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MIGRAINE - RECENT DEVELOPMENTS AND FUTUREOPPORTUNITIES

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ABSTRACT

Migraine is a brain disorder that produces a wide array of neurological and systemicsymptoms, commonly including severe head pain; sensitivity to lights, sounds, and smells; neck or shoulder pain; ringing in the ears; nausea and vomiting; andirritability. Migraines can be a primary diagnosis or a symptom of an underlying medical (meningitis, hormone changes) or psychological (depression, anxiety disorder, post-traumatic stress disorder) condition. For more than 90% of sufferers, migraines interfere with education, work, or social activities. Four phases have been identified in migraine attacks. The migraine pipeline looks to take advantage of the ever-growing need for novel therapies, as well as innovative delivery systems. Several old drugs are being reworked into new formulations to decrease time to onset, provide localized treatment, and extend duration of action.

KEYWORDS: Migraine, Meningitis, Depression, Novel Therapies, Innovativedelivery systems.

INTRODUCTION

Migraine is defined as "an episodic headache associated with certain feature, such as sensitivity to light or movement or recurring syndrome of headache associated with other symptoms of neurological dysfunction in varying admixture"

Migraine is a specific syndrome that affect a significant fraction of the world population with higher prevalence in female (15%) than in male (6%).[1]

The syndrome has some associated feature like intense and throbbing lateral headache. Associated with anorexia, nausea, vomiting, photophobia, phonophobia (common migraine).

Migraine is the complex genetic disorder with heritability estimates as high as 50% and with likely polygenic multifactorial in heritance.[2]

Here, we review advances regarding the mechanism of the primary brain dysfunction leading to the onset of a migraine attack and to episodic activation of the trigeminovascular pain pathway.

History and Physical

Four Phases of Migraine Attacks

Four phases have been identified in migraine attacks.

Prodromal: premonitory symptoms associated with hypothalamus activation(dopamine)

- Around 77% of patients suffer prodromal symptoms for up to 24 to 48 hours before headache onset. It is more common in females than males (81 to 64%).
- Frequent symptoms are yawning (34%), mood change, lethargy, neck symptoms, light sensitivity, restlessness, difficulties in focusing vision, feeling cold, craving, sound sensitivity, sweating, excess energy, thirst, and edema.[1]

Aura: Changes in cortical function, blood circulation, and neurovascular integration occur in about 25% of cases. It can precede the headache, or it can present simultaneously. They are typically gradual, less than 60 minutes in duration, more often visual, and have positive and negative symptoms.

- Positive symptoms are caused by active release from central nervous system neurons (bright lines or shapes, tinnitus, noises, paresthesias, allodynia, or rhythmic movements).
- Negative symptoms indicate a lack or loss of function (reduction or loss of vision, hearing, sensation, or motion).
- They have to be fully reversible.
- It usually consists of tingling sensations on one side of the face or a limb They are considered paresthesias.
- The most common positive visual symptom is the scintillating scotoma (anarea of absent vision with a shimmering or glittering zigzag border)
- The most common negative visual symptom is visual field defects.
- Visual auras are the most frequent ones.
- Sensory auras are also common. They can follow visual symptoms or occurwithout them.
- Language auras are not frequent. They consist of transient dysphasia.
- Motor auras are rare. They consist of complete or partial hemiplegiainvolving limbs and the face.[1]

Headache

Additional changes in blood circulation and function of the brainstem, thalamus,hypothalamus, and cortex

- Often unilateral, generally with a pulsatile or throbbing feature andincreasing intensity within the first hours.
- The intensity can correlate to nausea, vomiting, photophobia, phonophobia,rhinorrhea, lachrymation, allodynia, and osmophobia.
- It can take place over hours to days.
- Patients may seek relief in dark places, as the pain usually resolves in sleep.[21]

