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Review Article

"Recent Advances in Drug Therapy of Migraine"

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ABSTRACT

Migraine is one of the foremost disabling diseases that preponderantly affects the feminine population. The clinical spectrum of migraine encompasses four stages- the prodrome, aura, the headache phase and also the postdrome. The management of migraine is directed at aborting and preventing the headache, the associated incapacitating symptoms (like photophobia, phonophobia, olfactive hypersensitivity, allodynia, nausea, vomiting, etc.) and also the symptoms of aura (like visual phenomena, sensory phenomena, language aura etc.). The pathophysiology of migraine includes the neuronal theory, the activation of the trigeminovascular system and cortical spreading depression. The present pharmacotherapy is directed against these mechanisms. The drug therapy of migraine includes abortive and prophylactic medications. Abortive medications presently in use embody nonspecific medication like NSAIDS and neuroleptics/ antiemetics, and specific medication like triptans, ergot alkaloids and CGRP (calcitonin gene related peptide) receptor antagonists. The newer medication under investigation include 5-HT 1F agonists, nNOS (neuronal nitric oxide synthase) synthase inhibitors, TRPV1 (transient receptor potential vanilloid) receptor modulators, drugs functioning on glutamatergic targets, propofol and benzopyran derivatives. Prophylactic medications are necessary only if the attacks are too frequent or severe. The drugs used are beta blockers, calcium channel blockers, anticonvulsants, antidepressants and onabotulinium toxin A. monoclonal antibodies against CGRP pathway, benzopyran derivatives, dual orexin receptor antagonists, nonspecific phosphodiesterase inhibitors and angiotensin receptor blockers are being investigated as potential new targets for migraine prevention. These treatments should be used suitably and judiciously to forestall complications and to enhance the standard of life in migraine patients.

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INTRODUCTION:

Migraine comes from the Greek word "hemikranios" that refers to the unilateral distribution of pain that 60-75% of individuals with migraine experience.[1] The migraine attack consists of four parts- the premonitory phase, the aura phase, the headache phase and also the postdrome. The headache phase has associated symptoms like photophobia, phonophobia, olfactory hypersensitivity, cutaneous allodynia, nausea and emesis. migraine is also classified as follows:

Table 1-Classification of Migraine

1. Migraine without aura
2. Migraine with aura
   a. Migraine with typical aura
   b. Migraine with brainstem aura
   c. Hemiplegic migraine
   d. Retinal migraine
3. Chronic migraine
4. Complications of migraine
   a. Status migrainosus
   b. Persistent aura without infarction
   c. Migrainous infarction
   d. Migraine aura-triggered seizure
5. Probable migraine
   a. Probable migraine without aura
   b. Probable migraine with aura
6. Episodic syndromes that maybe associated with migraine
   a. Recurrent gastrointestinal disturbance
   b. Benign paroxysmal vertigo
   c. Benign paroxysmal torticollis

Adapted from ICHD-3 beta version[2]

The lifetime prevalence of migraine is about thirty third in girls and thirteen in men.[1]Migraine causes substantial pain and incapacity. There's a genetic predisposition for developing migraine. Majority of migraine patients have 1-4 attacks per month. This is often known as episodic migraine with headaches on fewer than fifteen days per month. Two patients have chronic headache with headaches on at least fifteen days per month. About 2.5% of individuals with episodic migraine transform to chronic migraine every year.[1] Triggers of a migraine attack include- emotional stress, fluctuating female hormones, missed meals, weather factors, sleep disturbance, odors, certain visual stimuli, alcohol, muscle tension, physical exertion, and being overheated.

Migraine is one amongst the foremost disabling medical sicknesses. The socioeconomic burden of treating migraine is incredibly high and also the annual treatment prices accounts for about $17 billion that is why the illness must be diagnosed early and managed suitably.[3]

Symptoms:

The prodrome consists of symptoms like fatigue, excessive yawning, excessive thirst, blurred vision etc.

