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PHARMACOTHERAPY OF MIGRAINE

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ABSTRACT

Migraine is defined as recurrent attack of headaches that are commonly unilateral and accompanied by gastrointestinal and visual disorder. Migraine is more prevalent in females than males. It is primarily a complex neurovascular disorder involving vasodilation of intracranial, extracerebral blood vessels and simultaneous stimulation of surrounding trigeminal sensory nervous pain pathway that results in headache. The activation of trigeminovascular system causes release of various vasodilators, especially CGRP that induces pain response and at the same time, decrease level of neurotransmitter serotonin have been observed in migraine patients. The calcitonin gene-related peptide (CGRP), a neuropeptide play an integral role in the pathophysiology of migraine. This paper discusses the hypothesized role of CGRP in migraine and reviews the mechanism of this neuropeptide in migraine pathophysiology. The increase CGRP synthesis and release might be mediated by activation of mitogen-activated protein kinase pathway. Blocking synthesis of cyclooxygenase by NSAIDs decrease the synthesis of prostaglandin or blocking synthesis of CGRP, which are involved in the pathophysiology of migraine headache. The migraine specific drugs such as triptans, monoclonal antibodies, NSAIDs and new class of drug most commonly used therapies for the migraine attack. serotonin receptors have been found on the trigeminal nerve and cranial vessels and their agonists especially triptans prove effective in migraine treatment. Currently CGRP receptor antagonists, triptans are used for antimigraine therapeutics.

KEYWORD: Chronic migraine, Diagnosis, management of migraine Triptans, NSAIDs, Onabotulinum toxin A.

INTRODUCTION

Headache disorders, generally characterized by recurrent headache are among the most common disorders of the human nervous system. Headache itself is a very painful feature of a small group of primary headache disorders such as tension-type headache, migraine and cluster headache.[1] Amongst these all, the migraine headache debilitative, pervasive, the most usual and essentially treatable, but still under-rated and left under-treated by many.[2] Migraine is one of the most common chronic headache disorders, mostly characterized by recurrent attacks which last for 4–72 hours, of a pulsating quality, moderate to severe intensity exasperated by routine body activity and interconnected with nausea, vomiting, photophobia or phonophobia.[3] Due to its significant impact on the Quality Of Life (QOL) of sufferer, migraine has been termed the seventh disabler.[4] It is one of the most frequent causes of headache in pediatrics and adolescents. The study of migraine in the pediatric population is condemning as it can cause burden on children and their families and the diagnostic andtherapeutic difficulties determined by varying phenotypeand possible differential diagnosis.[5] The most common headache type is tension headache however, the most common complaint in headache is migraine in clinical practice. Migraine affects approximately 13% of adults in the U.S., and its prevalence ranges between 12% and 20% in various countries around the world.1 Migraine is more common in females than males, with a prevalence of 19% and 7%, respectively. Approximately 80% of patients report a family history.[6,7] Migraine is more common in females than male population (25-50 year old age group). It is a public health issue having direct and indirect costs. Direct costs are healthcare costs, approximately one billion annually, which is 70% higher for a family with a migraine sufferer than a non-migraine affected family.[8] The pharmacotherapy of migraine is complex, and the appropriate use of abortive agents and preventative medications requires an understanding of the various medications available and when they are best used in migraine management.[9]

Pathophysiology

Whilst the development of migraine theories has evolved over time without consensus as to its pathophysiology, there are currently two major schools of thought with regards to the underlying mechanism of migraine in general—one which suggests that migraines are

generated by external triggers and another which suggest that migraines are largely generated from changes within the brain itself[10] [figure 1]. The initiation of migraine attacks occurred via activation of perivascular nerves innervating major cerebral vessels.