Postdrome

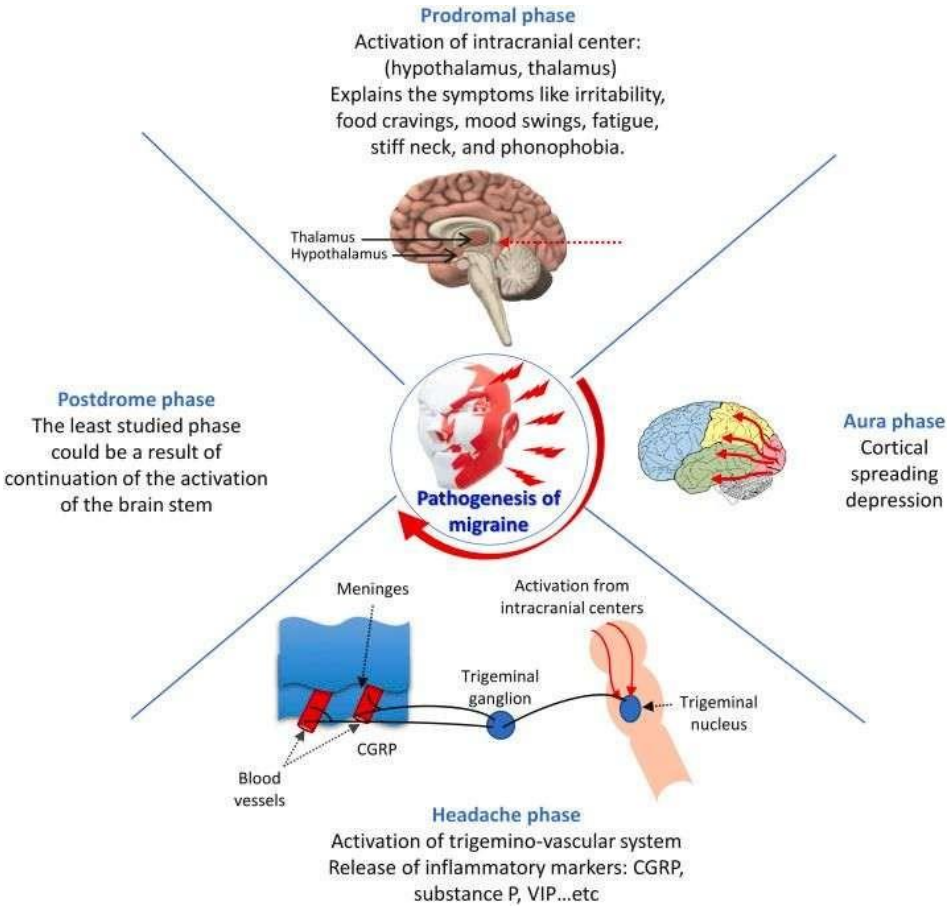
- Persistent blood changes with symptoms after headache termination
- This phase consists of a movement-vulnerable pain in the same location as theprevious headache.
- Common symptoms can be exhaustion, dizziness, difficulty concentrating, and euphoria.[21]

MODERN THEORIES OF MIGRAINE

By the 20th century the antimigraine efficacy of ergotamine was established, with the advantage over ergot that the occurrence of ergotism was less frequent. However, due to the lack of any scientific studies there was still a controversy between the opposing vascular and neurogenic theories of migraine. Fortunately, in the late 1930's, Harold Wolff became the first researcher to place migraine on a scientific basis. During a significant number of migraine attacks, pulsations in the temporal branches of the external carotid artery were demonstrated using an external tambour, and pain could be relieved either by physical compression or by ergotamine. These and other findings seemed to establish the vascular theory of migraine beyond doubt.[3]

In the late 1930's, Harold Wolff became the first

researcher to place migraine on a scientific basis, Wolf measured the diameter of the extra cranial (temporal) arteriesin patients suffering migraine attacks and found them to be dilated. These patients were treated with vasoconstrictors (ergotamine) which relieved the pain and decreased the arterial dilation.[9]



Although subsequent events leading to headache (and associated symptoms) are notcompletely understood, the increased vascular pulsation may activate stretch receptors. This would, in turn increase the activity of neuropeptide containing (mainly calcitonin gene-related peptide (CGRP) perivascular nerves which may ultimately cause pain and other associated symptoms. In line with the finding that carotid arteriovenous anastomoses dilatation play a role in the pathogenesis of migraine, it is reasonable to believe that compounds which produce cranioselectivevasoconstriction may have a potential therapeutic use in the treatment of migraine. In anaesthetized dogs and pigs acutely acting antimigraine drugs, ergot alkaloids (ergotamine and dihydroergotamine and triptans (sumatriptan and second generation triptans) produced potent vasoconstriction in the canine and porcine.[13]

Epidemiology of Migraine

Migraine affects over a billion people worldwide and brings with it a huge burden of disability. It is a disease which disproportionally affects the working age population which heightens its economic impact, both at the individual family levelland the societal level. Women are significantly more affected by migraine at every age and in all social and geographical groups. At the most severe end of the spectrum, chronic migraine is associated with poorer overall physical and mental health as well as increased risk of unemployment and lower household income. Estimates of the incidence and prevalence of migraine vary with sex, race, ethnicity, geography, socioeconomic, and educational status, suggesting there are many factorsat play.[4]

Symptoms of Migraine

A number of different factors can increase your risk of having a migraine. These factors, which trigger the headache process, vary from person to person and include:[4,5]