Aura: the most common aura includes visual phenomena (positive and negative scotomas). The other aura symptoms include sensory phenomena

(usually unilateral) like paresthesias and numbness, language aura (e.g. expressive dysphasias), unilateral motor weakness (Hemiplegic Migraine) or brainstem aura (with symptoms like diplopia, dysarthria, hypacusis, ataxia, etc.). Aura which is not followed by headache is called as a migraine equivalent or acephalgic migraine.

The headache phase consists of moderate to severe throbbing pain that is unilateral in 60-75% of patients but bilateral in the rest.[1]Nausea, vomiting and neck pain are frequent accompaniments. Vomiting can lead to dehydration and decreased absorption of orally administered drugs. There is hypersensitivity to visual, auditory, cutaneous (cutaneous allodynia) and olfactory stimuli during the attack. The headache phase lasts from 4-72 hours. If the headache is prolonged beyond 72 hours a diagnosis of status migrainosus may be made.

The migraine postdrome: lasts for 24 hours following a migraine attack and includes symptoms like fatigue, excessive thirst, hypersensitivity to visual and auditory stimuli, dizziness and neck stiffness, commonly referred to as the migraine hangover.

Migraine Genetics:

Familial Hemiplegic Migraine (FHM) is a type of migraine with aura that has an autosomal dominant pattern of inheritance. In FHM, patients have unilateral motor weakness along with typical aura symptoms. The weakness may persist for several days as opposed to the other aura symptoms which disappear in 24 hours. So far 3 genes have been identified for FHM.

Table 2 – Genes associated with familial hemiplegic migraine[1]

S.No.	Gene	Type of FHM	Location	Function
1.	CACNA1A	FHM1	Chromosome 19p13	Codes for brain specific voltage gated P/Q type calcium channel
2.	ATP1A2	FHM2	Chromosome 1q23	Codes for a major subunit of sodium potassium ATPase pump
3.	SCN1A	FHM3	Chromosome 2q24	Codes for neuronal voltage gated sodium channel

A meta-analysis of 29 genome wide association studies identified 12 loci associated with migraine susceptibility. The genes identified were involved in glutamate regulation, modulation of synaptic transmission, sensing cold and cold-pain, controlling neuronal resting membrane potential and neuronal excitability.[4]

Pathophysiology:

Neuronal factors:

The migraine attack is due to an alteration in normal brain function. Atypical brain function during migraine involves widespread areas of the brain. The substantial co-occurrence of symptoms during a migraine attack suggests "parallel alteration" in the functional activity of several different brain regions/ networks.

Cortical spreading depression:

It is considered as the electrophysiological substrate of the migraine aura. It starts at the occipital pole and spreads forward over the cerebral hemispheres at a rate of 2-4mm/min. This wave causes disruption in ionic gradients and depolarization followed by hyperpolarization. This period of brain activation followed by brain deactivation corresponds with the pattern of positive symptoms (visual scintillations) followed by negative symptoms (visual scotoma) typical of the migraine aura. Cortical spreading depression evokes a series of cortical, meningeal and brainstem events consistent with the development of headache. But cortical spreading depression does not occur prior to onset of migraine without aura.

The trigeminocervical System and Migraine Headache:

Activation of the trigeminocervical system leads to release of vasoactive neuropeptides (like CGRP, substance P, VIP, NO, PACAP) from sensory afferents that innervate the major intracranial arteries resulting in vasodilation, plasma protein extravasation, inflammation that causes the headache of the migraine attack. Recurrent / prolonged activation of the trigeminocervical system leads to peripheral and central sensitization. Sensitized neurons have lower thresholds for activation and increased spontaneous activity. Sensitization increases the pain and discomfort that is experienced during the attack and also reduces the effectiveness of migraine abortive therapies.

