concerns there due to its liver toxicity issues. To date, two placebo-controlled trials have been conducted for the first time by Lipton et al., in which 50 mg and 75 mg doses reduced migraine attacks with no adverse effects. Another study conducted by Diener in which 100mg butterbur was given for 12 weeks showed promising results by reducing migraine attacks compared to placebo [137,138].

1.4 **Tanacetum parthenium**—Little evidence is available to date. One large study conducted by 170 migraine patients was given 625 mg of feverfew extract, which reduced attacks; multiple studies failed to show a positive effect of feverfew on migraine [137,138].

1.5 **OnabotulinumtoxinA-** Botulinum toxin is used as a muscle relaxant for pain. In 2010 FDA approved botulinum toxin (Brand name –Botox) for migraine prevention based on two large trials [137].

2. Behavioural Techniques

2.1 **Relaxation Technique—R**elaxation techniques (RT) include meditation, autogenic training and muscle relaxation. RT does not only help in relaxing muscles but also reduces stress. It also enhances self-efficacy, self-esteem and self-control. RT includes deep breathing, intense progressive muscular RT, guided imagery RT, etc. Studies suggest that RT can reduce migraine attack frequency to 41% and 43% [139].

2.2 **Cognitive Behavior Therapy-** Cognitive behaviour therapy (CBT) is mainly used for managing stress, anxiety, depression, sleep disorders, migraine pain, etc. CBT is mainly used when medication does not positively affect patients, such as during pregnancy, history of allergy to a specific medicine or medical comorbidities. CBT showed positive results with proper pharmacological therapies. CBT helps in the self-management of migraine pain; in a recent randomized trial, 135 children and adolescents were compared based on CBT plus amitriptyline with headache education plus amitriptyline. The CBT shows a positive result by reducing headaches to 11.5 in comparison to 20 weeks. In one study, CBT reduces stress; in another study, CBT reduces stress by 4% to 12%, and one CBT study helped reduce medication frequency by 20% to 25% [141,142].

2.3 **Mindfulness-** Mindfulness is becoming popular in the United States, but MF has a long relation with Buddhism, Hinduism and Daoism. Langer and colleagues were the first US researchers to examine the effect of MF on patients. MF-based stress reduction (MBSR) was developed by Kabat –Linn which is effective in chronic pain. Standard MBSR is an eight week two hours groups with a mindfulness retreat as a conclusive session of 6 hours. Well et al. conducted the first randomized controlled trial on 25 people with episodic migraine. After one month of MBSR, there was a reduced headache with enhanced self-efficacy. Acceptance and Commitment is the

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newest member of MF-based interventions. ACT is based on psychological flexibility in which the patient, day-to-day life obstacles and other life circumstances are addressed. ACT is divided into six core processes, i.e., acceptance, cognitive delusion, contact with the present, self-values and Commitment to action. In one study, patients receiving MF reduced the frequency of headaches to 50%. MF-based intervention reduces the symptoms of chronic pain, and still, further studies need to be done [140,141].

3 **Surgical Techniques for Migraine-** Surgical management for migraine was first attempted by Dr. Harvey Cushing, but his attempt was unsuccessful. Migraine surgery became famous in 1999 when two patients got relief from headaches after forehead rejuvenation. In this surgery, part of the globular muscles is removed around the supraorbital and supratrochlear nerves with an incision on the eyelid or endoscopically and skeletonizing the nerves. Still, research needed to be done on surgery as it is not only a brain disorder. It also involves functional and structural plasticity of both the central and peripheral nervous systems [140,141].

3.1 Complementary Alternative Medicine (CAM)

Complementary Alternative Medicine (CAM) for migraine includes a variety of non-conventional therapies, such as acupuncture, herbal supplements, chiropractic care, and relaxation techniques. While these treatments are not universally recommended, many people turn to CAM approaches to complement traditional medical treatments, seeking to reduce the frequency and severity of migraine attacks and improve their overall quality of life.

3.2 Acupuncture—Acupuncture is an ancient Chinese therapy based on the theory of disease causation secondary to an energy imbalance in the body. In acupuncture, needles are interested in acupoints (specific points along the energy meridians) in the body, which releases obstructed energy, which helps bring the body to balance and disease. A meta-analysis reported that acupuncture led to a 5% reduction in headache frequency. Acupuncture needs 6-8 sessions to manage symptoms of migraine. However, Acupuncture has adverse effects ranging from minimal effects like therapy failure or change in pain intensity to severe issues like bleeding, pneumothorax, infection, and nerve injury. Patients in whom pharmacological therapies are not effective are seen opting for acupuncture [137–139].