- Sudden changes in weather or environment
- Too much or not enough sleep
- Strong odors or fumes
- Emotion
- Stress
- Overexertion
- Loud or sudden noises
- Motion sickness
- Low blood sugar
- Skipped meals
- Tobacco
- Depression
- Anxiety

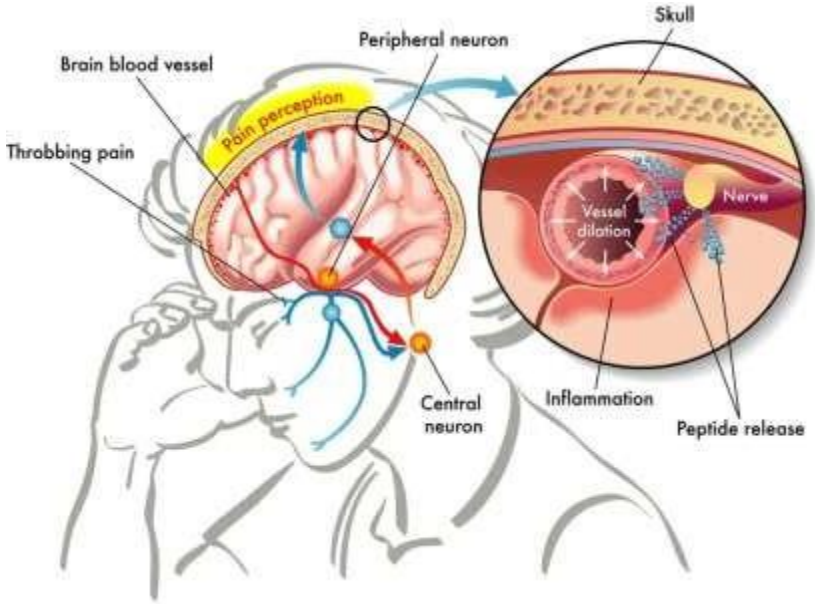
- Head trauma
- Hangover
- Some medications
- Hormonal changes
- Bright or flashing lights

Pathophysiology

Headache has been known for almost 600 years. The modern concept of chronic migraine was known at the beginning of the 17th century. In the early days, the pathophysiology of migraine was principally based on neurological or vascular mechanisms. The metabolic aspects of this disorder were reported only relatively recently. Migraine is divided into four phases including (Premonitory, Aura, Headache and Postdromal). These phases can occur sequentially or may show significant overlap.[1]

Migraine is best described as a neuronal event that may be caused by a hereditary susceptibility of the brain and various environmental triggers. It may occur in patients who have a genetically sensitive nervous system. The pathophysiology of migraine continues to be studied, and numerous theories have been proposed.

The most recent and widely studied theory involves the trigeminovascular system, which—under the influence of a variety of external and internal triggers—results in the release of various inflammatory peptides, including calcitonin gene-related peptide (CGRP), substance P, neurokinin A, and nitric oxide. The resultant perivascular inflammatory response influences the trigeminal nucleus caudalis in the brainstem (the migraine generator) and cervical cord area, transferring pain data to the upper areas of the brain, including the thalamus and cortex. This leads to a state of hyper excitability or cortical sensitization, resulting in the pain of migraine and associated features, including gastrointestinal (GI) and visual changes. Although other neurotransmitters may be involved in the pathophysiology of migraine, the serotonergic (serotonin, or 5-hydroxytriptamine [5-HT]) system may have significant involvement. Documented changes in 5-HT processing and metabolism during a migraine attack suggest that migraine is a result of a central neurochemical imbalance secondary to dysfunction of the serotonergic system. Although the exactseries of events involved is not fully understood, low levels of 5-HT appear to cause activation of the trigeminovascular system.[5]



Pharmaceutical treatment

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are mainstay choices and have the greatest strength of evidence. Ibuprofen, naproxen sodium, acetylsalicylic acid (ASA), and diclofenac potassium all have double-blinded randomized controlled trial evidence for efficacy that has analysis in systematic reviews. NSAIDs include aspirin, naproxen, ibuprofen, tolfenamic acid, diclofenac, piroxicam, ketoprofen, and ketorolac.

Acetaminophen and the combination of acetaminophen/aspirin/caffeine have also demonstrated consistent evidence of efficacy for acute migraine.[6]

Mechanism of Action

NSAIDs inhibit prostaglandin synthesis. NSAIDs reversibly inhibit cyclooxygenase (COX) 1 and 2. The NSAIDs that inhibit prostaglandin E2 synthesis are effective intreating acute migraine attacks. Aspirin acts as an irreversible COX 1 and 2 inhibitor.