Role of CGRP:

Migraine-specific triggers cause primary brain dysfunction with consequent dilatation of cranial blood vessels innervated by sensory fibers of the trigeminal nerve. The dilatation mechanically activates the perivascular fibers with a pain message then conveyed to the brainstem and higher brain centers and release of vasoactive peptides, such as substance P (SP) and CGRP from trigeminal fibers. SP is a potent mediator of increased microvascular permeability, and CGRP is an extremely potent vasodilator. These peptides are responsible for neurogenic inflammation with increased blood flow, edema formation, and recruitment of inflammatory cells to the local area, and with degranulation of mast cells and release of proinflammatory and inflammatory molecules. The process can activate meningeal nociceptors with further increase in the level of activation of the sensory trigeminal fibers, perpetuating the release of vasoactive peptides, including CGRP. As migraine progresses, sensitization occurs in spinal cord and brainstem centers that are the first to receive the nociceptive impulses from the trigeminal afferents. As a consequence, migraine pain increases and hypersensitivity develops to environmental and other stimuli. [5]

The Hyperexcitable Migraine Brain:

The migraine brain has greater activation of regions that facilitate stimuli perception as compared to the non-migraine brain as seen with functional MRIs.[6] In addition, there is hypoactivity of pain inhibitory pathways of the brainstem during an attack leading to increased pain.

Treatment and Management:

The disability caused due to migraine is assessed with the help of a questionnaire called the Migraine Disability Assessment Score (MIDAS). Based on the scores the patients are classified into little or no disability, mild disability, moderate disability and severe disability.[7] Goals of treatment include restoration of function, reduction of disability and suffering and reduction in disease progression and future expression. Treatment often centers on pharmacotherapy. In addition lifestyle modification (reduction of excessive caffeine intake and alcohol intake, cessation of smoking, diet correction, avoidance of irregular sleeping habits) should also be practiced. The use of drugs known to cause headaches (reserpine, nifedipine, theophylline derivatives, vasodilators including long acting nitrates and alcohol) should be discontinued or other substitutes should be prescribed. Migraine triggers must also be identified and avoided.

Pharmacotherapy:

Pharmacotherapy has two aspects

1. Symptomatic (acute/ abortive) therapy
2. Prophylactic therapy

SYMPTOMATIC THERAPY:

The patient should be made to rest in a quiet dark room with an ice pack on the head. Stratified care is the preferred acute management strategy. Treatment should be started as early as possible since it is very difficult to abort a fully developed

attack with oral agents. This is because of poor gastrointestinal motility and absorption. Acute treatment should be restricted to 2 to 3 days per week to avoid medication overuse headache. [8]

Nonspecific Acute Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDS)/acetaminophen (paracetamol):

NSAIDS like aspirin, ibuprofen, diclofenac, indomethacin maybe used alone or in combination with other agents for treatment of migraine. NSAIDS may be used in combination with caffeine which may aid absorption, induce vasoconstriction and reduce the firing of serotonergic brainstem neurons. NSAIDS may also be used in combination with antiemetics. Ketorolac maybe administered IV in the emergency room if needed. Acetaminophen is less potent than NSAIDS but well tolerated.

Table 3 – NSAIDS for acute treatment of Migraine[8]

Drug	Formulation	Dosage
Aspirin	Tablet, oral solution	650-1000 mg
Ibuprofen	Tablet, oral suspension, capsule	400-800 mg Maximum initial dose of 1 g
Ketorolac (renal toxicity is a concern)	Tablet	10 mg
Naproxen	Tablet, oral suspension	125-550 mg
Naproxen controlled release	Tablet	750 mg Maximum initial dose of 825 mg
Meclofenamate	Capsule	50 mg,100 mg
Diclofenac potassium	Tablet, powder pack	50 mg
Etodolac	Tablet, capsule	200-500 mg
Ketoprofen	Capsule	50-75 mg
Ketoprofen extended release	Capsule	200 mg

Neuroleptics/ antiemetics

D2 receptor antagonists may be used alone or in combination with other agents for the treatment of headache and the associated nausea in migraine.

