

Advanced Neurotherapeutic Targeting and Precision Medication in Multifactorial Migraine Pathogenesis: Challenges and Future Perspectives

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ABSTRACT

Migraine is a complex, disabling and prevalent neurologic disorder characterized by dysregulated signalling of receptors and eccentric signal transduction across central and nociceptive pathways. Pathological activation of the trigeminovascular system derives the release of neuropeptides most critically Calcitonin Gene Related Peptide (CGRP) that act on cognate receptors to propagate neurogenic inflammation and peripheral sensitization. This review mentions the receptor-level mechanisms underpinning migraine pathophysiology, with particular emphasis on CGRP levels, ion channel dysregulation during Cortical Spreading Depression (CSD), and downstream signalling cascades mediating the trigeminovascular sensitization (TVS). Further it evaluates how mechanistic understanding of these pathways has directly led to the development of targeted therapeutics, including small-molecule CGRP antagonists called gepants, receptor-targeted monoclonal antibodies (mAbs), and neuromodulatory strategies that modulate aberrant signal transduction. The absence of validated receptor-based predictive biomarkers remains a significant translational gap. Bridging receptor pharmacology with precision medicine frameworks represents the most promising trajectory for optimizing individualized migraine neurotherapeutics and improving clinical outcomes.

Keywords: Migraine; Trigemino-vascular system; CGRP signalling; Neuromodulation; Biomarkers; Neuroinflammation; Cortical spreading Depression; Precision neurotherapeutics.

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1. INTRODUCTION

Migraine is a multifaceted neurological condition stemming from intricate interactions between peripheral and central brain neurons [1-4]. According to contemporary models, migraine can be outlined as a condition characterized by abnormal brain excitability and maladaptive sensory processing, which is influenced by genetic susceptibility, cortical network dysfunction, and TVS [5-8]. These biological systems further underline diverse sensory, autonomic, and cognitive manifestations as the key characteristics of migraine, which results in marked inter- and intra-individual variability in clinical presentation, disease progression, and therapeutic response [9-12].

Despite the complexity of migraine biology, it brings a health burden and global socioeconomic impact, as it affects economic stability and individuals' productivity and economic stability. The 2021 analysis by the Global Burden of Diseases reported that migraine is the second biggest contributor to years lived with disability (YLD) worldwide, affecting more than 1.16 billion people and has been escalating since 1990 in prevalence and disability,

with India being the foremost contributor to the global disease load having substantial socioeconomic burden of INR 18,000 crore, underlining its effect on the workforce efficiency and national economic burden [13-19]. An analysis found that the number of migraineurs increases with an increase in age and peaks at the age of late 30s, while women consistently have elevated levels compared to men across every age group [20].

In the last two decades, pivotal role has been played by experimental neurobiology in reshaping migraine research. The mechanistic advances have shifted from isolated vascular hypotheses to the integrated models of TVS, CSD, CGRP signaling, serotonin receptor subtypes, ion-channel dysfunction, maladaptive neuronal-glial interactions, hormonal factors, and genetic dysfunction [6,21-23]. Despite these developments, variation remains significant in the presentation of migraine, and its long-term outcomes as well as its therapeutic efficacy. Several patients still suffer from treatment resistance, suboptimal responses, or adverse effects. These findings underline the one-size-fits-all therapeutic paradigms' shortcomings and the need for

biomarker-guided and data-driven precision approaches[24-26].

Despite there have been extensive studies performed on clinical, mechanistic, and therapeutic perspectives of migraine, the limitations still exist on much extent. Therapy focus remained solely on neuropeptide signalling, CSD, or TVS, ignoring how the therapeutic developments are influenced by these experimental discoveries[27-29]. The focus of the clinical-based reviews is placed on treatment guidelines or pharmacological advancements without integrating the neurobiological principles that led to these innovations[30,31]. Therefore, the field lacks a cohesive framework for mapping this bridge between experimental migraine to mechanistically driven therapies, and eventually to personalized and data-driven clinical management.

This review seeks to address the current evidence linking migraine pathophysiology to evolving therapeutic strategies, with the emphasis on translational advancements and emerging approaches aimed at improving treatment stratification. By mapping neuropeptide signaling and integrating existing mechanistic frameworks with the clinical outcomes, we aim to provide a structured perspective on the current state and future direction of mechanism-driven migraine care and management.

2. Pathophysiology and biological basis of migraine

The pathophysiology of migraine is still not well understood. Two theories come on surface regarding the root of migraine; one contends that migraine triggers are due to external factors, while the other suggests that migraine originates due to the changes in the brain itself[9].

2.1 Neurovascular theory of migraine

TVS afferents are composed of numerous receptors, out of which transient receptor potential channels are the targets of nociceptive and vasoactive substances, which induce allodynia and hyperalgesia, thus triggering headache[21]. Activation of the trigeminal results in the release of neuropeptides like, including CGRP, Substance P (SP), glutamate, neurokinin A/B, serotonin, PACAP, and amylin in the trigeminovascular space[32,33]. Release of these peptides leads to dilated meningeal blood vessels and increased vascular permeability, resulting in neurogenic inflammation and plasma extravasation. The inflammatory reactions cause mast cell degranulation, which in turn releases histamine and cytokines, which sensitizes the nociceptors. The continual nociceptive input centrally sensitizes the Trigemino-cervical Complex (TCC), enhancing the pain signal further to the thalamus and somatosensory cortex, leading to migraine headache and related symptoms like photophobia and phonophobia[34]. Fig.1 schematically depicts the series of trigeminovascular activation, neuropeptide release, and neurogenic inflammation.

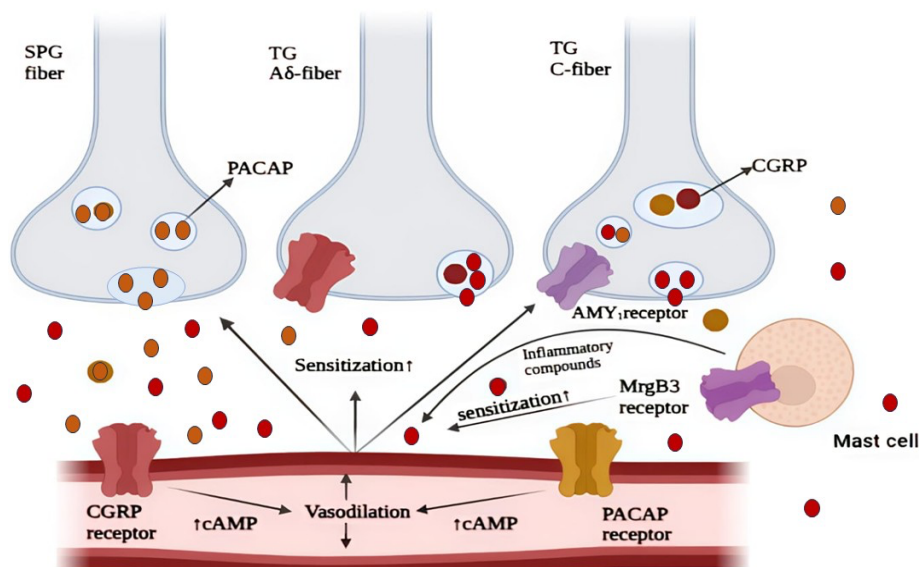


Figure 1 Activation of the trigeminovascular system induces the release of vasoactive neuropeptides, including CGRP and SP, from trigeminal afferents.