Although not entirely understood, the current thought is that acetaminophen affects central processes, such as positive effects on the serotonergic descending inhibitory pathways. It also may affect opioidergic systems, eicosanoid systems, and the nitric oxide-containing pathways.

Administration

Aspirin: Peroral (PO) tablet with standard dosages of 325 mg, 500 mg. and 400 mg effervescent; treatment dosage of up to 1000 mg

Naproxen: PO tablet with standard dosages of 220 mg, 275 mg, 500 mg, and 550 mg; treatment dosage of 550 to 1100 mg per day in divided dosages

Ibuprofen: PO tablet with standard dosages of 200 mg, 400 mg, 600 mg, and 800 mg; treatment dosage of 200 to 800 mg

Tolfenamic acid: PO tablet with standard and treatment dosage of 200 mg

Diclofenac: PO tablet with standard dosages of 50 mg; treatment dosage of 50 to100 mg

Piroxicam: PO capsules with standard dosages of 10 mg, 20 mg; treatment dosageof 40 mg

Ketorolac: Parenteral dosing with standard dosages of 30 to 60 mg; treatment doseof 30 to 60 mg

Adverse Effects

The most common adverse effects of NSAIDs are GI symptoms, which include dyspepsia, abdominal burning or discomfort, and diarrhea. Other less common symptoms include easy bruising, pruritus, rash, and hypersensitivity response in asthmatics, gastritis, esophagitis, GI bleeding, renal failure, hepatic impairment, and cardiovascular events. Besides allergic reactions, no serious side effects have been observed with acetaminophen when taken in appropriate dosages. After higher doses or prolonged duration of taking acetaminophen, hepatotoxicity, and nephrotoxicity (less common) can occur.

Contraindications

In addition to NSAID hypersensitivity reaction, another agreed-upon absolute contraindication is for those in the preoperative period of coronary artery bypass graft surgery. Warnings include those with significant cardiovascular disease, renal insufficiency, gastrointestinal.

Beta-Blockers

Propranolol, timolol, bisoprolol, metoprolol, atenolol, and nadolol have shown positive outcomes in migraine prevention studies. Beta-blockers with intrinsic sympathomimetic activity (such as acebutolol, alprenolol, oxprenolol, and pindolol)are not effective for migraine prevention.[7]

Administration

Propranolol: PO immediate-release and long-acting formulations available; dose for immediate release ranging from 80 to 240 mg/day divided every 6 to 8 hours; dose for long-acting release is 80 to 240 mg/day

Timolol: PO formulation with doses of 20-30 mg/day Bisoprolol; PO formulation with doses of 2.5 to 10 mg/day

Metoprolol: PO formulation with doses of 50 to 200 mg/day twice daily Atenolol: PO formulation with doses of 50 to 200 mg/day

Nadolol: PO formulation with doses of 40 to 240 mg/day

Mechanism of Action

The mechanisms of action of beta-blockers in migraine prevention are not entirely understood. The thinking is that the beta-1 mediated effects could inhibit noradrenaline release and tyrosine hydroxylase activity, accounting for Prophylactic action. Other possibilities include serotonergic blockade, inhibiting thalamic activity, and nitrous oxide blockade.

Adverse Effects

Common adverse effects include drowsiness, fatigue, dizziness, and weakness. Other adverse effects include weight gain, symptomatic hypotension, nausea/vomiting, diarrhea, feelings of coldness in extremities, and dry skin/mouth/eyes, bradycardia, bronchospasm dyspnea, alopecia, visual disturbances, insomnia, sexual dysfunction, and metabolism alterations.

Contraindications

Asthma and chronic obstructive pulmonary disease have been classic contraindications because of the potential for beta-blockers to cause bronchospasm. Cocaine intoxication is another contraindication because of the risk of coronary vasospasm.

Triptans

Seven triptans have approval from the FDA and marketed for acute treatment of migraines. They include sumatriptan, eletriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, and almotriptan. Triptans are significantly more expensive than NSAIDs as a class. They are often therapeutic choices if other therapies have failed (i.e., NSAID, acetaminophen) or if the headache is severe.[8,9]

Mechanism of Action

Triptans are serotonin-receptor agonists with a high affinity for 5-HT1B and 5- HT1D receptors, and variable affinity for 5-HT1F receptors. The proposed mechanism of action involves binding postsynaptic 5-HT1B receptors on the smooth muscle cells of blood vessels and presynaptic 5-HT1D receptors on the trigeminal nerve terminals and dorsal horn neurons.

Administration

Sumatriptan: PO tablet with standard dosages of 100, 50, and 25 mg; also available parenteral (though IV contraindicated because of its potential to cause vasospasm)

Eletriptan: PO tablet with standard dosages of 40 and 20 mg; contraindicated in patients with renal failure, arrhythmias, and heart failure.