Table 4- Neuroleptics/ antiemetics in the acute treatment of migraine[8]

S.No	Medication	Dose	Uses
1.	Dopamine Antagonists a. Prochlorperazine	5-10 mg 10 mg	Maybe used alone or in combination with NSAIDS or triptans. Parenteral formulations are more effective. Treats the associated gastroparesis allowing better
	b. Metoclopramide		absorption of other oral agents. Used in combination with aspirin or paracetamol
	c. Chlorpromazine	25-100 mg	Side effects include sedation and orthostatic hypotension
2.	Antihistamine - Promethazine	25-50 mg	Treats nausea associated with migraine
3.	5-HT_3 Antagonist – Ondansetron	4 mg	Maybe used in combination with other agents where dopamine antagonists are not tolerated.

Corticosteroids:

Corticosteroids maybe helpful in aborting an acute attack and may be helpful in reducing the risk of headache recurrence. A dose of prednisolone 20mg every 6 hours initially followed by a rapidly tapering dose over the next 2-3 days will help in aborting an attack of status migrainosus. A single oral dose of dexamethasone may be helpful in preventing headache recurrence after a course of NSAIDS or triptans.

Specific Acute Treatment

Triptans

Impaired 5-HT transmission is a typical migraine trait. Triptans are 5-HT_{1B}/5-HT_{1D} receptor agonists. 5-HT_{1B} receptor mediates cranial vasoconstriction. 5-HT_{1D} receptor inhibits release of sensory neuropeptides from the perivascular trigeminal afferents and mediate presynaptic dorsal horn stimulation. The 5-HT_{1B}/5-HT_{1D} agonists act both at the central and peripheral components of the trigeminal vascular system. Triptans may also enhance descending inhibitory pain pathways and influence the function of 5-$HT1_F$ receptors. The triptans are considered first line drugs for treatment of moderate to severe migraine pain. The triptans start taking effect within 20-60 minutes after an oral dose and may be repeated after 2 hours if necessary. They are most most effective when taken early in the attack.

Sumatriptan can be administered by oral, intranasal or subcutaneous route. 6mg subcutaneous injection appears to be more efficacious. 7 triptans are available in the United States, all of which are beneficial in reducing both pain and associated symptoms (like nausea, photophobia and phonophobia) which improve the patient's ability to return to normal functioning. Side effects are usually mild to moderately severe causing local reaction and a mild tingling or flushing sensation. Heaviness or pressure like sensation in the neck and chest may occur in a few patients. Sumatriptan has been proved to produce a small reduction in coronary artery diameter and hence caution must be exercised in patients who have significant risk factors for coronary artery disease. Its not safe to administer triptans within 24 hours of ergot preparations or other members of triptan class. 5-HT_{1F} agonists are under development as alternatives to triptans. They lack the property of vasoconstriction. Naratriptan, almotriptan and frovatriptan have favourable side effect profiles. The triptans maybe combined with metoclopramide for improving their oral bioavailability.

Table 5 – Triptans in the treatment of migraine[1]

Drug	Route	Dose	Maximum daily dose
Fast acting triptans			
Almotriptan	Oral	6.25, 12.5 mg	25 mg
Eletriptan	Oral	20, 40 mg	80 mg
Rizatriptan	Oral	5, 10 mg	30 mg
Sumatriptan	Oral Subcutaneous Intranasal	25, 50, 100 mg 4, 6 mg 5, 20 mg	200 mg 12 mg 40 mg
Zolmitriptan	Oral Intranasal	2.5, 5 mg 5 mg	10 mg 10 mg
Slower onset triptans			
Frovatriptan	Oral	2.5 mg	7.5 mg
Naratriptan	Oral	1, 2.5 mg	5 mg

Ergots

They can act as vasoconstrictors or vasodilators, the action depends upon their dosage and the resting tone of target vessels. They are 5-HT agonists (less specific than triptans). Pretreatment with an anti-emetic may be necessary. Oral preparations are less effective than rectal or parenteral formulations. 2mg of ergotamine

tartrate should be taken as soon as an attack of migraine is recognized and the dose maybe repeated after an hour if necessary along with an analgesic-caffeine combination. Rectal suppository is far more effective metoclopramide can be taken for nausea. If more than 6mg ergotamine is required per week an alternative preparation should be used. Ergots are contraindicated in pregnancy and coronary artery disease, hypertension, renal and hepatic failure.
Dihydroergotamine (DHE) can also be used in migraine. It has poor oral bioavailability hence used as parenteral or intranasal formulation.