Trigeminovascular system activation and neurogenic inflammation in migraine. Trigeminal Ganglion (TG) afferents of the dura mater and cerebral vasculature result in the discharge of vasoactive and pronociceptive agents,

such as CGRP, Substance P, PACAP and glutamate. These mediators cause neurogenic inflammation through the induction of meningeal vasodilation, vascular permeability and mast cell degranulation. Adjacent TG afferent endings

become sensitized to inflammatory mediators which enhances peripheral nociceptive signaling. Repeated afferent stimulation facilitates central sensitization of the trigeminocervical complex (TCC), this increases the transmission of pain to the thalamus and the cortex and leads to the migraine headache and other peripheral symptoms of sensations such as photophobia and phonophobia.

2.2 CSD and Migraine Aura

Visual aura is visual disturbances, where migraineurs may perceive photopsia or scintillating scotomas before the onset of migraine headache[35]. CSD is a gradually advancing wave of neuronal and depolarization of glial cells throughout the cerebral cortex, which results in an inhibition of cortical activity and alterations in cerebrovascular blood flow leading the aura[22]. CSD

initiates with an increase in extracellular Potassium (K^+) inducing neuronal depolarization by reducing the resting membrane potential and facilitating the opening of voltage-gated Sodium (Na^+) and calcium (Ca^{2+}) channels. This further depolarizes neurons and induces glutamate release into the extracellular region activating the N-methyl-D-aspartate (NMDA) receptors and sustaining the depolarization, and enhancing the wavefront[31,32]. NMDA receptor channels are physiologically blocked by Magnesium ions (Mg^{2+}). Reduced Mg^{2+} availability can elevate NMDA activation, thus increasing excitability and heightened CSD, aiding migraine formation[38]. CSD activates TVS and relays nociceptive signals to the thalamus, linking the aura to the headache phase[22,39]. Fig. 2 summarizes the molecular connection between ionic fluxes, CSD, and the subsequent activation of trigeminovascular nociceptive pathways.

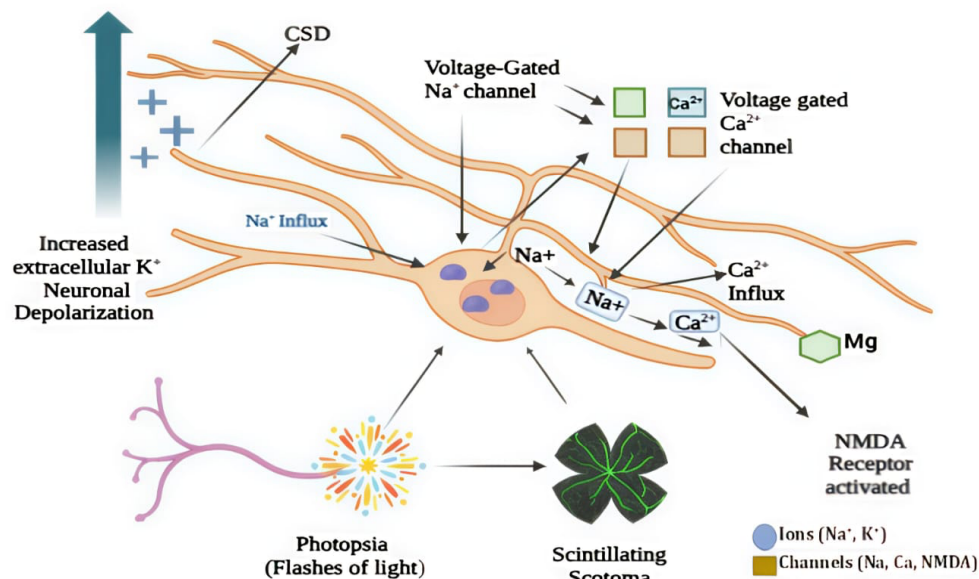


Figure 2. Ionic fluxes and glutamate mediated NMDA receptor activation leads to cortical hyperexcitability and subsequently leading to CSD and migraine aura.

CSD a slow spreading cortical wave of depolarization of neurons and glia, followed by long-term cortical inhibition. CSD is physiological with extracellular Potassium (K^+) build up, glutamate release, NMDA receptor activation and temporary changes in cerebral blood circulation. These occurrences heighten the cortical excitability and release of inflammatory mediators which stimulate meningeal nociceptors. CSD provides a relationship between the cortex dysfunction preceding migraine aura and the later activation of pain pathways and headache production via trigeminovascular interactions.

2.3 Neuropeptides and neurotransmitters

Serotonin can induce vasoconstriction or vasodilation via 5-hydroxytryptamine (5-HT) G-Protein-Coupled Receptors (GPCRs), where 5-HT₁ shows inhibitory action and causes vasodilation, and 5-HT₂ shows excitatory action and leads to vasoconstriction. A drop in serotonin levels results in dilated intracranial and extracerebral blood vessels and leads to migraine. Dilation of blood vessels triggers TVS to release vasodilators like CGRP, worsening the migraine[6]. CGRP sensitizes the central and Peripheral Nervous System (PNS). In PNS, CGRP targets blood vessels, glial cells, mast cells, trigeminal afferents of the meninges, and satellite glia and cell bodies in the trigeminal ganglia. In the meninges, CGRP causes

vasodilation of the dura by initiating the release of neuron-sensitizing agents by mast cells [40]. PACAP-38 acts similarly to CGRP causing the degranulation of mast cells[41]. A notable rise in SP is seen during migraine. SP produces inflammatory mediators, such as oxygen radicals, histamines, and cytokines, encouraging leukocyte

recruitment, which intensifies the inflammatory response and thus migraine[42]. Fig. 3. represent how neurogenic inflammation and nociceptive transmission are maintained by modified serotonin signalling and pathways regulated by CGRP and PACAP.

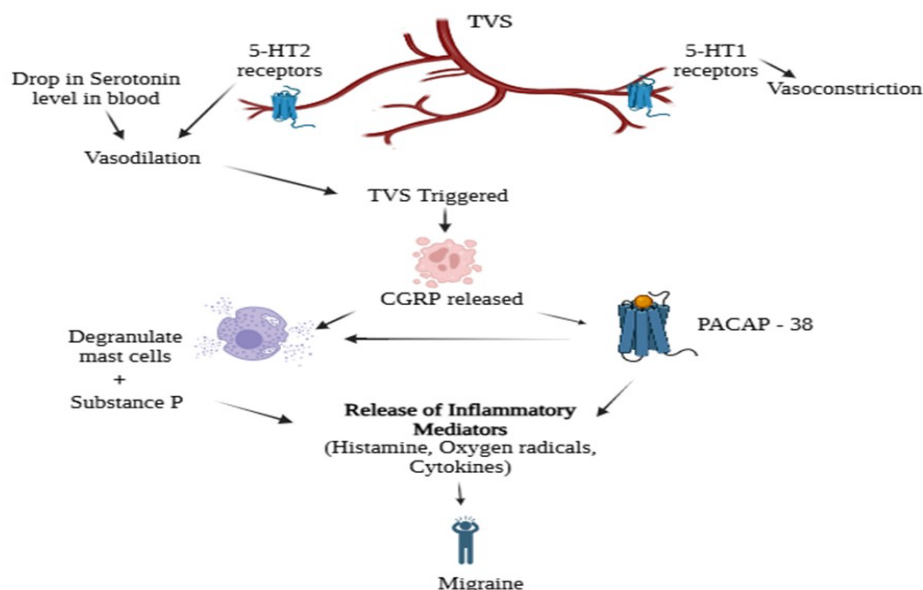


Figure 3. Altered serotonergic tone together with increased CGRP, PACAP, and SP enhances neurogenic inflammation and amplifies nociceptive transmission leading to migraine.