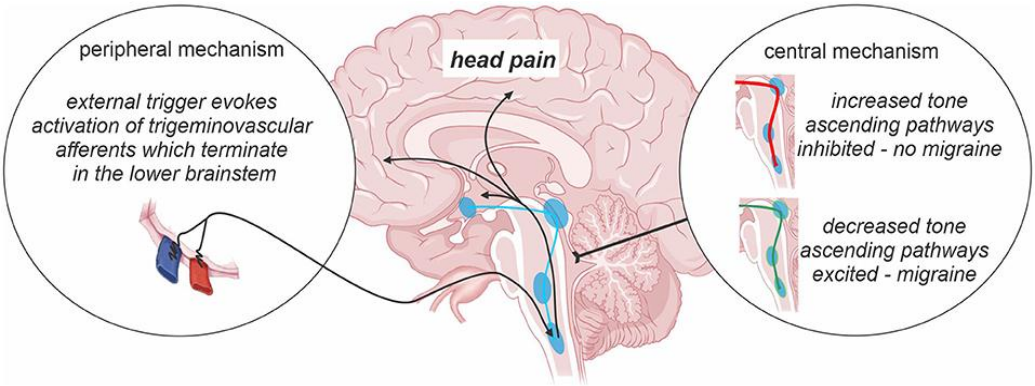

Figure 1: Mechanism of migraine central vs peripheral. In peripheral mechanism activation of trigeminovascular afferent nerve & In central mechanism decrease tone of ascending pathway which are ultimately responsible for the presence of a migraine event.

The neuropeptide calcitonin gene-related peptide (CGRP) has long been postulated to play an integral role in the pathophysiology of migraine.[11] Generally migraine is unilateral pulsatile headache due to inflammation and dilation of cerebral vessels. CGRP [Calcitonin Gene Related peptide] is main principal mediator of neurogenic inflammation of migraine and vasodilation.[12]

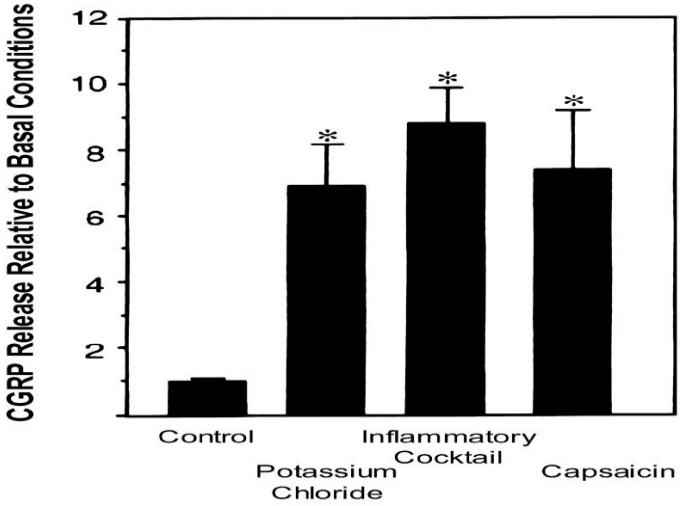

Figure 2: Indicates the expression and release of CGRP from cultured trigeminal neurons.[13] The relative amount of CGRP released in 1hr from untreated control cell or

cells treated with 60 mM kcl & inflammatory agent 10uM capsaicin. The mean basal rate of CGRP release was 148 ±5.

The peptide CGRP exacerbate vasodilation and cause neurogenic inflammation characterized by degranulation mast cell, leakage of blood vessels and vasodilation that causes severe headache.[14] Serotonin [5-HT] vasoconstricts blood vessles and nerve ending and causes severe pain. Low serotonin [5-HT] level dilates the blood vessles and initiates the migraine.[15] Migraine sufferer's report that the headache stop after they have vomited. Vomiting stimulate the intestinal motility and raise the blood serotonin [5-HT].[16]

Types of Migraine

The International Headache Society has classified the different types of migraine and describe it in International Classification of Headache Disorder [2nd edition].[17]