Treatment of migraine in the emergency department

When the migraine attack becomes intolerable the patient comes to the hospital.
Treatment options in the emergency department include:

- Sumatriptan 6mg subcutaneously
- Metoclopramide 10 mg with 0.5-1mg of DHE I.V
- Prochlorperazine 10 mg with or without DHE I.V
- Chlorpromazine 0.1 mg/kg body weight I.V at the rate of 1 mg/mt maybe infused. It can cause hypotension so the patient must be properly hydrated.
- Ketorolac 60 mg I.M
- Infusion of 1 gm of magnesium sulphate may be helpful in migraine with aura
- Dexamethasone, in combination with other antimigraine agents, maybe useful in the treatment of intractable migraine.
- 500 mg sodium valproate maybe infused I.V over 1 hour for the treatment of intractable migraine.
- An opioid may be administered, combined with a drug for nausea if the pain is truly severe.

NEWER DRUGS FOR SYMPTOMATIC TREATMENT

Calcitonin Gene Related Peptide (CGRP) Antagonists

Calcitonin gene related peptide is a vasodilator that is released both from central and peripheral neurons. It is implicated in the transmission of pain signals and is released during severe migraine attacks. The CGRP receptor antagonists have no effect on the cerebral or systemic hemodynamics.

Table 6 – CGRP receptor antagonists [9]

Drug Name	Status of clinical studies	Efficacy of treatment
Olcegepant (BIBN-4096BS)	Development terminated because only I.V administration was possible	Better than placebo
Telcagepant (MK-0974)	Development terminated because of increased liver enzymes.	Effective in treatment of acute migraine.
MK-3207	Development terminated because of delayed asymptomatic liver test abnormalities.	Better than placebo. Exhibits higher affinity to the CGRP receptors than Telcagepant.
Rimegepant (BMS-927711)	No further plans to continue development of the drug	Better than placebo
BI 44370 TA	Development terminated for unknown reasons	Better than placebo
Ubrogepant (MK-1602)[10]	Phase 2b trial completed	Better than placebo with adverse effects of nausea and dizziness.

Serotonin 5-HT$_{1F}$ Receptor Agonist

Activation of 5-HT$_{1F}$ receptors have no vascular effects. In preclinical studies, lasmiditan was found to inhibit plasma protein extravasation evoked by stimulation of trigeminal ganglion. Lasmiditan also inhibited activation of cells in the trigeminal nucleus caudalis evoked by trigeminal stimulation. Side effects of I.V administration include dizziness, paresthesias and sensation of heaviness in the limbs. The side effects of oral administration include dizziness, vertigo and fatigue. The drug maybe used in individuals who have cardiovascular conditions in whom triptans are contraindicated.

Table 7- 5-HT$_{1F}$ receptor agonists[9]

Drug Name	Status of clinical studies	Effects
Lasmiditan COL-144	Phase 2 proof of concept study	Better than placebo
Lasmiditan COL-144	Phase 3 study started in 2015	Better than placebo in phase 2
LY-334370[11]	Development terminated due to liver toxicity	Better than placebo

Neuronal Nitric Oxide Synthase (nNOS) Inhibitors

CGRP and nNOS are important mediators of migraine. The **NXN-188** is a combined 5-HT$_{1B/1D}$ agonist and a nNOS inhibitor. The drug has completed phase 2 study and showed moderate effect against placebo. It is well tolerated with no serious adverse effects but needs further evaluation. A **non-selective NOS inhibitor (L-NG methyl arginine hydrochloride; 546C88**) had shown good results in the treatment of migraine. But further development was stopped because of cardiovascular safety concerns and an unfavorable pharmacokinetic profile. The **GW274150, an inducible nitric oxide synthase inhibitor** was not effective in migraine treatment. [9]