Neurotransmitters and neuropeptides together enhance the transmission of migraine. Disturbed serotonin signaling mediate the vascular tone and nociceptive transmission whereby low serotonin levels promote vasodilation and CGRP release. CGRP and PACAP facilitate the vasodilation, mast cell activation, and peripheral and central nociceptive pathway sensitization. SP promotes the action of inflammatory cytokines, leukocyte recruitment, and plasma extravasation. These mechanisms maintain neurogenic inflammation and strengthen peripheral and central sensitization in the migraine attacks.

2.4 Inflammatory and Oxidative Mechanisms

CGRP triggers glial cells and Trigeminal Ganglion Neurons (TGN) to secrete cytokines, namely Interleukin -1 β (IL- β), Interleukin -6 (IL-6), and Tumour Necrosis Factor - α (TNF- α). In turn, these cytokines subsequently

enhance CGRP synthesis through Mitogen Activated Protein Kinase (MAPK) and Cyclooxygenase -2 (COX-2) pathways, creating a bidirectional, self – perpetuating inflammatory loop, creating sustained nociceptive sensitization[7]. CSD, along with levels of CGRP, can also affect levels of Nitric Oxide (NO). High concentrations of NO and CGRP damage the mitochondrial respiratory chain components, leading to reduced Adenosine Triphosphate (ATP) production and excessive Reactive Oxygen Species (ROS) production, resulting in oxidative stress and causing migraine due to neural dysfunction[43]. The intricate relationship between oxidative stress and inflammatory mediators in migraine chronification has been illustrated in Fig.4 the depictions highlight the self-sustaining CGRP, cytokine, and NO axis that propels persistent neuronal sensitization.

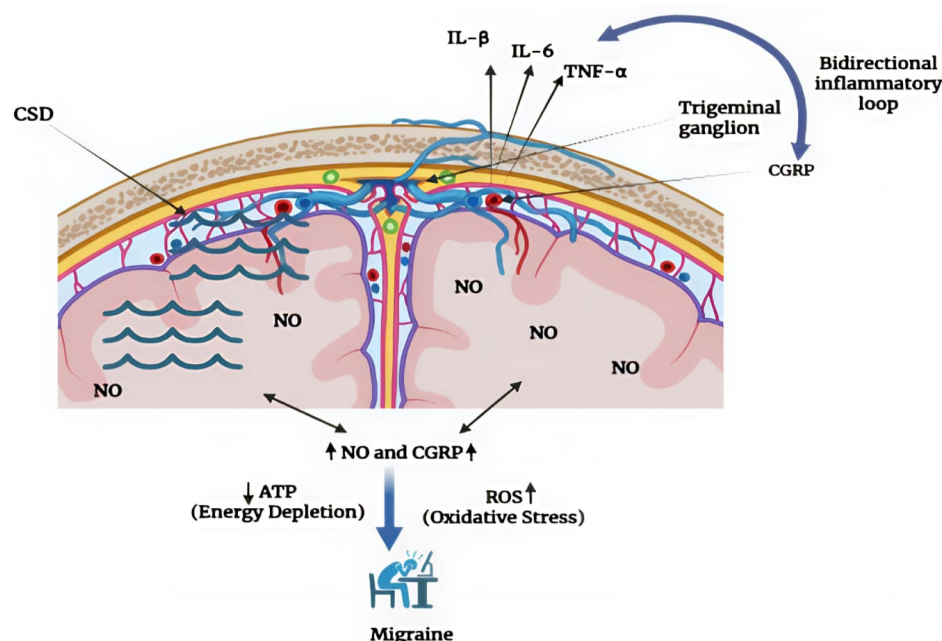


Figure 4. Neuroinflammatory and oxidative stress pathways contribute to sustained TVS sensitization in migraine.

Trigeminal neurons emit CGRP, which triggers glial cells and trigeminal ganglion neurons to generate pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. Through MAPK and COX-2 activation, these cytokines further increase CGRP production, resulting in a self-amplifying inflammatory cascade. At the same time, CSD and increased CGRP levels raise Nitric Oxide (NO) synthesis, which causes mitochondrial dysfunction, decreased ATP production, and an excess of reactive oxygen species. These mechanisms encourage long-lasting neural sensitization and reduced nociceptive thresholds.

2.5 Hormonal factors

A key theory in migraine suggests a drop in serum estradiol level just before menstruation triggers migraine in susceptible women[44]. Table 1 mentions the International Classification of Headache Disorders (ICHD-3) criteria for menstruation-related migraine and pure migraine [45]. Progesterone participates as a modulating key element of the TVS and cortical excitability system. Progesterone Receptors (PR) are expressed in the trigeminal ganglion,

dura mater, and pain-processing brain regions. Activation of PRs enhances neuronal excitability and increases susceptibility to CSD [46]. Testosterone binds with androgen receptors on sensory neurons of the trigeminal ganglion, where it seems to reduce the release of CGRP and thus lessen neurogenic inflammation, modulating vascular responses in migraine[47]. Prolactin plays a pronociceptive effect by increasing trigeminal neuronal excitability, stimulating CGRP release, and sensitizing Transient Receptor Potential Vanilloid 1 (TRPV1) channels. In contrast, oxytocin showcases an antinociceptive impact by suppressing TRPV1 activity, downregulating central sensitization pathways, and decreasing trigeminal nociception through Gamma-Aminobutyric Acid (GABA) modulation [48]. Migraine has a bidirectional relationship with thyroid dysfunction. Altered levels of thyroid hormones, affect neurotransmitter balance, neural excitability, and cerebral metabolism, elevated levels of CGRP, enhancing migraine susceptibility [49]. Hormonal effects on migraine susceptibility are mechanistically illustrated in Fig.5.

Table 1. Menstrual-related and pure menstrual migraine diagnostic criteria for ICHD-3

Menstruation-related migraine	
A	Attacks that meet the criteria for migraine without or with aura and criterion B below
B	Occurring on day 1 $\pm$ 2 (days -2 to +3) of menstruation in at least two of the three cycles, as well as other points during the cycle.
Pure menstrual migraine	

A	Attacks that meet the criteria for migraine without or with aura and criterion B below
B	Occurring only on day 1±2 (days -2 to +3) of menstruation in at least two of the three cycles, and not any other point during the cycle.