Naratriptan: PO tablet with standard dosages of 2.5 and 1 mg; has a sulfa group.

Zolmitriptan: PO tablet with standard dosages of 5

and 2.5 mg; also available as wafer and nasal spray; wafer contains phenylalanine.

Rizatriptan: PO tablet with standard dosages of 10 and 5 mg, also available as a wafer; wafer contains phenylalanine.

Frovatriptan: PO tablet with a standard dose of 2.5 mg.

Almotriptan: PO tablet with standard dosages of 12.5 and 6.25 mg; has a sulfa group.

Adverse Effects
The most common adverse effects of triptans include pressure or tightness sensations of the chest, throat, or jaw; limb heaviness; myalgias; and fatigue. Less common adverse effects include flushing, paresthesias, dizziness, asthenia, and mental cloudiness.

Contraindications
Triptans have associations with increased blood pressure, and providers should avoid giving them to patients with uncontrolled hypertension, ischemic cardiac syndrome, cerebrovascular syndrome, or peripheral vascular condition. Patients should also not take them within 24 hours of administration, another triptan, or ergot- type medication.

Antidepressants
The most studied antidepressants that have shown efficacy for migraine prevention are the tricyclic antidepressant (TCA) amitriptyline and the selective serotonin reuptake inhibitor (SSRI) fluoxetine. Other TCAs and the serotonin norepinephrinereuptake inhibitor venlafaxine have been studied and may be effective for migraineprevention, though the evidence is short.[10]

Administration
Amitriptyline: PO formulation of 10 to 150 mg/day
Fluoxetine: PO formulation of 20 to 40 mg/day.

Mechanism of Action
Similar to other migraine prevention medications, the role of antidepressants in migraine prevention is unclear. Amitriptyline is a mixed serotonin-norepinephrine reuptake inhibitor and has the following mechanisms: alpha2-adrenoceptor agonist, sodium channel blockade contributing to ant muscarinic and antihistamine effects, and cortical spreading depression. Fluoxetine is a selective serotonin reuptake inhibitor leading to increased levels of serotonin. Noradrenaline reuptake occurs at higher doses.

Adverse Effects
Adverse effects of tricyclic antidepressants include ant muscarinic effects such as dry mouth, blurry vision, constipation, urinary retention, increased body temperature, and excessive sweating, other side effects include morning sedation, tachycardia, vivid dreams, weight gain, hypotension, sexual dysfunction, confusion, and QT prolongation. Adverse effects of selective serotonin reuptake inhibitors include sexual dysfunction, drowsiness, weight gain, insomnia, dizziness, headache, dry mouth, blurry vision, nausea, rash, tremors, and constipation. SSRIs can also prolong the QT interval.

Contraindications
For TCAs, coadministration with monoamine oxidase inhibitors (MAOI) is contraindicated due to the increased risk of serotonin syndrome. Hypersensitivity reactions and co-administration of cisapride are also contraindicated. For SSRIs, coadministration of medications that significantly increase the risk of serotonin syndrome is contraindicated. These medications include monoamine oxidase inhibitors, linezolid, and methylene blue. Other contraindications include hypersensitivity reactions and co-administration with pimozide or thioridazine.

Antiepileptics
Several antiepileptic drugs (AEDs) have been studied and proven effective for migraine prevention, with topiramate and valproate having the best evidence.[11,12]

Administration
Topiramate: PO formulation with doses of 25-200 mg/day.

Valproate: PO formulation of extended (once daily) and delayed (2 divided doses daily) releases are available; doses of 500-1500 mg/day.

Mechanism of Action
Similar to the beta-blockers, it is unclear what effect antiepileptics have or migraine prevention. For topiramate, it blocks multiple channels such as voltage dependent sodium and calcium channels. It also has been shown to inhibit glutamate-mediated excitatory neurotransmission, facilitate GABA-A-mediated inhibition, inhibit carbonic anhydrase activity, and reduce CGRP secretion from trigeminal neurons. For valproate, similar to topiramate, multiple mechanisms may contribute to migraine prevention. They include enhancing GABAergic inhibition, blocking excitatory ion channels, and downregulating the expression of CGRP in brain tissue.

Adverse Effects
Common adverse effects of topiramate include nausea/vomiting, diarrhea somnolence, dizziness, weight loss, paresthesias, fatigue, nasopharyngitis, and weight loss. Other adverse effects include tachypnea, palpitations bleeding, mood changes, dysuria, hematuria, and increased frequency of urination. Common adverse effects of valproate include nausea/vomiting, diarrhea, abdominal pain, headache, drowsiness, hair loss, tremors, dizziness, visual disturbances, tinnitus, changes in appetite, and weight gain. Other adverse effects include confusion, severe drowsiness, bleeding, and

inflammation.