Type 1:- Migraine without Aura	Type 2:-Migraine with Aura
This is most common form. About 80 % of cases reported with migraine headache without aura. Associated with nausea vomiting or both. Frequently accompanied by sensitivity of light, sound. If untreated, this headache can last up to 72 hrs.	Approximately 10% of the migrainers experience this classical type. Subtypes of migraine with aura are :- Migraine headache with typical aura. Non-Migraine headache with typical aura. Typical aura without headache. Familial hemiplegic migraine [FHM]:- this is the rare mendelian dominant form of migraine which is more relevant in monozygotic twins than that of dizygotic one.[18,19]

Sporadic hemiplegic migraine - This is the non-familial form of migraine associated with motor weakness.[20]

Basilar-type migraine – This is an uncommon type of migraine with aura. This type mimics vertibrobasilar attacks and hence its name.

Childhood periodic syndromes – The syndromes occur in children and having following two subtypes.

Abdominal migraine – The abdominal migraine is a recurrent abdominal pain associated with vomiting and nausea.

Benign paroxysmal vertigo of childhood – In benign type migraine, occasional attacks of vertigo is experienced by children.

Menstrual Migraine:- Migraine headaches are influenced by changes in the ovarian hormones that occur during the menstrual cycle. Menstrual migraine has two subtypes which are as follows.[21]

Menstrual related migraine without aura.

Pure menstrual migraine without aura.

Diagnosis of Migraine

Differential diagnoses for migraine include primary headache disorders (Table 1) and secondary headache disorders.

Table 1: Characteristic of primary headache disorder.[22]

Headache Disorder	Headache duration	Headache location	Pain intensity	Pain characteristics	Accompanying symptoms	Routine physical activity
Migraine	4-72 hrs	Usually unilateral	Usually moderate or severe	Usually pulsating	Nausea, vomiting, phonophobia, photophobia.	Often aggravated by routine physical activity
Tension – type headache	Hours to days or unremitting	Bilateral or circumferential	Usually mild or moderate	Usually tightening	Sometime nausea or sometime photophobia or phonophobia	Not provoked by routine physical activity
Cluster headache	15-180 minute	Strictly unilateral and supraorbital, orbital or temporal	Very severe	Overpowering	nasal congestion and lacrimation	Agitation or restlessness

Table 2: Red flags associated with secondary headache.[23,24]

When to look	Red flag	Indication
Patient history	Atypical aura Head trauma Thunderclap headache Headache brought on by sneezing, coughing or exercise	Stroke, epilepsy, ischemic attack Haemorrhage Intracranial space lesion
Physical examination	Neck stiffness Unexplained fever Focal neurological symptoms	Meningitis, haemorrhage Meningitis Secondary headache

MANAGEMENT OF MIGRAINE ATTACK

There are three broad approaches to treat chronic migraine.[25]

1. Lifestyle and trigger management.
2. Non-pharmacological therapies.
3. Pharmacological treatment

1. Lifestyle and trigger management

When patient have chronic severe headache, it can be difficult to recognize specific trigger. Regularity of regimen with regards to stress, meal, sleep and hydration is always helpful in reducing the tendency to migraine.[26]

Many patients with chronic migraine will have other problems that include Anxiety, Depression, other pain syndrome such as Localized pain in head, fibromyalgia, sleep apnoea and tachycardia syndrome.[27]

2. Non-pharmacological therepies

Neuromodulation is a promising emerging treatment for pharmacologically non-responsive or intractable chronic migraine. Non-invasive neurostimulation modalities include transracial magnetic stimulation, transcutaneous stimulation, transracial direct current stimulation.[28,29] Invasive method includes sphenopalatine ganglion stimulation, vagus nerve stimulation and deep brain stimulation.[30,31] The recent technological developments in neuromodulatory methods have presented greater opportunity for the successful treatment of chronic migraine.

3. Pharmacological management of migraine

A. Serotonin Receptor Agonist [Triptans]

The Triptans are the drug of choice for the abortive management of migraine attack, specially that patient who have not responded to or cannot tolerate NSAIDs, simple analgesic.[32,33,34] The mechanism of action of triptans are although similar to that of ergot alkaloids, triptans are more selective serotonin receptor agonist i.e. specifically acting on 5-HT 1b/1d agonist. The triptans derivative on market, they available in various dosage forms are shown in table 3.