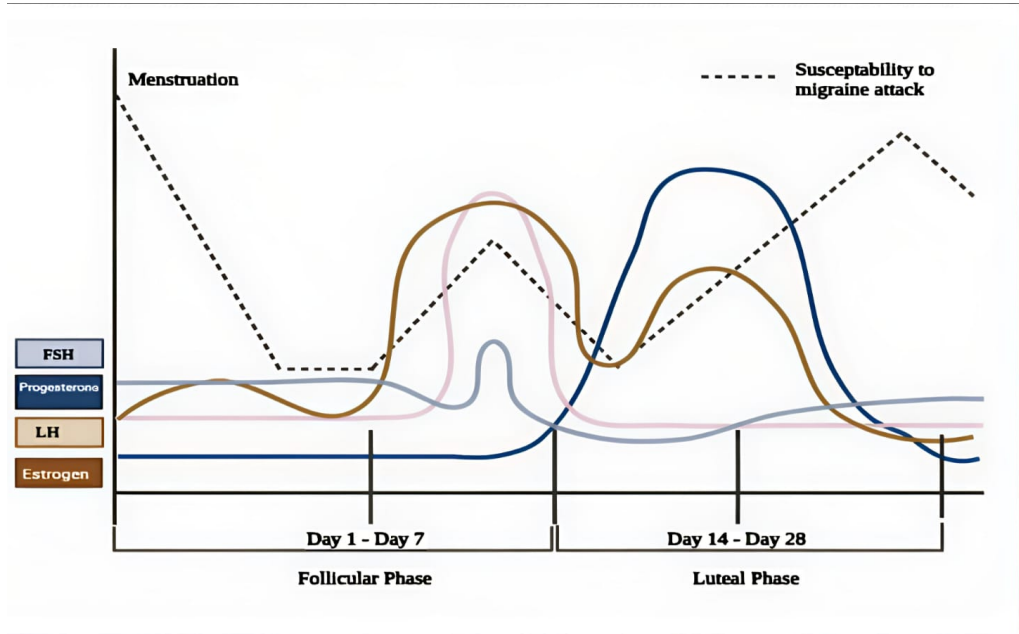


Figure 5. Fluctuations in estrogen and other hormones alter neuropeptide release and nociceptive processing, contributing to sex-specific migraine phenotypes.

The vulnerability to migraine is greatly influenced by hormonal changes. Menstrual migraine is exacerbated by decreasing estrogen levels, which also increase cortical excitability and trigeminovascular sensitivity. Progesterone may influence a person’s vulnerability to CSD by regulating neuronal excitability. While testosterone has protective effects by reducing neurogenic inflammation, prolactin enhances trigeminal excitability and CGRP release. By inhibiting TRPV1 and central pain pathways, oxytocin lowers nociceptive signals. Endocrine dysfunction is linked to migraine risk because thyroid hormone imbalance further modifies neurotransmitter modulation and CGRP signaling.

2.6 Genetics

Familial Hemiplegic Migraine (FHM) describes a form of migraine with aura that is inherited in an autosomal dominant manner. Namely, three genes have been found in studies to be associated with FHM phenotype: CACNA1A, ATP1A2, and SCN1A, which are linked with FHM1, FHM2, and FHM3, respectively. They increase susceptibility for migraine [50]. These genes encode the ion channels and ion-transporting ATPases; voltage-gated Ca²⁺ channels, the neuronal Na⁺/K⁺ - ATPase channels, and the Na⁺ channels and respectively. Any alterations in them

lead to alterations in synaptic ion gradients and neuronal excitability, facilitating CSD and TVS and migraine[51].

3. Experimental Biology Driving Migraine Target Discovery

Experimental studies have been crucial in determining the biological drivers of migraine and translating these findings into personalized therapies. Using validated cellular, tissue-based, and *in-vivo* models, scholars have showcased how TVS activation, Neuropeptide signaling, ion-channel dysfunction, and inflammatory-metabolic stress led to migraine initiation and its progression. This section summarizes how experimental findings lead to the early selection of target sites for migraine.

3.1 Cellular and Molecular models for Trigemino-vascular activation

Early experiments on TGN cultures showcased that depolarizing or inflammatory stimulation can enhance the release of CGRP, and forming a causal link between trigeminal activation and nociceptive signaling[52,53]. These research studies demonstrated that Ca²⁺ and ion-channels can regulate the release of CGRP, identifying presynaptic release mechanisms as key control points of migraine management.

Further studies refined this perspective by including non-neuronal components of the TVS. Culture and organotypic studies showed that neuron-derived CGRP activates the Satellite glial cells (SGC), enhancing purinergic signalling and cytokine release through ERK-dependent pathways[54,55]. Meningeal models showed that Mast cell degranulation and histamine release can be promoted by CGRP, thus amplifying the inflammatory response and sustained nociceptor sensitization [56]. Moreover, these responses were prevented by CGRP antagonism, suggesting that the neurogenic inflammation is caused by active peptide signalling rather than passive vascular leakage.

3.2 Experimental Modulation of Neuropeptide Signalling

Experimental studies examined the effects of neuropeptide modulation on Trigemino-vascular signalling. In Trigeminal Neuron Cultures (TNC), dura mater preparations, and *in-vivo* models, reduced stimulus-evoked nociceptive transmission was observed by inhibiting CGRP release or receptor activation[57,58]. These observations highlight that trigeminal excitability can be balanced by CGRP signalling.

Serotonergic modulation insights on presynaptic control mechanisms. 5-HT-1B/1D receptors activation suppresses Ca-Channel-dependent release of CGRP and glutamate from TGN, explaining the attribution of triptans effectiveness at a molecular level [53]. Triptans reduce TRPV1-mediated excitability in trigeminal afferents and the central trigeminal nuclei [59].

Corresponding studies mentioned PACAP as another contributor to migraine. Upon administration of PACAP-38, migraine-like photophobia and behavioral sensitization was noted. While neutralizing with anti-PACAP antibodies, these effects subsided without affecting CGRP signalling [60].

Collectively, these studies established neuropeptide signalling as a driver of migraine that can be modified, contributing to the development of gepants, mAbs, ditans, and emerging PACAP-based investigations.

3.3 Ion Channels and Cortical Excitability Models

Ion-channel function and cortical excitability, focused experimental models clarified our understanding of migraine and central sensitization. Models of CSD showcased that NMDA receptor activation can sustain depolarization propagated by triggers like elevated extracellular K^+ and glutamate levels[61]. These electrophysiological outcomes correlate ionic dysregulation to transient neurological symptoms and subsequent activation of trigemino-vascular pathways.

In TGN, ion-channel studies showed that Transient Receptor Potential (TRP), Ca, and K channels control the

regulation of both neuropeptide release and neuronal excitability. Also, it demonstrated that TRPV1 enhanced the activation of nociceptive transmission and CGRP, while TRPV1 antagonism reduced *in-vivo*, trigemino-vascular activation[62]. Concurrent investigations revealed that TRPM8 activation counteracts TRPV1-mediated sensitization[63].

TRPV1 activation was observed to induce Ca-dependent transcriptional responses through AP-1 signalling, linking peripheral channel activation with long term gene regulation and neuronal plasticity [64]. These findings suggest ion-channels influence both acute migraine attacks and chronic vulnerability.

