



PHARMACOVIGILANCE IN MIGRAINE TREATMENT: ASSESSING ADRS AND PATIENT SAFETY

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Abstract

Migraine is a common neurological illness with frequent episodes of headache, usually of moderate to severe intensity, frequently preceded or accompanied by nausea, vomiting, and sensitivity to light and sound. Drug treatments like triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), calcitonin gene-related peptide (CGRP) inhibitors, beta-blockers, and anticonvulsants are generally prescribed for the treatment of both acute and prophylactic stages. Yet, prolonged application of such treatments involves serious risks of adverse drug reactions (ADRs) from mild gastrointestinal side effects up to severe cardiovascular and neuropsychiatric complications. Pharmacovigilance is essential to maintain drug safety by detection, observation, and assessment of ADRs induced by migraine medications.

The pharmacovigilance situation with migraine treatment is discussed in this review, emphasizing the most commonly detected ADRs, post-marketing surveillance information, and regulatory actions. Particular focus is placed on new migraine therapies, including CGRP inhibitors, with enhanced efficacy but novel safety issues. The contributions of spontaneous reporting systems, electronic health records, and patient-reported outcomes to ADR detection are also highlighted. Enhancing pharmacovigilance can enhance therapeutic success, minimize medication-related harm, and inform regulatory policy for safer migraine treatment. Future studies must be based on real-world evidence and individualized medicine strategies to maximize drug safety in migraine treatment.

Keywords: Pharmacovigilance, Migraine, Adverse Drug Reactions, Triptans, CGRP Inhibitors, Drug Safety, Post-Marketing Surveillance

I. Introduction

Migraine is a neurological chronic disorder that has an estimated 1 billion sufferers worldwide and represents one of the most disabling and common conditions. It manifests as periodic headaches, which are usually one-sided (unilateral) and pulsating in character. The pain is usually moderate to severe, lasting from 4 to 72 hours, and is often accompanied by vomiting, nausea, photophobia, and phonophobia.

Epidemiology and International Impact

Migraine occurs more in women than in men, with a female-to-male ratio of around 3:1 mainly because of hormonal factors. It is seen most in individuals in the range of 20–50 years and has a great impact on work productivity and quality of life. Migraine is the second most leading cause of disability worldwide, according to the Global Burden of Disease Study (GBD). Economic burden comprises direct healthcare expenditures (e.g., medical visits, diagnostic examinations, and drugs) and indirect losses from lost productivity at work and absenteeism.

Types of Migraine

Migraine is categorized into various types by clinical presentation:

1. Migraine without Aura (Common Migraine) – The most common one, which occurs with headaches with no prior neurological symptoms.
2. Migraine with Aura (Classic Migraine) – Includes sensory disturbances (aura) preceding the headache, like visual disturbances (flashes, blind spots), tingling, or speech difficulty.
3. Chronic Migraine – Is characterized by having migraines on 15 or more days out of a month for a minimum of three months.
4. Menstrual Migraine – Associated with hormonal changes, usually occurring in women during the menstrual cycle.
5. Hemiplegic Migraine – A rare and severe type with temporary paralysis or weakness on one side of the body, simulating a stroke.
6. Vestibular Migraine – Dizziness, vertigo, and balance problems, usually without severe headache.

Pathophysiology of Migraine

The precise etiology of migraine is still unknown, but neurological, vascular, and genetic factors contribute significantly. The major mechanisms involved are:

1. Cortical Spreading Depression (CSD) – A neuronal excitation-inhibition wave that causes aura symptoms as well as induction of inflammatory responses.
2. Trigeminal Nerve Activation – The trigeminal system releases neuropeptides including calcitonin gene-related peptide (CGRP), substance P, and neurokinin A, causing vasodilation, neurogenic inflammation, and pain transmission.
3. Serotonin (5-HT) Dysregulation – Migraine has been linked to alterations in the levels of serotonin, impacting vascular tone and pain regulation.
4. Genetic Susceptibility – There is a significant genetic factor, according to studies, with gene mutations in CACNA1A, ATP1A2, and SCN1A being responsible for familial hemiplegic migraine.
5. Hypothalamic Dysfunction – The hypothalamus, which controls sleep, appetite, and the biological clock, plays a role in the development of migraine, particularly to stimuli such as stress and sleep disorder.