Contraindications
Hypersensitivity to topiramate is a contraindication to the drug Contraindications tovalproate usage include hepatic dysfunction mitochondrial disorders, hypersensitivity, urea cycle disorders, and pregnancy.

Ergotamines
Triptans have largely replaced ergotamines, as studies have shown more efficacy fortriptans. Dihydroergotamine has demonstrated some efficacy, while the effectiveness of ergotamine is uncertain. In one systematic review, dihydroer gotamine was not as effective as triptans, but when combined with an antiemetic, was found to be as effective as ketorolac opiates, or valproate. Dihydroergotamine may be a useful option when patients do not respond to other medications, including triptans.[9,13]

Mechanism of Action
Ergotamines, like triptans, are potent 5-HT 1/1d receptor agonists. They involve constricting the theorized pain-producing intracranial extracerebral blood vessels at the 5-HT1B receptors and inhibit the trigeminal neurotransmission at both peripheral and central 5-HT1D receptors. They also interact with other serotonin, adrenergic, and dopamine receptors. They cause constriction of peripheral and cranial blood vessels.

Administration
Dihydroergotamine: Parenteral dosing with dosages between 0.5-1 mg; intranasal formulation available (4 mg).

Adverse Effects
The most common side effects include nausea and vomiting. Administer with an antiemetic. Dysphoria is another observed side effect (central 5-HT1A agonism).

Contraindications
Similar to triptans, those with cardiovascular disease should avoid the use of ergotamines. The peripheral vascular constrictive effects of ergotamines are more pronounced than triptans since triptans do not have activity at adrenergic and 5 HT2A receptors.

Antiemetics
When a migraine is associated with nausea/vomiting, an antiemetic is excellent choice for treatment. The administration of an antiemetic is often in combination with either an NSAID or triptan, but can be used as monotherapy. Two common antiemetics used include metoclopramide and prochlorperazine. Metoclopramide has the greatest evidence for efficacy in migraine and is associated with a less likelihood of extrapyramidal side effects than prochlorperazine, but both are good initial options. Domperidone, promethazine, chlorpromazine are other examples of antiemetics.[14]

Mechanism of Action
Metoclopramide is a benzamide that antagonizes the D2 receptor at lower doses and 5HT-3 at higher doses Prochlorperazine and chlorpromazine are dopamine antagonists (D2 receptor), providing antiemetic and migraine relief effects.

Administration
Metoclopramide: PO and parenteral formulations available; treatment dosages of 10-20 mg
Prochlorperazine: PO, parenteral and rectal formulations available; treatment dosageof 10 mg (PO and parenteral) and 25 mg (rectal)
Chlorpromazine: PO and parenteral formulations available; treatment dosage of 0.1mg/kg up to 25 mg.

Adverse Effects
Most antiemetics used for migraines are associated with a risk of QT interval prolongation and torsades de pointes. Metoclopramide prochlorperazine, and chlorpromazine can cause dystonia, tardive dyskinesia, and akathisia (collectively known as extrapyramidal symptoms). Coadministration with diphenhydramine can prevent these symptoms. Other side effects are uncommon and can include headaches and allergic reactions such as anaphylaxis.

Contraindications
Considering the dopamine antagonists, contraindications include known hypersensitivity reactions and know extrapyramidal symptom reactions. NSAIDs inhibit prostaglandin synthesis. NSAIDs reversibly inhibit cyclooxygenase (COX) 1and 2. The NSAIDs that inhibit prostaglandin E2 synthesis are effective in treating acute migraine attacks. Aspirin acts as an irreversible COX I and 2 inhibitor. Although not entirely understood, the curent thought is that acetaminophen affects central processes, such as positive effects on the serotonergic descending inhibitory pathways. It also may affect opioidergic systems, eicosanoid systems, and the nitric oxide-containing pathways.

Calcium Channel Blockers
Flunarizine is the best studied of the calcium channel blockers for migraine prevention (however not available in the U.S.). Verapamil and cinnarizine are other meds that are off-label for migraine prevention. Verapamil is probably the most commonly used calcium channel blocker for migraine prevention in the U.S.[15]

Administration
Flunarizine: PO formulation of 5 to 10 mg/day
Verapamil: PO formulation of 120 to 480 mg/day in 3 divided doses

Mechanism of Action
Similar to the other migraine preventive treatments, the role of calcium channel blockers in migraine prevention is unclear. Flunarizine is a nonselective calcium antagonist. In addition to calcium channel activity, it

blocks voltage-gated sodium channels, acts as a D2 dopamine antagonist, and increases leptin levels.