3.4 Oxidative Stress and Neuroinflammatory Experimental Pathways

Acute and chronic migraine, like hyperalgesia, were induced by NO soluble guanylyl cyclase-cGMP pathway activation, as demonstrated by NO donor models[65]. Nociceptive behaviors were inhibited by inhibition of this pathway, indicating that NO signalling is a trigger.

As per cellular models, oxidative stress modifies neural susceptibility via influencing the expression of mitochondrial activity and inflammatory enzymes. Redox equilibrium is related to neuronal stress responses, as evidenced by the modulation of COX-2 and inducible Nitric Oxide synthase (iNOS)[66]. Pro-inflammatory mediators enhanced CGRP synthesis and release through COX-2- PGE₂ signalling cascades in cytokine exposure studies[55].

Agents that target the inflammatory or NO-related pathways inhibit CGRP levels, cytokine expression, and neural activation markers in Nitroglycerin (NTG) induced migraine models, providing *in-vivo* confirmation[67,68]. The results highlighted that migraine-related sensitization is actively sustained by metabolic stress and inflammatory pathways.

3.5 Translational integration

Studies on migraine have consistently converged on an array of biologically validated targets across a diverse experimental platform. In Trigemino-vascular models, Neuron-glia-immune interactions and CGRP release were determined to be the core drivers of peripheral sensitization. Neuropeptide modulation studies showed that nociceptive signalling is inhibited by selective pathway inhibition. While the basis of cortical excitability and aura was clarified by electrophysiological and ion-channel models. Migraine chronification mechanisms were revealed by inflammatory and metabolic studies.

Migraine management development was directly influenced by these experimental results. Presynaptic neuropeptide regulation studies turn up CGRP mAbs, gepants, and ditans and other non-CGRP approaches.

In comprehension, experimental biology established migraine as a disorder driven by distinct, targetable biological pathways and continues to highlight the need for refinement of mechanism based personalized migraine

therapies. Table 2 presents verified cellular and *in-vivo* models that directly impact therapeutic target selection and expedited translational development in migraine.

Table 2 Experimental models characterizing the molecular drivers of migraine and their therapeutic implication

Experimental model	Sample tested	Target/ Pathway	Key Experimental Finding	Translational relevance	Reference
Primary cultured TGN (rat)	OnabotulinumtoxinA, EGTA, Rizatriptan, APETx2	CGRP release, ASIC3	K ⁺ depolarization enhanced Ca ²⁺ dependent CGRP release. Proton evoked CGRP release mediated by ASIC3	Identified CGRP release machinery and ASIC3 as a therapeutic target	[52]
TRPV1-expressing sensory neurons	Capsaicin, PAR2 agonists	TRPV1-PAR2 signaling	PAR2 activation sensitized TRPV1, enhances Ca ²⁺ influx and CGRP/SP release	Established inflammation sensitization of TRPV1 in pain signaling	[69]
TGN-satellite glial cell co-cultures	Bradykinin, CGRP, Sumatriptan	CGRP-purinerbic signaling	Neuron derived CGRP activated the satellite glial cells and cytokine release	Demonstrated neuron glia as migraine amplifier	[54]
PC12 neuronal cell line	Hydrogen peroxide (H ₂ O ₂)	Oxidative stress, COX-2, iNOS	Low dose oxidative stress induced COX-2 and iNOS mediated neuroprotection	Linked oxidative signaling to neuronal stress adaptation	[66]
Primary TGN (Adult rats)	Serotonin (5-HT)	5-HT 1B/1D receptors, Ca ²⁺ channels	Serotonin inhibited CGRP and glutamate release via Ca ²⁺ channel inhibition	Provided mechanistic basis for triptan efficacy	[53]
TGN and Nucleus Caudalis slices	Sumatriptan Capsaicin	TRPV1 mediated excitability	Sumatriptan suppressed TRPV1-driven inward currents and synaptic excitation	Linked triptans to peripheral and central TRPV1 modulation	[59]
<i>In-vitro</i> and <i>in-vivo</i> migraine models	VL-102, NTG	NO-sGC, cGMP pathway	sGC activation induced acute and chronic migraine like hyperalgesia	Identified NO-sGC axis as migraine trigger	[65]

<i>Ex-vivo</i> trigeminal tissues and <i>in-vivo</i> rodent models	Lasmiditan, Sumatriptan	CGRP release inhibition	Both agents suppressed CGRP release, and Lasmiditan acted prejunctional	Supported ditans as non-vasoconstrictive antimigraine agents	[57]
Primary TGN cultures	Grape seed extract	CGRP release, GABAergic signaling	Reduced CGRP secretion and enhanced GABA receptor expression	Suggested nutraceutical modulation of Trigeminal excitability	[70]
Primary TGN cultures	IL-1 β , Indomethacin Parecoxib	COX-2 CGRP coupling	Cytokines enhance CGRP release via COX-2- PGE ₂ signaling	Linked inflammation to CGRP driven migraine	[55]
NTG induced migraine rat model	Emodin	cGMP-PKG signaling	Reduced NO, CGRP, cytokines, and c-Fos expression	Demonstrated anti-migraine effects through NO pathway suppression	[67]
<i>In-vivo</i> trigeminovascular activation models	JNJ-38893777 JNJ-17203212	TRPV1 channel	TRPV1 antagonism reduced c-fos activation and CGRP release	Validated TRPV1 as therapeutic target	[62]
Cell-based assays and PC12 cells	TRPM8 agonists	TRPM8-TRPV1 interaction	TRPM8 activation inhibited TRPV1-mediated nociception	Identified counter-regulatory ion-channel strategy	[63]
Primary neonatal rat Trigeminal neurons	NGF, BoNT/A, BoNT/EA	SNARE-mediated CGRP exocytosis	NGF sensitized TRPV1-dependent CGRP release via SNAP-25 domains	Linked NGF signaling to migraine sensitization	[71]
HEK-293 cells expressing TRPV1	Capsaicin, Resiniferatoxin	TRPV1-AP-1 transcription	TRPV1 activation induced Ca ²⁺ -dependent AP-1 transcription	Connected ion-channel activation to gene regulation	[64]
<i>In-situ</i> Guinea pig dura mater	Sumatriptan, capsaicin, NO donors	CGRP release	Sumatriptan inhibited Ca ²⁺ -dependent CGRP release from dura	Validated dura mater as migraine research model	[58]