3.3 Homoeopathic medicine—Several individuals frequently use homoeopathic medicine for migraine attacks. Damiana is the most popular homoeopathic medicine for migraine. Ceanothus is used when a patient has a migraine due to acidity. When a patient has a frontal headache with nausea, Iris V is effective. A few more homoeopathic medicines are available for migraine treatment and management: Onosmodium, Ptelea, Robin, etc. Evidence for their use is still lacking and further research is required to understand their role in the management of migraine [139–141].

3.4 **Chiropractors**- Chiropractors are the most common complementary and alternative medicine (CAM) for treating and managing migraine. Roland et al. conducted an evidence-based chiropractic study that needs to be done based on guidelines even considering type, frequency, dosage, and duration of treatment [142]. Adverse effects of chiropractic study were seen in a controlled trial conducted by Aleksander et al. in which tenderness was seen [143]. Craig et al. highlighted important questions about the therapeutic approach to chiropractic migraine management that warrant further investigation. They reported that more primary research is needed to evaluate how chiropractors approach headache and migraine management, as well as to understand the prevalence, burden, and comorbidities of migraine within chiropractic patient populations [144].

Future Directions and Conclusion

Migraine is an episodic headache disorder that is more prevalent in women than men, with both male and female sex hormones playing significant roles in its pathophysiology. The estrogen withdrawal hypothesis is crucial in understanding hormonal therapy for migraine in females, although authentic evidence supporting this is lacking. Treatment for migraine includes abortive and preventive therapies, with triptans and NSAIDs falling under abortive therapy, and preventive therapies like SSRIs and propranolol mainly used for chronic cases. A recent meta-analysis of seven randomized clinical trials found that greater occipital nerve (GON) block significantly reduced the

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severity of pain in migraineurs compared to a control intervention. GON block is primarily used for prophylaxis in chronic migraine and in acute attacks of pediatric migraine, although its use in acute attacks of migraine is still limited.

Additionally, a non-hormonal correlation has been proposed as an alternative explanation for menstrual migraine, with studies showing lower ferritin levels in women with chronic recurrent migraine and a strong association between iron deficiency anaemia and menstrual migraine. Clinical evidence and genetic findings suggest a role for dopamine in migraine pathophysiology, with dopaminergic systems being correlated with multiple phases of migraine. Dopamine may modulate nociception pathways or alter cerebral blood flow, and dopaminergic hypersensitivity has been observed in the interictal state via neuroendocrine tests. Dopaminergic neural stimulation is influenced by sex steroids, particularly estrogen, which increases striatal dopamine synthesis and release. The correlation between the fall in estrogen levels and the risk of migraine attacks has been well-established. Apart from pharmacotherapy, nutritional supplements like vitamin B12 and behavioural techniques like CBT and mindfulness have shown positive results in migraine management. While migraine surgery, acupuncture, and homoeopathic medicine have also shown promise, further research is needed in these areas. Migraine treatment is not solely based on sex hormones, and all therapeutic interventions can be used for both male and female patients.

In conclusion, there is a significant gender-based difference in the manifestation pattern and response to therapy of migraine. Further studies are necessary to deepen our understanding of this aspect and enable more efficient management. Future research areas could include animal studies to elucidate the role of sex steroids in migraine pathophysiology, clinical studies on pharmacokinetics, and epidemiological studies to establish improved diagnostic criteria for faster and more effective treatment.

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Abbreviations

TMC	Trigeminal Nucleus Caudalis
EAAT1	Excitatory Amino acid transport
CSD	Cortical Spreading Depression
NE	Norepinephrine
CGRP	Calcitonin Gene Related Peptide
HRT	Hormone Replacement Therapy
COCs	Combined Oral Contraceptives
PCOS	Polycystic Ovary Syndrome
REM	Sleep Rapid Eye Movement Sleep
eNOS	endothelial Nitric Oxide Synthase
MAO	Monoamine Oxidase
NSAIDs	Non Steroidal Anti-inflammatory Drugs
SSRIs	Selective Serotonin Reuptake Inhibitors
RT	Relaxation Techniques
CBT	Cognitive Behaviour Therapy
MBSR	Mindfulness based Stress reduction
GON	Greater Occipital Nerve

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