Adverse Effects

Adverse effects include constipation, cardiac conduction defects at higher doses, dizziness, constipation, headache, nausea/vomiting, flushing. edema, drowsiness, and hypotension. Lesser common adverse effects include sexual dysfunction, gingival overgrowth, and liver dysfunction.

Contraindications

Contraindications include hypersensitivity reactions, acute coronary syndrome, hypertrophic obstructive cardiomyopathy, severe stenotic heart valve defects, and cardiac conduction disorders.

Migraine Treatments in Pregnancy

Ergotamine is contraindicated during pregnancy and was in FDA category X underthe prior pregnancy drug rating system. NSAIDs are not advised for use in the third trimester as they may increase the risk of prematurely closing the fetal ductus arteriosus.[16] Valproate is contraindicated during pregnancy and was also in FDA category X. First-trimester exposure to topiramate correlates with cleft lip/palate. Topiramate was in FDA category D.[17]

Migraine Treatments in Children

Of the abortive medications discussed, which include NSAIDs/acetaminophen, triptans, antiemetics, and dihydroergotamine, there are variable age restrictions/recommendations. No abortive class agents discussed here have an absolute contraindication. Dosing will typically be weight-based or smaller than adult doses. As for preventive treatments, although data is limited in the pediatric population, the classes of medications discussed here (eta-blockers, antiepileptics, calcium channel blockers, and antidepressants) have all been used.[18.19]

Other and Future Considerations Triptans with NSAIDs

Research has shown the combined use of a triptan and an NSAID to be more effective than using either drug class alone for acute migraine treatment. The best- studied combination is sumatriptan plus naproxen PO. The two classes of drugs having different mechanisms of action are thought to provide better relief. Multiple studies have used sumatriptan 85 mg plus naproxen 500 mg and sumatriptan 50 mg plus naproxen 500 mg. In a meta-analysis review article, no significant difference was found between using the sumatriptan 85 mg - naproxen combo and the sumatriptan 50 mg - naproxen combo.[22,23,27]

Lasmiditan

Lasmiditan is a serotonin 5-HT1F receptor agonist that has been shown effective for acute migraine treatment. The utility of this medication is that it lacks vasoconstrictor effects such as those seen in triptans, and thus offers those with cardiovascular disease an alternative to triptans. Studies have used up to lasmiditan 200 mg PO with good effect; however, there were frequent reports of adverse effects. In a recent phase, three multicenter, double-blind, randomized controlled studies, between 25.4% to 39.0% of patients receiving lasmiditan reported adverse effects. The most common adverse effects were dizziness, somnolence, and paresthesias.[20,21]

Calcitonin Gene-Related Peptide (CGRP)

CGRP monoclonal antibodies (mAbs) are the only class of currently used preventives explicitly developed for the treatment of migraines. The current thinkingis that CGRP mediates the vasodilatory component of neurogenic inflammation, as CGRP is a widely distributed vasodilator. The CGRP mAbs target either the CGRP molecule itself or the CGRP receptor. In network meta-analysis, the CGRP mAbs seemed to be as effective as other preventive treatments, but have fewer side effects. Long-term data on safety, however, is limited. These medications include erenumab, fremanezumab, and galcanezumab.[24,25,26]

Alternative Treatment

Lifestyle changes; must be a commitment from the patient; however, social supportis of great importance to improve mental health to help the patient's involvement,[18,19]

- Regular exercise
- Yoga
- Relaxation training
- Cognitive-behavioral therapy
- Biofeedback
- Reduction of triggers
- Detoxification
- Butterbur
- Melatonin

Diagnostic study

Diagnosis of Migraine and Demographic Characteristics.—Approximately half (48%) of IHS-defined migraineurs (41% of males and 51% of females) reported a physician diagnosis of migraine (Figure 1). These proportions are higher than those estimated in the 1989 survey in which 38% of IHS-defined migraineurs (29% of males and 41% of females) reported a physician diagnosis9,12 (Figure 1). Rates of diagnosis varied with certain sociodemographic characteristics (Table). Diagnosed migraineurs were more likely to be females than undiagnosed migraineurs (79.4% versus 71.7%, P.001). Diagnosis was also associated with age (P.05); older age groups were more likely to be diagnosed. Moreover, household income was associated with diagnosis (P.001); those with incomes more than $50000 per year were more likely to be diagnosed. Regardless of whether they had received a physician diagnosis of migraine, many migraineurs reported a physician diagnosis for other headache types. The

proportions of physician-diagnosed and undiagnosed migraineurs reporting other headache types were 44% and 32.3% for tension-type headache, 43.1% and 42% for sinus headache, 17.9% and 6.5% for cluster headache, and 13.1% and 7.8% for "sick" headache, respectively.[28]