Human and rat trigeminal ganglia	CGRP antibodies	CGRP- receptor localization	CLR and RAMP1 localized primarily to satellite glial cells	Identified peripheral CGRP receptor sites	[72]
Hemisectioned rat skull dura	CGRP, Histamine	CGRP-mast cell signaling	CGRP induced histamine release from meningeal mast cells	Linked mast cell activation to migraine inflammation	[56]
Adult rat trigeminal neuron and organ cultures	None (culture induced changes)	Neuropeptide regulation	Differential regulation of CGRP, SP, and PACAP expression	Demonstrated temporal neuropeptide plasticity	[73]
Organ-cultured trigeminal ganglia	MEK/ERK inhibitors (U0126)	ERK1/2 CGRP regulation	ERK1/2 inhibition reduced CGRP expression	Identified ERK pathway as CGRP regulator	[74]
Isolated cortical mouse brain slices	NMDA, elevated extracellular K ⁺	CSD, microglial Kir Channels	NMDA driven K ⁺ elevation activated microglial Kir channels	Explained cortical excitability during aura	[61]
Rat and human trigeminal ganglia	Lasmiditan, Botox (Target localization)	PACAP, CGRP, 5-HT receptors	Distinct localization of PACAP, CGRP, and therapeutic targets	Guided site-specific drug targeting	[75]
Rhesus monkey trigeminal ganglia	CGRP antagonist MK-3207	CGRP receptor binding	High CGRP receptor density in the trigeminal ganglia	Validated TG as accessible drug target	[76]
Mouse behavioral migraine models	PACAP-38, anti-PACAP mAb	PACAP signaling	PACAP induced photophobia independent of CGRP	Supported PACAP as non-CGRP migraine pathway	[60]
NTG induced migraine rat model	Xingshao Zhitong Recipe (XZR)	NF-κB, NOS, CGRP	Reduced inflammation, mast cell degranulation, and CGRP levels	Supported multi-target herbal therapy approach	[68]

4. Mechanism-driven therapeutic evolution in migraine
Migraine management through therapeutics has shifted from empirical vascular suppression to physiologically focused modulation of specific nociceptive pathways [77-

79]. Present therapeutic management is grounded on experimental studies on TVS activation, peptide release, and CSD[80,81]. Thus, forming the base of pathway-centric therapeutic intervention.

4.1 CGRP Targeted Therapies

Trigeminal experimental models consistently indicated CGRP release during nociceptive activation [82-84]. Enhanced levels of CGRP in plasma and saliva during migraine attacks prove its functional role in it [85]. Selective inhibition of CGRP signalling was thus targeted for attenuating peripheral sensitization and reducing central transmission[10,11]. mAb targeting either the CGRP ligand or its receptor were thus developed [89]. Clinical trials confirmed significant inhibition in monthly migraine days, supporting peptide-directed prevention [90,91].

Gepants have enhanced mechanistic targeting to acute and preventive contexts [92,93]. Preclinical studies demonstrating suppression of TVS following CGRP receptor inhibition aided their translational development[94]. Clinical outcomes confirm effective relief from migraine headache with cardiovascular safety profiles, setting them as a better option than vasoconstrictive treatments [95,97].

Active immunization are emerging strategy targeting CGRP with the aim to provide sustained peptide suppression via adaptive immune engagement [98]. Early phase clinical trials demonstrate lasting antibody generation without severe safety concerns, representing future long-acting modulation [99].

4.2 Serotonergic modulation and Ditans

Serotonergic signalling regulates TVS neurotransmitter release via presynaptic receptor subtype[100]. Earlier triptans acted by 5-HT_{1B}-mediated vasoconstriction in addition of neuronal inhibition. Recognizing that migraines can be triggered by sensory pathway hyperexcitability led refinement toward neuron-specific targeting[101]. Selective 5-HT_{1F}-receptor antagonism reduces TVS sensitization without activating coronary vascular receptors. Lasmiditan, a second-generation non-indole agent, showcased that central receptor modulation alone can terminate migraine induced headache without vasoconstriction. This therapeutic evolution demonstrates that neuronal signal attenuation is effective as an acute therapeutic efficacy[102-106].

4.3 Botulinum toxin and synaptic inhibition

Chronic migraine involves sustained synaptic release of excitatory neuropeptides from peripheral TGN terminals. CGRP exocytosis occurs within these terminals via SNARE-mediated vesicle fusion[107]. Onabotulinumtoxin-A cleaves SNAP-25, resulting in inhibited vesicular neurotransmitter release[108]. Clinical studies suggest a suppression in headache frequency in chronic migraineurs, along with suppression of persistent peripheral input. Experimental results show that toxin exposure reduces TRPV1 membrane insertion, further lowering nociceptor sensitivity[109-111]. These findings support synaptic inhibition as an effective technique for modulating chronification processes.

4.4 Neuromodulation Technologies

CSD propagation can be disrupted by regulating the cortical excitability inhibiting migraine aura. Single-pulse transcranial magnetic stimulation reduces cortical hyperexcitability and mitigates aura-associated phenomena[112,114]. Whereas vagus nerve stimulation alters brainstem nuclei involved in TVS[115-119]. Non-invasive cervical stimulation has been studied in clinical trials and found to be effective in reducing migraine frequency and headache intensity[120]. These methods target circuit-level recalibration rather than receptor blockade targeting[121]. Closed-loop stimulation devices that integrate physiologic biomarkers with adaptive output are being developed to improve precise regulation [122].

4.5 Emerging Targets and Future Therapeutics

Despite the success of CGRP-targeted therapies, heterogeneity in treatment response highlights that additional pathways contribute to migraine pathogenesis[27]. PACAP has gained prominence following experimental evidence, and mAbs targeting are being developed[123]. In the human provocation studies, stimulation of the ATP-sensitive-K-channel was found to be trigger[124,125]. Selective channel inhibition, like TRP, is being studied for a prophylactic approach. These research strategies show steady shift from peptide blocking to ion-channel and intracellular signalling precision [126]. Table 3 demonstrates the evolution from mechanistic understanding to targeted neurotherapeutic interventions.

Table 3 Mechanism aligned therapeutic strategies in migraine.

Therapeutic class	Mechanistic Target	Mode of Action	Example	Clinical Role	References
CGRP mAbs	CGRP ligand or receptor	Neutralize peptide signaling; reduce sensitization	Erenumab, Fremanezumab, Galcanezumab, Eptinezumab	Preventive	[84, 127-129]

Gepants	CGRP receptor	Competitive antagonism of CGRP receptor	Ubrogepant, Rimegepant, Atogepant, Zavegepant	Acute/ Preventive	[130-133].
Ditans	5-HT _{1F} receptor	Inhibit trigeminal neurotransmission without vasoconstriction	Lasmiditan	Acute	[100]
Botulinum toxin	SNARE complex	Inhibits neuropeptide exocytosis	Onabotulinmtoxin A	Chronic migraine	[134]
Neuromodulation	Cortical excitability, vagal pathways	Circuit-level modulation	sTMS, nVNS	Actute/ Preventive	[113,118]
Emerging Target	PACAP, TRP channels, KATP channels	Peptide, ion-channel and intracellular signaling modulation	PACAP mAbs	Experimental	[123].

5. Precision Neurotherapeutics in Migraine

5.1 Biological Heterogeneity

Migraine is termed as biological heterogeneous disorder as it dominate differently in different migraineurs[77,135]. This heterogeneity thus results in variable clinical response for mechanism-based therapies[136,137]. Migraineurs tend to have an incomplete response or show no response at all for CGRP-targeted-interventions, explaining the heterogeneous effect; not all patients exhibit a dominant CGRP-driven pathophysiology of migraine[135,138].

Emerging studies data indicate inter-individual variability in TGN and SGC for the CGRP receptor component, thus displaying altered therapeutic sensitivity[139]. Clinical phenotypes with severe photophobia or substantial cranial autonomic symptoms may represent subgroups with greater neuropeptide involvement[140]. Migraineurs who have altered neurochemical systems as their trigger points, respond inadequately to CGRP-centered therapy[27,141].