Table 3: Serotonin Receptor Agonist [Triptans]

Drug (Brand)	Formulation/ Dosage form	Pharmacokinetic	Comments	Patent	References
Sumatriptan [Imitrex] cost consideration with SC form	Oral 25-50 mg; q 2 hrs. Max. Dose 200-300 mg / 24 hours. Intranasal 5-10 mg spray 1 nostril per dose maximum dose 40 mg/day Subcutaneous 6 mg ; may repeat in 1 hour. maximum 12 mg q 24 hours [auto injector]	Bioavailability:15 % Oral onset :0.5 to 1.5 hrs High first –pass metabolism. Bioavailability : 17 % Intranasal onset :15-20 min Subcutaneous onset:10-15 min Bioavailability :97% Half –life all dosage form about 2 hours.	Metabolism [MAO-A] A new combination product with naproxen [Treximet] is now available. Dose Sumatriptan 85 mg + 500 mg naproxen Fast onset especially Subcutaneous	GlaxoSmithKline sells popular brand name drug Imitrex	[35]
Naratriptan (Amerge)	Oral 1-2.5 mg ; may repeat in 4 hours Maximum dose 5 mg daily	Half- life : 6 hours Onset : 1-3 hours Bioavailability : 60-70 %	Metabolism [CYP 450] slow onset long duration 50 % excreted unchanged by kidney	Trade name Amerge Marketed by GlaxoSmithKline	[30]
Rizatriptan (maxalt) Maxalt-MLT(Dissolving form)	Oral 5-10 mg ; may repeat in 2 hours, maximum dose 20-30 mg daily If taking propranolol only 15 mg MLT product dissolve on tongue,no need of water	Half –life 2-3 hours Onset :30-120 minutes Bioavailability : 45 % MLT : shows the faster onset	Metabolism by MAO-A Fast onset of action	Merck pharmaceutical make brand maxalt	[36]
Zolmitriptan (Zoming) Zoming – ZMT dissolving form	Intranasal 5 mg ; may repeat q 2 hours ; maximum dose 10 mg Oral 2.5-5 mg ; may repeat in 1-2 hours maximum	Half-life 3 hours Onset : 45 min to 1 hours Bioavailability : 40 %	Metabolism CYP 450 1A2, MAO Active metabolite two to six time more potent than parent drug	AstraZeneca & Grunanthal marketed the zoming	[37]

	10 mg daily ZMT product e dissolve on tongue ; no need of water	Intranasal : 15-20 min ZMT : shows the faster onset	Fast onset		
Almotriptan (Exert)	Oral 6.25-12.5 mg ; may repeat in 2 hours Maximum 25 mg daily	Half –life: 3-4 hours Onset : 30 min to 2 hours Bioavailability : 70 %	Metabolism by CYP 450, 3A4, 2D6, & MAO-A 40% excreted by kidney in unchanged form	Janssen Pharms Manufacture patent Axert	[38]
Frovatriptan (Frova)	oral 2.5 mg ; may repeat in 2 hours maximum 7.5 mg daily	Half –life : 26 hours Onset : 2-4 hours Bioavailability : 30 %	Metabolism by CYP 1A2 Slow onset &long duration of action	Brand Frova developed by Vernalis & the product licensed by Endo Pharmaceuticals	[39]
Eletriptan (Relpax)	Oral 20-40 mg ; may repeat one time Maximum 80 mg dose daily	Half –life : 4-6 hours Onset of action :1-2 Hours Bioavailability : 50%	Metabolism by CYP 450, 3A4 Fast onset of action	Pfizer manufacture brand Relpax	[34]

CYP-cytochrome; MAO-monoamine oxidase; SC-Subcutaneous.