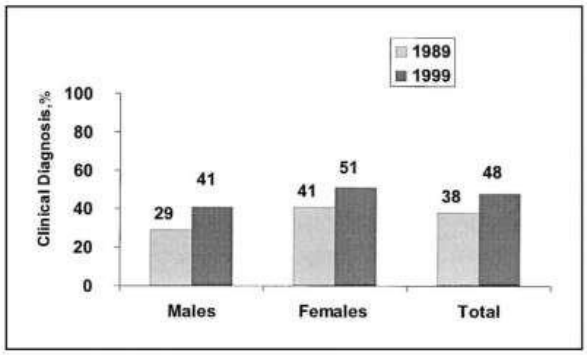


Fig 1.—Self-reported physician diagnosis of migraine among International Headache Society-defined migraineurs: 1989 and 1999.

Medication Use

A total of 41% of IHS-defined migraineurs used prescription drugs for headaches, a finding similar to that observed in the American Migraine Study in which 37% reported use of prescription drugs for headaches (Figure 2). The proportion of IHS-defined migraineurs using only over-the-counter medications to treat their headaches was 57% in 1999, compared with 59% in 1989 (Figure 2). A very small subgroup used no medication at all.[28]

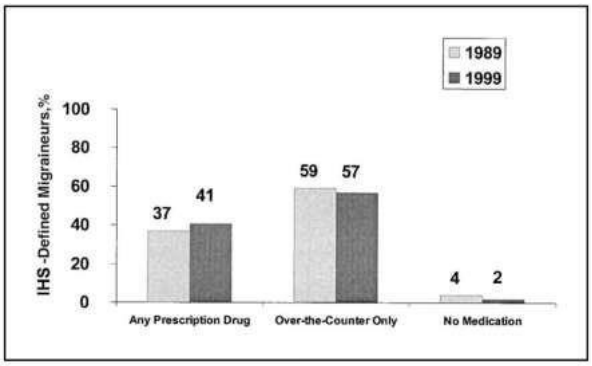


Fig 2.—Patterns of medication use among International Headache Society-defined migraineurs from the 1989 and 1999 American Migraine Studies.

FUTURE: Novel Therapies and Innovative Delivery Systems

According to market research trends, $4.34 billion was spent on migraine drugs worldwide in 2021, with the number projected to rise to $8.79 billion by 2030.6 The migraine pipeline looks to take advantage of the ever-growing need for novel therapies, as well as innovative delivery systems.

Several old drugs are being reworked into new formulations to decrease time to onset, provide localized treatment, and extend duration of action. Dihydroergotamine derivatives for nasal and subcutaneous injection; zucapsaicin, currently available as a topical agent for pain relief, for intranasal administration; and a novel botulinum containing neurotoxin, daxibotulinumtoxin A, whose effects last up to 6 months, are just some of the medications in the migraine pipeline.[29]

Research is also being conducted into novel therapeutic targets, including pituitary adenylate cyclase-activating polypeptide, adenosine, δ-opioid receptors, potassium channels, transient receptor potential ion channels, and acid-sensing ion channels.

The perfect migraine treatment has yet to be discovered. Medication AEs often limit long-term use, and medications are not always able to provide complete relief.

The effects of chronic migraine are so debilitating that combination therapies are often employed, using both pharmacological and non-pharmacological measures, to decrease morbidity and increase the patient's quality of life.

With millions of migraine sufferers and billions of potential dollars at stake, the future of migraine treatment lies in the medication that can decrease migraine frequency, duration, and severity while minimizing AEs and the need for redosing.[30]

CONCLUSION

Migraine is common cause of headache, early diagnosis and prompt treatment of migraine enhances the quality of life; prevent conversion of episodic migraine to chronic migraine. As there is growing interest in pathophysiology, new armatarium targeting the different pathways are being discovered. Migraine treatment has been described over the centuries by shamans and by countless physicians. Their writings from ancient times to the present, mirror the evolution of scientific thought, with migraine metamorphosing from a disease of supernatural causes to a molecular disorder. With this long history, notwithstanding, it is extremely surprising that effective ant migraine drugs had been, until very recently, limited in number. Indeed, in comparison to other areas of pharmacology, the therapeutic approaches to headache have advanced minimally over the past 100 years. Fortunately, in the last decades, there have been big steps in understanding the pathophysiology of migraine and in the development of ant migraine drugs. Evidently, new approaches need to be explored (e.g. drugs that inhabit the trigeminal-vascular system) in order to obtain selective drugs with less cardiovascular adverse effects.

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