Heterogeneity in the CSD patterns is another reason that causes alterations in the treatment responsiveness of migraineurs[142]. Some migraineurs were observed to have heightened cortical response and substandard habituation during attacks, while a few showed more normalized response[143]. These variations influence how migraineurs respond to the neuromodulation techniques[144].

Neuroinflammatory adds to this heterogeneity. The oxidative stress indicators, circulating cytokine profiles, and glial activation remain different. Clinical

investigations show that migraineurs with central sensitization and substantial allodynia can augment inflammatory signalling, affecting their effectiveness for anti-inflammatory or neuromodulatory migraine management strategies[145]. Thus, understanding the response variability is critical for enhancing neurotherapeutic strategies, as one-size-fits-all treatment approaches do not account for this multidimensional biological variation [146, 147]. In simpler terms, some migraineurs respond because the targeted pathway is critical to their migraine origin, while others do not, as alternative pathophysiology dominates their migraine phenotype[148,149]. Recognizing and describing these primary factors can be the foundation of precise migraine management[32, 150].

5.2 Biomarker-guided selection

Measurable markers which can identify the underlying pathophysiology of migraine are necessary for bridging the gap between biological understanding and clinical application. Growing evidences demonstrate that, in certain subgroups, circulating CGRP levels may be correlated with disease activity, notwithstanding their variability. Thus, CGRP-related markers continue to be promising, but they are still unproven clinically [145].

Electrophysiological indicators may provide additional predictive value in precision care[143,144,151,152]. In exploratory research, functional MRI connectivity patterns have also been associated with treatment outcomes, specifically within pain-modulatory and visual

networks[153]. These imaging indicators show the possibility of a mechanism-aligned section once they are clinically standardized[145,154]. Figure 6 depicts the conceptual architecture of a typical integrative model.

Inflammatory markers, such as cytokine profiles and oxidative stress metrics, have likewise been studied as stratification tools[145,155]. Management approaches that

indirectly reduce neuroinflammation can be more beneficial for migraineurs with higher pro-inflammatory markers [156]. However, emerging evidence from several studies indicates that no single biomarker sufficiently captures the broad heterogeneity of migraine, supporting the development of multimodal panels rather than isolated markers [157].

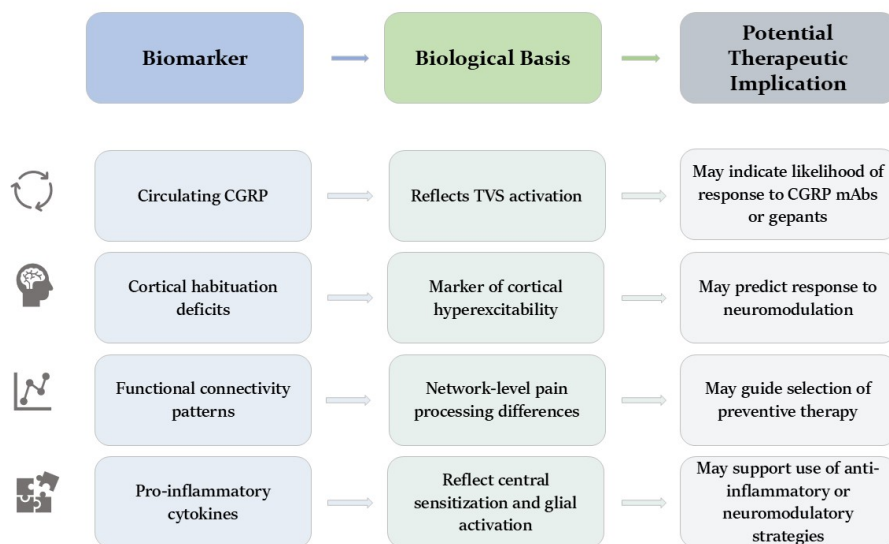


Figure 6: Biomarker-guided stratification framework for precision migraine therapeutics.

This figure illustrates a biomarker-guided framework for precision migraine therapeutics by linking key biomarkers with their biological basis and potential therapeutic implications. It highlights how biomarkers such as CGRP, cortical habituation deficits, functional connectivity patterns, and pro-inflammatory cytokines can help predict treatment response and guide personalized therapy selection.

5.3 Pharmacogenomic and Phenotypic Influences

Genetic variability contributes to inter-individual differences in receptor expression, ion-channel function, and neurotransmitter metabolism[158]. Emerging evidence indicates that CGRP receptor components or serotonin receptors that are affected by polymorphism can be modulated by therapies, although the impact size remains small [51,159,160]. Variability in drug-metabolizing enzymes, such as CYP isoforms, may alter the therapeutic efficacy of triptans and gepants even raising tolerability concerns [158,161].

Gender related biological differences are clinically significant. Since hormonal modulation of trigeminovascular signalling may influence disease expression as well as therapeutic response, especially in women due to menstrual migraine [162,164]. Furthermore, compared to episodic migraine, chronic migraine seems to include more severe cerebral sensitization and network

reconfiguration, which may alter responsiveness to preventive therapies [165]. While genetic variations are biologically significant, they are not yet predictive enough to guide the formulation of therapies for day-to-day practice [166,167]. However, future stratification may be improved by combining genetic data with clinical and biomarker information [78,145,168].

5.4 Emerging precision frameworks

Digital phenotyping constitutes a revolutionary method for documenting real-world fluctuations in migraine occurrences[24]. Continuous monitoring of individual attack patterns is made possible by wearable devices that continuously monitor stress-related parameters, physical activity, heart-rate variations, and sleeping patterns[169-172]. Recent investigations recommend combining physiological information with patient-reported outcomes that can improve the prediction of attack onset and may help in preventive migraine strategies[173,175].

Biological heterogeneity, biomarker development, and longitudinal digital data can all be integrated for precision migraine management[154]. Emerging studies evidence that there is no single pathway that defines all migraineurs, and therapeutic success depends on aligning treatment mechanisms with dominant disease triggers[176]. Migraine management strategies are leaning towards

customized neurotherapeutic approaches that anticipate migraine biology[24].

Multidimensional data streams can be synthesised by ML-based adaptive treatment algorithms to suggest individualized therapeutic modifications[177,178]. AI applications have shown promising results in predicting the likelihood of attacks and identifying responders to particular preventive therapies[179]. The research has further evolved into using gene-editing technologies like CRISPR to alter the neuropeptide signalling pathways and ion channels [180]. These methods demonstrate the theoretical potential of directly addressing the pathogenic genetic drivers and the need of clinical translations for further assurance [181].

6. Challenges and future directions

6.1 Variability in therapeutic response

Triggers differ due to the different nature of migraineurs, as they have different susceptibility to neurobiological signals. This heterogeneity results in the limited effectiveness of pathway-centred medications[11,182,183]. Clinical trials performed on migraineurs indicated that while CGRP-targeted medicines markedly reduced monthly migraine days on a population scale, a considerable number of migraineurs exhibited partial or no response, suggesting that CGRP signalling is not the sole pathogenic factor across several phenotypes [183,184].