B. NSAIDs [Non-steroidal anti-inflammatory drugs]

NSAIDs have been effective in abortive therapy of mild to severe migraine,[40,41] The proposed mechanism of action is achieved via anti-inflammatory effects on vasoactive peptide –induced inflammation, which occurs during the migraine attack.[42,43] The use of NSAIDs in combination with caffeine [vasoconstrictor] or other abortive agent beneficial in some patients.[44,45]

Table no 4: NSAIDs drugs.

Drug (Brand)	Formulation / Dosage form	Pharmacokinetics	Comments	Patent	References
Ibuprofen (Advil migraine, Motrin)	Advil migraine liquid gel 200-400 mg Motrin tablet	Oral onset 15-30 minutes Half –life :2-4 hours Oral onset 20-30 minutes Half-life:- 1.8-2 hours	Metabolism by CYP 2C9 Fast onset of action	Pfizer make brand Advil	[46]
Naproxen (Aleve)	Aleve tablet 220 mg dose Maximum dose 660 mg	Onset of action : 1 hours Half –life :12-17 hours Bioavailability : 95 %	Metabolism by CYP1A2 & CYP2C9 95% protein binding	Bayer healthcare Syntex pharma. (Naprosyn)	[47]
Ketorolac (Toradol)	Iv NSAIDs Maximum dose 30 mg/ml	Onset of action : 10 min Half-life : 5-6 hours Bioavailability :80-100%	Metabolism by CYP2C8 & CYP2C9 Highly protein bound 99%	Syntex Pharma.	[48]
ASA (Aspirin)	Tablet 50 mg dose	Onset of action :60 min Half –life :20 min Bioavailability :50%	Metabolism by CYP2C9 & N-Acetyltransferase	Bayer healthcare	[49]
Acetaminophen (Tylenol)	Tablet, iv Maximum dose 650 mg	Onset of action:15 sec to 30 min Half –life 2-3 hours Bioavailability:63-89 %	Metabolism by CYP2E1 Fast onset of action Iv	McNeil consumer healthcare & subsidiary of Johnson & Johnson	[50]

ASA=Aspirin; Iv= Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs

C. Monoclonal Antibody:

Calcitonin gene –related peptide [CGRP] is a 37 amino acid neuropeptide present in the peripheral and central nervous system.[51,52] A release of CGRP has been shown to induce migraine attacks. CGRP monoclonal antibodies act to weaken the migraine signalling pathway.[53]

Table no 5: Administration of Anti-CGRP Monoclonal Antibodies.

Drug name	Dosage form	Dosing Interval	FDA Approval	Company name	References
Erenumab	Subcutaneous injection Dose : 70 mg or 140 mg	Once monthly	May 17,2018	Amgen Inc.	[54]
Fremanezumab	Subcutaneous injection Dose : 225 mg or 675 mg	Once monthly or once every 3 month	September 14,2018	Teva pharmaceutical Industries Ltd	[55]
Galcanezumab	Subcutaneous injection Dose : 120 mg or 240 mg	Once monthly	September 27,2018	Eli Lilly and Company	[56]
Eptinezumab	Intravenous infusion Dose : 100 mg or 300 mg	Once every 3 months	February 21,2020	Lundbeck Inc.	[57]

D. Ergot alkaloids

The ergot alkaloids were the first specific agents indicated for the abortive management of migraine.[58,59] In recent year their use has been decline because of the emergence of the more selective 5-HT receptor agonist [Triptans]. The ergot alkaloids that are used as migraine abortive include follows table 6.

Table no 6: Ergot alkaloids for management of migraine.

Name of drug	Dosage form	Administration	FDA approval	Company name	References
Dihydroergotamine Mesylate[DHE] (Migranol)	Nasal spray	As needed ; a dose 0.725 mg into each nostril may be repeated a minimum of 1 hours after first dose	September 2,2021	Impel Neuro Pharma, Inc.	[60]
Ergotamine tartrate (Vasograin) (Ergomar)	Tablet [1 mg ergotamine + 100 mg caffeine +250 mg paracetamol+2,5 mg prochlorperazine] Sublingual tablet	Should be taken first sign of migraine headache [No more than 2 tablets should be taken for any single migraine attack]	September 16, 2005	Candila pharma Mikart,Inc.	[61]

Adapted from references,.