Transient Receptor Potential Vanilloid (TRPV1) Receptor Modulators

TRPV 1 receptors are involved in peripheral pain perception. TRPV1 receptor activation stimulates the release of CGRP which activates the trigeminal nucleus. Two drugs were investigated in this category. **SB-705498** showed no benefit and **civamide** showed some benefit in the treatment of migraine but it wasn't satisfactory. [9]

Drugs acting through Glutamatergic Targets

Ketamine is a NMDA antagonist. It also modulates the activity of opioid receptors and monoamine transporters. In animal models, ketamine can inhibit cortical spreading depression. In human trials 25mg of intranasal ketamine was shown to reduce the duration and severity of the neurological deficit accompanying migraine aura. [9]

Tezampanel (LY293558) is an AMPA antagonist. The drug had a better response rate compared to placebo. **LY466195** is a selective competitive antagonist at the iGlur5 (kinate) subtype of ionotropic glutamate receptors. It showed a good response in the treatment of migraine. Both the drugs were less efficacious when compared to sumatriptan, and visual side effects (hazy vision) were severe. **BGG492**, an AMPA antagonist, was not effective in the treatment of migraine. **ADX10059** is a negative allosteric modulator of mGluR5 subtype of glutamate receptors. mGluR5 receptors are implicated in animal pain models. The drug was better than placebo but development was terminated owing to increased liver enzymes. [9]

Propofol

Propofol is a sodium channel blocker and also potentiates GABA$_A$ receptor activity. Phase 2 study completed. Phase 2/3 study was started in children in 2015. It had a comparable efficacy to sumatriptan but it has addictive potential.

Tonabersat

Tonabersat is a benzopyran derivative. It can inhibit cortical spreading depression and cerebrovascular responses to trigeminal nerve stimulation in animal pain models. The drug showed inconsistent results in phase 2 trials and development was terminated.[9]

5-HT$_{1D}$ Agonist

PNU-142633 is a selective 5-HT$_{1D}$ agonist. It was not found to be very efficacious but side effects like QT prolongation and first degree heart block were observed.

PROPHYLACTIC TREATMENT

A preventive treatment is necessary only when attacks occur as often as 1 to 2 days a week, when the duration or frequency of attacks seriously impairs the patient's lifestyle, when there are severe or prolonged neurological symptoms or lack of response to symptomatic treatment. The most effective prophylactic treatments reduce headache frequency by 50% in nearly 50% patients. The American migraine prevalence and prevention study foumd that only 12% of the American subjects with severe migraine were on proper preventive management which highlights the need for early and appropriate prophylactic treatment.[8]

The prophylactic drugs are titrated to their minimum effective or maximum tolerated dosage. This target dosage is maintained for 3 months if beneficial, then continued for 6-12 months to achieve clinical stabilization.

The possible mechanism of action by which prophylactic drugs act might include stabilization of reactive nervous system centers, enhancement of antinociceptive pathways, inhibition of central and peripheral sensitization, and inhibition of cortical spreading depression. Inhibition of cortical excitation and restoration of central nociceptive modulation might also be a possible mechanism.

The patient should be monitored to prevent medication overuse, co morbid conditions should be taken into account, and combination therapy can be considered in refractory patients. The drugs should be tapered once the headache is controlled. The goals of prevention are to reduce attack frequency and severity, reduce associated disability, return the patient to normal function, and improve response to treatment of future acute attacks.

Guidelines for the Preventive Treatment of Migraine

The American academy of neurology and the American headache society have provided guidelines on the drugs that are useful in the prophylaxis of migraine.[12]

The drugs have been classified into 4 categories as follows:

Level A: The following medications are established as effective and should be offered for migraine prevention:

- Antiepileptic drugs (AEDs): divalproex sodium, sodium valproate, topiramate
- β-Blockers: metoprolol, propranolol, timolol
- Triptans: frovatriptan for short-term Menstrually associated Migraine (MAMs) prevention

Level B: The following medications are probably effective and should be considered for migraine prevention:

- Antidepressants: amitriptyline, venlafaxine
- β-Blockers: atenolol, nadolol
- Triptans: naratriptan, zolmitriptan for short-term MAMs prevention

Level C: The following medications are possibly effective and may be considered for migraine prevention:

- ACE inhibitors: lisinopril
- Angiotensin receptor blockers: candesartan
- α-Agonists: clonidine, guanfacine
- AEDs: carbamazepine
- β-Blockers: nebivolol, pindolol

Level U: Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention:

- AEDs: gabapentin
- Antidepressants
    - Selective serotonin reuptake inhibitor/selective serotonin-

norepinephrine reuptake inhibitors: fluoxetine, fluvoxamine
    - Tricyclics: protriptyline
- Antithrombotics: acenocoumarol, Coumadin, picotamide
- β-Blockers: bisoprolol
- Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil
- Acetazolamide
- Cyclandelate

β Adrenergic Blockers

Timolol and propranolol are FDA approved for migraine prophylaxis. Side effects include lethargy, depression, hypotension, bradycardia, impotence, nightmares and insomnia. It is contraindicated in patients with asthma and severe depression and should be used with caution in people who are taking insulin and OHAs. Propranolol can be given at doses of 80-240mg per day. Consideration should be given to avoiding beta-blockers in patients with elevated body mass index, diabetes or a family history of diabetes, and migraine with aura since beta blockers might cause increased risk of diabetes and possible ischemic stroke and prolongation of aura in these patients.

Calcium Channel Blockers

It has been proposed that they work either by blocking serotonin release or by interfering with neurovascular inflammation or cortical spreading depression. They also potentiate opioid and acetaminophen induced analgesia and inhibit CGRP release. L-type calcium channel blocker verapamil in doses of 80-160mg three times a day reduces the incidence of migraine with aura but it is not very useful in migraine without aura. Flunarizine is also useful in migraine prophylaxis. Limiting side effects may include constipation, dizziness, hypotension, and, at higher doses, cardiac conduction blocks.

Antidepressants

Amitryptiline and other tricyclic antidepressants (nortryptiline, imipramine, desipramine) can be used at doses of 10 to 150mg. Dose has to be titrated to minimum effective or maximum tolerated dose. Amitryptiline can also stabilize sleep. It's antinociceptive effect has been attributed to its ability to inhibit serotonin and norepinephrine reuptake. Side effects include morning drowsiness, dryness of mouth, weight gain tachycardia, constipation etc. Serotonin norepinephrine reuptake inhibitors like venlafaxine maybe effective in prophylaxis of migraine. They are of benefit in treating the associated generalized anxiety disorder or panic disorder.

Anticonvulsants

Valproate and topiramate are FDA approved for the prophylaxis of Migraine. Valproate/divalproex sodium is used at doses equal to or lower than that used for epilepsy. It is contraindicated in pregnant women because of the risk of neural tube defects. Side effects include nausea, weight gain, tremor and alopecia. Other effects include hepatitis, pancreatitis, agranulocytosis, encephalopathy and elevation of liver enzymes. It's use as a prophylactic agent is important in special cases e.g migraine with coexisting bipolar disorder.

Topiramate is used in doses between 100 and 200mg. It may be started at 15 to 25mg and then titrated upward. Patients should be advised to expect side effects like paraesthesias and altered taste sensation. Cognitive side effects (like delayed word retrieval) may also blunted by this slow dose escalation. It may cause oral cleft in the foetus id given to pregnant females.

Other antiepileptic drugs that may be used in migraine prophylaxis include carbamazepine, levetiracetam, zomisamide, gabapentin and pregabalin. Gabapentin is the most commonly used among these at a dose of around 900mg. It is well tolerated with somnolence as the most common side effect.

Neurotoxins

Injection of onabotulinium toxin A may help in the treatment of chronic migraine. The clinical effect may be delayed or transient after the first set of injections. Repeated injection sets every 3 months is required for maintenance of benefit.