Common Migraine Triggers

There are several factors which can trigger the onset of migraines, such as:

- Dietary Factors – Caffeine, alcohol, chocolate, processed foods, and artificial sweeteners.
- Hormonal Changes – Changes in estrogen levels, particularly during menstruation, pregnancy, or menopause.
- Environmental Factors – Bright lights, loud noises, pungent odors, or weather changes.
- Lifestyle Factors – Insufficient sleep, stress, dehydration, and irregular meal times.

Diagnosis of Migraine

Migraine diagnosis is largely clinical, from history and patterns of symptoms. No single test proves migraine, but some investigations are useful to exclude other etiologies.

1. Clinical Criteria (ICHD-3)

Migraine is divided into:

- Migraine Without Aura – A minimum of 5 attacks with durations of 4–72 hours, featuring symptoms such as unilateral, pulsating headache, moderate-to-severe in intensity, exacerbated by activity, and accompanied by nausea, vomiting, photophobia, or phonophobia.
- Migraine With Aura – At least 2 attacks with visual, sensory, or speech disturbances that develop over time and last 5–60 minutes before or during the headache.

2. Neurological Examination

A normal neurological examination confirms a diagnosis of migraine. If neurological deficits or other warning signs emerge, further testing is indicated.

3. When is Imaging Indicated?

Brain imaging (MRI/CT) is not standard but indicated if red flags are present:

- Sudden, severe headache
- New-onset headache after age 50
- Progressive worsening
- Neurological signs (confusion, seizures)

4. Laboratory Tests

Laboratory tests (CBC, ESR, CRP) are performed to exclude infections, inflammation, or metabolic disorders causing headaches.

5. Differentiating Migraine from Other Headaches

Migraine is mistakenly diagnosed as:

- Tension headaches (bilateral, non-throbbing, no nausea).
- Cluster headaches (extreme, unilateral, with eye redness and tearing).
- Medication-overuse headaches (due to regular painkiller use).

II. Treatment of Migraine

Treatment of migraine is focused on relieving acute attacks, preventing recurrence, and decreasing disability. It comprises acute (abortive) therapy, preventive (prophylactic) therapy, and lifestyle changes.

1. Acute (Abortive) Treatment

Reserved to terminate a migraine attack once it has started. Most effective when administered early during the attack.

A. Non-Specific Analgesics (First-Line for Mild to Moderate Migraine)

- Paracetamol (Acetaminophen) – 1000 mg oral, useful in mild migraines.
- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) – Suppress prostaglandins to suppress pain and inflammation.

Ibuprofen (400–800 mg)

Naproxen (500–1000 mg)

Diclofenac (50–100 mg)

Aspirin (900 mg)

Advantages: Widely available, good tolerance.

Disadvantages: GI discomfort, kidney damage with chronic use.

B. Triptans (Selective Serotonin Receptor Agonists) – First-Line for Moderate to Severe Migraine

Triptans exert their effect by stimulating 5-HT_{1B/1D} receptors, producing vasoconstriction and suppressing pain pathways.

- Sumatriptan – 50–100 mg (oral), 6 mg (subcutaneous), 20 mg (nasal spray)
- Rizatriptan – 10 mg (oral, dissolvable)
- Zolmitriptan – 2.5–5 mg (oral, nasal)
- Eletriptan – 40 mg (oral)

- Almotriptan, Naratriptan, Frovatriptan – Longer duration, less side effect.

Benefits: Active within 1–2 hours.

Drawbacks: No use in patients with cardiovascular disease (vasoconstriction risk).

C. Ergot Alkaloids (Less Used)

Ergot derivatives cause vasoconstriction and block neuropeptide release.

- Ergotamine + Caffeine – 1 mg/100 mg per dose.

- Dihydroergotamine (DHE) – 1 mg IV/IM/Nasal spray.

Advantages: Effective in prolonged migraines.

Disadvantages: More side effects (nausea, vasospasm).

D. Anti-Emetics (For Nausea and Vomiting)

- Metoclopramide (10 mg IV/Oral)

- Domperidone (10 mg Oral)

- Prochlorperazine (10 mg Oral)

Advantages: Reduces nausea, increases drug absorption.

E. CGRP Antagonists (Newer Therapy)

Calcitonin Gene-Related Peptide (CGRP) plays a role in migraine pain.

- Rimegepant (75 mg oral)

- Ubrogepant (50–100 mg oral)

Advantages: No cardiovascular side effects like triptans.

Disadvantages: Costly, long-term safety unknown.