E. Other drugs

Barbiturate combination in migraine

Drug	Dosage form	Comments	References
Butalbital and ASA/caffeine (Fiorinal) Also available with codeine	1-2 tablet or 1-2 capsule Q 4-6 hours Do not take more than 6 tablet /capsule in 24 hours	Contraindicated in Hypersensitivity Haemorrhagic diathesis Peptic ulcer or serious gastrointestinal lesions	[62,63]
Butalbital and APAP / caffeine (Fioricet) Also available with codeine	1-2 tablets or capsule Q 4-6 hours Do not exceed 6 tablet or capsule in 24 hours	Contraindicated in Porphyria Bronchopneumonia Cardiac Arrhythmia	[64,65]

APAP = Acetaminophen, ASA= Aspirin.

2. Opiate combinations in migraine

Drug	Dosage form	References
Propoxyphene with APAP (Darvocet)	Tablet 100 mg Maximum dose 6 tablet per day	[66]
Codeine with APAP (Tylenol)	Tablet (codeine 20 mg + Acetaminophen 300 mg) Maximum 8 pills of 325 mg per day	[67]
Oxycodone with APAP (Percocet) Oxycodone with ASA (Percodan)	Tablet (oxycodone 10 mg +APAP 325 mg) One or two tablet every 6 hours for adult Tablet (10 mg 0xycodon + 325 ASA) One tablet every 6 hours	[68]
Butorphanol (Stadol)	Nasal spray 1 mg One spray in one nostril ; may repeat in 1 hour Maximum 4 spray daily	[69]

APAP =Acetaminophen; ASA= Aspirin.

3. Phenothiazine in migraine

Phenothiazine derivative [Prochlorperazine, chlorpromazine] and prokinetic agent Metoclopramide.

Drug	Dosage form	References
Prochlorperazine (Compazin)	Suppositories 25 mg	[70]
Chloropromazine (Thorazin)	Tablet 100 mg	[71]
Metoclopramide (Reglan)	Tablet 10 mg q.i.d. 30 min before each meal	[66]

4. Sympathomimetic

Midrin capsule contains 65 mg Isometheptene, 100 mg Dichloralphenazone, 325 acetaminophen.[72]

5. Anticonvulsants

Depacon 500mg injection contains valproate.[73,74]

F. Onabotulinumtoxin A: (OBT-A)

OBT-A is only treatment specifically approval for the prevention of chronic migraine in the EU. OBT-A it has the highest level of recommendation for the prophylactic treatment of chronic migraine.[75,76,77] Treatment should be repeated every 3 month.

G. New drug

Drug name	Drug class	Dosage form	Administration	FDA Approval	Company	References
Ubrogepant	Calcitonin gene related peptide (CGRP) receptor antagonist	Oral tablet	No more than 200 mg to be taken in 24hrs	Dec 23, 2019	Allergan plc	[78]
Rimegepant	Calcitonin gene related peptide (CGRP) receptor antagonist	Oral disintegrating tablet	No more than one dose 75 mg to be taken in 24hrs	Feb 27,2020	Biohaven	[73]
Atogepant	Calcitonin gene related peptide (CGRP) receptor antagonist	Oral tablet	Once daily	Sep. 28,2021	Abbvie Inc.	[73]

CONCLUSION

Preventive pharmacotherapy may also be necessary for many patients.[79] for the management of the migraine, prescriber must consider the severity of pain. patient with mild to moderate migraine attack can often be treated with NSAIDs or simple analgesics, with triptans or ergot derivatives for moderate to severe pain. Other option may have a role in refractory migraine or when contraindication for first line agent.combination therapy may be necessary for some

patients, and triptans or ergots combined with NSAIDs or other potential agents may provide additional benefits in migraine management.[80]

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