NEWER DRUGS FOR MIGRAINE PROPHYLAXIS

Monoclonal antibodies that target the CGRP pathway

Table 8- Monoclonal antibodies against CGRP[5]

Drug	Targeted against	Status of clinical studies	Effects
LY2951742	Humanized monoclonal antibody to CGRP Administered S.C	Phase 2 trial completed. Phase 3 trial is ongoing.	Better than placebo. No serious adverse effects
ALD403	Humanized monoclonal antibody to CGRP Administered I.V	Phase 2 study completed. Phase 3 trial started in june 2017 (PROMISE 1&2) trials	Better than placebo
AMG334	Human monoclonal antibody to CGRP receptor	Phase 2 study completed. 2 phase 3 trials are underway (ARISE & STRIVE)	Better than placebo
TEV-48125	Humanized monoclonal antibody to CGRP. Tested in phase 1 studies and non-human primates	Phase 2 study completed. Phase 3 trial will be started in october 2017	Found safe and efficacious. No serious adverse effects

Blockade of the CGRP pathway is an effective preventive strategy in migraine but none of the drugs have been tested long enough to exclude adverse events on long term use. Generation of autoantibodies to these antibodies is a possible serious complication. The results of the phase 2 &3 trials may shed some light on these concerns.

Tonabersat

Study results were inconsistent with this benzopyran derivative and development was terminated.

Dual Orexin Receptor Antagonists

The orexinergic system comprises neuropeptides orexin A&B produced in the hypothalamus. They act via G-protein coupled OX_1 and OX_2 receptors and modulate basal and dural evoked nociceptive activation in the trigeminocervical complex. The premonitory phase of migraine maybe regulated by the hypothalamus and its orexinergic neurons.

Filorexant is a dual OX_1 and OX_2 receptor antagonist that was developed for insomnia. It was investigated for the prevention of migraine but the trial was terminated due to lack of efficacy.[9]

Nonselective phosphodiesterase inhibitor

Ibudilast inhibits production of pro inflammatory cytokines and inhibits glial cell activation. Glial cells on activation become immunoresponsive and modulate pain by releasing neuroexcitatory signals that can increase neuronal excitability, activate neighboring glia and produce nociceptive mediators. Ibudilast did not show a better response when compared with placebo.[9]

Angiotensin II receptor antagonist

Candesartan was investigated in a phase 2 trial and its efficacy was found to be comparable to placebo.

Anticonvulsant Drugs

Carisbamate was investigated and found to be ineffective. Hence development was terminated.

Other treatment modalities:

The other treatment modalities include neuromodulatory approaches like

- Occipital nerve stimulation
- Sphenopalatine ganglion stimulation
- Single pulse transcranial magnetic stimulation
- Transcutaneous vagal nerve stimulation

- Transcutaneous supraorbital nerve stimulation

CONCLUSION:

Pharmacotherapy of Migraine is a challenging task. Migraine is a subjective phenomenon. Although various scales are available to measure the disability the outcomes are largely patient reported. Therefore the approach to any patient with migraine begins with reassurance and health education. Patients should also be thought to identify their triggers and avoid them. These methods help in minimizing the attack frequency and thus the need for prophylactic agents. International headache bodies have not come with a clear cut algorithmic approach to a patient with migraine. Therefore the drug therapy of migraine is completely oriented to the response of patient to a particular drug. The clinician has to decide on choosing a drug based on the patients response to previous attacks or do a trial of drug after he considers the contraindications to be avoided in a particular patient. General principles in pharmacotherapy is using the abortive therapy as early as possible during an attack of migraine and using drugs to alleviate the clinical symptoms associated with migraine thereby preventing the sensitization of the nervous system to pain. Prophylactic therapy revolves around the concept of preventing or reducing the frequency of migraine attacks in patients with a high frequency of migraine episodes. Patients with frequent attacks despite prophylaxis should be considered on timing of abortive drug therapy, improper management of triggers, inadequate drug titration, drug interactions altering the drug kinetics and patient compliance. If the above mechanisms are not operational in the patient change of the prophylactic drugs or neuromodulatory therapies should be planned.

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