2. Preventive (Prophylactic) Treatment

Used in patients with frequent migraines (>4 attacks/month) or disabling severity.

A. Beta-Blockers (First-Line)

Decrease sympathetic activity, stabilizing blood flow.

- Propranolol (40–160 mg/day)

- Metoprolol (50–200 mg/day)

- Atenolol (50–100 mg/day)

Strengths: Effective, well-established.

Weaknesses: Not for asthma/COPD patients (risk of bronchospasm).

B. Antiepileptic Drugs

Stabilize neuronal hyperexcitability.

- Topiramate (50–100 mg/day) – Induces weight loss.

- Valproate (500–1000 mg/day) – To avoid in pregnancy (teratogenic).

Strengths: Suitable for patients with comorbid epilepsy, mood disorders.

Disadvantages: Side effects on cognition (Topiramate), hepatotoxicity (Valproate).

C. Calcium Channel Blockers

- Flunarizine (5–10 mg/day) – For patients with migraine + vestibular symptoms.

Advantages: Well-tolerated.

Disadvantages: Weight gain, sedation.

D. Antidepressants (For Migraine with Mood Disorders)

- Amitriptyline (10–50 mg at bedtime) – A tricyclic antidepressant.
- Venlafaxine (75 mg/day) – An SNRI.

Advantages: Useful for migraine with depression/anxiety.

Disadvantages: Drowsiness, dry mouth.

E. CGRP Monoclonal Antibodies (Newer Preventive Therapy)

These act on CGRP, a central molecule involved in migraine pathogenesis.

- Erenumab (70–140 mg/month SC)
- Fremanezumab (225 mg/month SC)
- Galcanezumab (120 mg/month SC)

Benefits: Effective for chronic migraine, less side-effect profile.

Drawbacks: Very costly, long-term effects not known.

F. Botox (Onabotulinumtoxin A)

Indicated for chronic migraine (≥ 15 days/month).

- Dosage: 155–195 units injected in head, neck, and shoulders every 3 months.

Benefits: Decreases headache frequency.

Drawbacks: Costly, needs trained administration.

3. Non-Pharmacological & Lifestyle Modifications

- Dietary Changes: Avoid triggers (caffeine, alcohol, processed foods).
- Hydration & Sleep: Maintain consistent sleep and hydration.
- Exercise & Stress Management: Yoga, meditation, aerobic exercise reduce attack frequency.

4. Emerging Therapies

- Neurostimulation Devices (e.g., Cefaly, sTMS) – Use electrical/magnetic pulses to reduce pain.
- Gene Therapy & New CGRP Inhibitors – Under research for long-term migraine prevention.

III. LITERATURE SURVEY

1. Shijie Wei [2024] In a meta-analysis involving 24,089 patients and 53 trials, it proved the efficacy and good tolerance of all oral triptan class medications. There were five trials of CGRP system-targeted drugs Erenumab and Fremanezumab. A 12-week trial that included 1,130 patients showed that over a placebo, Fremanezumab highly decreased headache frequencies, and significant adverse effects included injection site reaction mostly marked by pain.

2. Parastoo Amiri [2022] For example, an online survey of 15,133 migraine patients and 77,453 controls revealed that insomnia, depression, anxiety, gastric ulcers and/or gastrointestinal bleeding, angina and epilepsy were all significantly more common among migraineurs compared to the control group ($p < 0.001$) (34).

3. Anna K. Eigenbrodt [2021] in >90% of individuals with the disorder, aura appears visually 4,16, classically as fortification spectra. Sensory symptoms appear in ~31% of individuals with the disorder and are typically felt as predominantly unilateral paraesthesia. Bilateral pain is, however, frequent; population-based evidence suggests that ~40% of persons with migraine describe bilateral pain during attacks

4. Farzin Zobdeh [2021], A recent randomised control trial has found that 67% of migraineurs developed migraine attacks following administration of CGRP as intravenous infusion. Further, CGRP levels have been found to be elevated in migraineurs, as opposed to the levels of vasoactive intestinal peptide, substance P and neuropeptide Y, which were found to be steady during migraine attacks.

5. Balakrishnan Ramasamy [2019] Incidence of Migraine is more in females (169,76%) compared to males (53, 24%). Most of the patients of migraine were of age group 18-29 years with an approximate count of 77 patients (34.65%). Frequency of migraine most frequently seen was 3-4 per month was seen in 64 patients (29%) and chronic migraine was seen in 19 patients (8.4%).