Genetic polymorphisms in the ion channels, serotonin receptors, and components of the CGRP pathway further influence interindividual heterogeneity for therapeutic efficacy [185]. However, the pharmacogenomic indicators that are currently available are still not sufficiently predictive for clinical implementation [147,158]. Moreover, compared to episodic migraine, chronic migraine seems to include more cerebral sensitization and maladaptive network rearrangement, which may change responsiveness to preventive measures [9].

6.2 Limitations of current evidence

The majority of the present data base on migraine, despite the substantial therapeutic advances, comes from randomized studies with relatively homogenous populations, often excluding migraineurs with significant complicated phenotypes, psychiatric comorbidities, or medication overuse[186,187]. This limits generalization to real-world practice[186,188]. Many pivotal trials have short follow-up periods, making it impossible to assess long-term migraine alterations[189,190].

There are only a few comparative effectiveness trials of novel agents, leaving uncertainty regarding optimal sequencing strategies for preventive therapies[191,192]. Additionally, biomarker integration in clinical trials

remains exploratory, preventing stratified enrolment based on mechanistic phenotypes[145, 193].

6.3 Biomarker and stratification barriers

Precision migraine management requires reproducible biomarkers capable of predicting treatment outcome in migraineurs[145,194]. However, candidate biomarkers such as inflammatory cytokines, circulating CGRP, neuroimaging signatures, electrophysiological measures, and oxidative stress markers fall short in sensitivity and specificity[195,196]. Studies on interictal CGRP levels show variations between chronic and episodic migraine, but significant overlap limits the clinical aptitude[197,198].

Studies on functional MRI reveal altered connectivity in pain-modulatory and visual networks, although methodological variation between centres hampers standardization and reproducibility[199,200]. Electrophysiological markers have been associated with preventive therapy response; however, multicentre validation studies are missing[152,201]. Recent discussions on multimodal integration have emphasized that merging genetic, digital phenotyping data, and images poses computational and infrastructural obstacles that prevent normal adaptation[202,203]. Until the biomarkers establish consistency, scalability, cost-effectiveness, precision stratification will remain experimental rather than a daily practice[5,145].

6.4 Translational and implementation challenges

Scientific advancement alone does not ensure equal implementation. Treatments remain more expensive than standard preventive medications, limiting availability in many healthcare systems[204-206]. Global assessments like YLD show significant differences in migraine management availability in the low-and middle-income countries[207-209]. Cost-effectiveness survey highlights that precise medicine may be economically viable in patients with extremely refractory chronic migraine, but payer-imposed constraints remain a major concern[204,210].

Obstacles in implementing digital platforms and AI-assisted prediction models include a lack of clinician training, privacy concerns, and integration issues with digital health records[211]. Mechanisms for regulating biomarkers to qualify migraine are still underdeveloped, limiting the implementation of precision techniques into practice [212]. Therefore, translational impediments are multidimensional, economic, regulatory, infrastructural, and educational[207,209].

6.5 Future research priorities

Large-scale longitudinal cohorts that can integrate the genomic data, neuroimaging, and digital phenotyping to find mechanistic clusters can be the future of migraine

neurotherapeutics [169,177,213,214]. Digital phenotyping using smartphone-based monitoring has shown promise in improving the temporal prediction of migraine attacks and customized prevention measures[215,216]. ML models applied to multidimensional datasets have demonstrated preliminary ability to predict therapy response, while external validation across a varied population is still required before clinical implementation [179,211].

Emerging research suggests that multimodal treatment methods for refractory disease should target both CGRP signalling and cerebral sensitization pathways [217]. Adaptive and biomarker-enriched trial designs are being advocated as a way to speed the transition from mechanistic discovery to personalized therapy [218]. Future research must prioritize reproducibility, external validation through clinical trials, cost-effectiveness, and fair implementation[219].

7. Conclusion

Migraine is now recognized as a complex neurobiological disorder. Advances in the experimental neuroscience have enabled the development of targeted therapies highlighting the translational impact of mechanistic discoveries. Migraine therapy has progressed remarkably with advances in clinical pharmacology and neuroscience, particularly through the identification of calcitonin gene-related peptide (CGRP) as a key mediator of the trigeminovascular system that enabled the development of CGRP receptor antagonists and monoclonal antibodies, which have significantly improved migraine prevention and treatment.

Despite of identifying promising therapeutic targets, current preclinical models fail to capture the heterogeneity and long-term progression of migraine. Refining these translational models is essential to improve the development of effective therapies. The increasing availability of targeted treatments has expanded clinical options but more challenges in treatment selection due to absence of reliable predictive biomarkers that limits the implementation of precision medicine.

Now-a-days, Mechanism-based therapies have transformed migraine management and validated the importance of the trigeminovascular system. Nevertheless, achieving truly personalized neurotherapeutics will require a systems-level understanding of migraine pathophysiology, enabling tailored combination or sequential therapies that address the diverse biological mechanisms underlying the disorder. Future research should focus on integrating mechanistic insights with comparative effectiveness studies, validated biomarkers, neuroimaging, and digital phenotyping to guide precision-based treatment-strategies. Strengthening the link between experimental research and clinical application will be

essential for achieving individualized and effective migraine management.

Ethics statement

This article is a review of previously published literature and does not involve any new studies with human participants or animals performed by the authors. Therefore, ethical approval and informed consent were not required.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Author Contributions

A Verma declares responsibility for the study design, data acquisition and analysis. Y.M.M.A.Alsayadi contributed to paper drafting and editing of the manuscript. S Ahalwat contributed to supervision and study conception for the work. All authors reviewed and approved the final manuscript.

Data availability statement

No new data were generated or analysed in this study.

Abbreviations: CSD- Cortical Spreading Depression; AI- Artificial Intelligence; CGRP- Calcitonin Gene Related Peptide; PACAP- Pituitary Adenylated Cyclase-Activating Polypeptide; TRP- Transient Receptor Potential; NO- Nitric Oxide; mAbs- Monoclonal Antibodies; TVS- Trigemino-vascular System; ML- Machine Learning; SP- Substance P; TCC- Trigemino-cervical Complex; TG- Trigeminal Ganglion; K⁺- Potassium; Na⁺- Sodium; Ca²⁺- Calcium; NMDA- N-methyl-D-aspartate; Mg²⁺- Magnesium ions; GPCR- G-Protein-Coupled Receptors; PNS- Peripheral Nervous System; IL-β- Interleukin - 1β; IL-6 - Interleukin -6; TNF-α - Tumor Necrosis Factor; MAPK- Mitogen Activated Protein Kinase; COX-2 - Cyclooxygenase; ATP- Adenosine Triphosphate; ROS- Reactive Oxygen Species; ICHD- International Classification of Headache Disorders; PR- Progesterone Receptors; TRPV1- Transient Receptor Potential Vanilloid 1; GABA- Gamma-Aminobutyric Acid; TSH- Thyroid-Stimulating Hormone; fT3- Free Triiodothyronine; fT4- Free Thyroxine; FHM- Familial Hemiplegic Migraine; SGC- Satellite glial cells; TNC- Trigeminal Neuron Cultures; NTG- Nitroglycerin.

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