IV. Adverse Drug Reactions (ADR) in Migraine Therapy

Adverse Drug Reactions (ADRs) are unwanted, harmful effects of drugs used for migraine treatment. These may be from mild side effects to life-threatening complications, impacting patient compliance and treatment response. ADRs are of Type A (dose-dependent, predictable) or Type B (idiosyncratic, unpredictable) in nature.

1. ADRs of Acute (Abortive) Migraine Drugs

A. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Drugs: Ibuprofen, Naproxen, Diclofenac, Aspirin
- Usual ADRs:
 - o Gastric irritation, peptic ulcers, nausea, vomiting
 - o Renal impairment (with long-term use)
 - o Increased risk of cardiovascular events (with high doses)

B. Triptans (Selective 5-HT_{1B/1D} Agonists)

- Drugs: Sumatriptan, Rizatriptan, Zolmitriptan
- Common ADRs:
 - o Chest tightness, vasoconstriction (mimicking angina)
 - o Hypertension, dizziness
 - o Flushing, tingling, serotonin syndrome (if combined with SSRIs/SNRIs)
- Serious ADRs: Avoid in patients with cardiovascular disease (risk of myocardial infarction).

C. Ergot Alkaloids

- Drugs: Ergotamine, Dihydroergotamine
- Common ADRs:
 - o Nausea, vomiting, muscle pain
 - o Peripheral vasoconstriction (ergotism) → Can cause gangrene
- Serious ADRs: Contraindicated in pregnancy (risk of miscarriage).

D. CGRP Receptor Antagonists (Newer Therapy)

- Drugs: Rimegepant, Ubrogepant
- Common ADRs:

- o Nausea, dizziness
- o Fatigue, hypersensitivity reactions

2. ADRs of Preventive (Prophylactic) Migraine Drugs

A. Beta-Blockers

- Drugs: Propranolol, Metoprolol, Atenolol
- Common ADRs:
 - o Bradycardia, hypotension
 - o Fatigue, dizziness, depression
- Serious ADRs: Avoid in asthma/COPD (risk of bronchospasm).

B. Antiepileptic Drugs

- Drugs: Topiramate, Valproate
- Common ADRs:
 - o Cognitive problems (memory disturbances, confusion) (Topiramate)
 - o Weight gain, hepatotoxicity (Valproate)
- Serious ADRs: Valproate is teratogenic (produces fetal abnormalities).

C. Antidepressants

- Drugs: Amitriptyline, Venlafaxine
- Common ADRs:
 - o Drowsiness, dry mouth, weight gain
 - o Sexual dysfunction (Venlafaxine)

D. CGRP Monoclonal Antibodies

- Drugs: Erenumab, Fremanezumab, Galcanezumab
- Common ADRs:
 - o Injection site reactions
 - o Constipation, muscle pain

V. Future Potential of Pharmacovigilance in Migraine

Pharmacovigilance (PV) of migraine treatment in the future will concentrate on smart ADR monitoring, safer drug discovery, and tailored treatment protocols.

AI & Big Data: Computer systems with artificial intelligence will streamline ADR tracking and early alerts.

- Patient Self-Reporting: Apps will enhance real-time tracking of ADRs.
- Post-Marketing Surveillance: Ongoing observation of CGRP inhibitors, gepants for ADRs for rare occurrences.
- Pharmacogenomics: Personalized treatment to estimate ADR dangers from genetic details.
- Safer Drug Delivery: New nasal sprays, patches, and neuromodulation devices to minimize systemic ADRs.
- Regulatory Strengthening: Increased international cooperation for more stringent ADR reporting and safer migraine treatments.
- Public Awareness: Patient and healthcare provider education to enhance ADR detection and reporting.

VI. Conclusion

Pharmacovigilance has a critical function to ensure safety and efficacy of migraine treatments through the monitoring and reduction of adverse drug reactions (ADRs). As new drugs like CGRP inhibitors and gepants have been introduced, ongoing post-marketing surveillance is necessary to identify long-term risks.

The future of PV in migraine treatment will be influenced by AI-based ADR detection, personalized medicine, and novel drug delivery systems for patient safety enhancement. Regulatory policy strengthening, international cooperation, and patient education will additionally optimize treatment outcomes. With the convergence of these developments, PV will contribute to safer, more effective, and patient-focussed migraine management.

