Migraine: What is New?

ABSTRACT

Migraine is a common disease in family practice as well as specialty practice. Progress in understanding the pathophysiology has resulted in development of new medicines to treat migraines. It is important to familiarize oneself with the therapeutic advances for patient benefit. This manuscript will point out the newer developments in the field of migraine therapy.

Key words: CGRP, Migraine, New therapies, Prophylaxis, Treatment of acute attacks

INTRODUCTION

In recent times, migraine can be construed as an episodic neurological disorder, the cardinal symptom of which is headache with several other associated features. Among the primary headaches, migraine carries the huge disease burden and impact. It has been ranked globally as the seventh most disabling disease among all diseases. The lifetime prevalence of migraine is 14% and near 2% of world population is suffering from chronic migraine.[1] Even now, around 50–70% of migraine patients remain under treated or unsatisfied with the treatment notwithstanding the various drugs prevailing in clinical use. Hence, the idea of this section is to acquaint the clinicians as to when and how to treat this common ailment with the uncommon and innovative therapies. This manuscript will focus on recent trends and developments.

PATHOPHYSIOLOGY: WHAT IS NEW?

Our current better understanding of the pathophysiology has made a host of newer therapies available. As we know, the diverse symptomatology highlights the complexity of this disorder. Each of the phases/symptoms of the migraine attack has its neural correlate as shown in Table 1.

The essentials of the underlying mechanisms are mentioned in Table 2.

Table 1: The clinical event and pathophysiology

The clinical migraine event	Pathophysiology
1. Premonitory phase: Non-painful symptomatology occurring few hours (or days) before onset of the attack, for example, fatigue, cognitive symptoms such as difficulty concentrating, excessive thirst, food cravings, and increased frequency of urination	Subcortical structures mainly hypothalamus and their altered connectivity
2. Migraine aura, that is, reversible neurological dysfunction developing gradually (5–20 min) m/c visual f/b sensory, language, motor, brainstem aura	Cortical spreading depression
3. Headache phase: Unilateral (60–75%), moderate-severe, throbbing, associated with hypersensitivity to various stimuli	Trigeminovascular system mediating nociception Hyperexcitable brain networks
4. Postdromal phase: Neuropsychiatric/GI/systemic symptoms (duration 18–25 h on average)	Diffuse cortical (mainly frontal) and subcortical (brainstem nuclei) involvement persistent reductions in cerebral blood flow following CSD

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Table 2: Mechanisms involved in the migraine event

Neuronal theory Migraine is primarily a dysfunction of brain/brain networks with secondary vascular effects[2]		
Cortical spreading depression[3] An electrophysiological substrate for migraine aura. It is described as a slowly propagating wave of depolarization followed by suppression of activity.	CSD is linked with: Massive release of NTs, for example, glutamate, ATP, and CGRP Activation of central and peripheral trigeminal nociceptive pathways mainly through CGRP	Vasoconstriction and transient cerebral hypoperfusion (rarely if severe, can lead to migrainous infarction) Activation of central and peripheral trigeminal nociceptive pathways mainly through CGRP
Trigeminocervical complex	The main interface between peripheral and central nociceptive pathways (trigeminal afferent transmit the pain impulses through TCC to thalamus and cortex)	
Hyperexcitable migraine brain	Explains exuberant responses to different sensory stimuli, for example, photophobia, phonophobia, olfactory hypersensitivity, cutaneous allodynia, etc.	

MANAGEMENT: STANDARD THERAPIES

Episodic Migraine

AHS (American Headache Society) evidence (2015–2016)	Medications
Level A[a]	NSAIDs
	Triptans
	Ergot – DHE Intranasal 2 mg
	Combinations Sumatriptan/Naproxen 85/500 mg ASA/acetaminophen/Caffeine 500/500/130 mg
Level B[b]	DHE s/c iv im 1 mg
	Opioids – tramadol

NSAIDs: Nonsteroidal anti-inflammatory drugs, DHE: Dihydroergotamine, ASA: Acetylsalicylic acid, s/c: Subcutaneous, im: Intramuscular. a. Level A=Medications are established as effective for acute migraine treatment based on available evidence, b. Level B=Medications are probably effective based on available evidence, c. Level C=Medications possibly effective

Tips for successfully treating an acute migraine attack

1. Ensure correct diagnosis of headache disorder
2. Use evidence-based recommendations as a guide to select an individualized treatment
3. Stratified approach for mild/moderate to severe headache
4. Optimize treatment, for example, parenteral or intranasal preparations if nausea/vomiting/gastroparesis
5. Assess response to the treatment, for example, MTOQ-4 (migraine treatment optimization questionnaire)
6. Troubleshooting the suboptimal response: First ensure that the treatment is early

No response: Change the route/drug	Partial response: Increase dose/ ensure a 2nd dose	Recurrence: 2nd dose/add longer acting drug	Overuse: Establish use limits, prophylactic drugs

Chronic Migraine

Consider preventive treatment when one or more of the following are present: [4]

1. Three or more moderate or severe headache days per month causing functional impairment and that are not consistently responsive to acute treatments
2. At least 6–8 headache days per month even if acute medications are effective
3. Contraindications to acute migraine treatment particularly bothersome symptoms even if infrequent attacks (e.g., migraine with brainstem aura, hemiplegic migraine)
4. Migraine has a significant impact on patient's life despite lifestyle modifications, trigger avoidance, and use of acute treatment
5. Patient is at risk of developing medication-overuse headache

Agents used for prophylaxis

AAN (American Academy of Neurology) evidence	Drugs	Side effects
Level A	Propranolol 80–240 mg Metoprolol 100–200 mg	Orthostatic/exercise intolerance, dizziness C/I: Asthma, heart failure, hypotension, bradycardia
	Topiramate 50–200 mg	Weight loss, neurocognitive symptoms Caution: Renal disease, nephrolithiasis
	Divalproex sodium 500–2000 mg	Weight gain, alopecia, tremor, hepatitis, pancreatitis Teratogenic
Level B	Amitriptyline 10–200 mg	Weight gain, dry mouth, constipation Caution: Suicidal thinking, cardiac arrhythmias
	Venlafaxine 75–225 mg	Caution: Renal and liver impairment
Level C	Candesartan 16–32 mg Lisinopril 10–40 mg	Caution: Renal impairment, hyperkalemia
	Magnesium citrate 400–600 mg Riboflavin 400 mg CoQ10 300 mg	

INTRODUCING NEWER MEDICINES

Calcitonin gene-related peptide (CGRP) has been identified as the new target for therapy of migraine. This peptide is released from the trigeminal afferent terminals and promotes neurogenic inflammation, which is important in the pathophysiology of migraine. Hence, medicines modulating CGRP have been developed and are tabulated below [Table 3]. These are mainly used for the preventive treatment of episodes of migraine and well as treatment of acute attacks. Botulinum toxin has also been used with varying success [Table 3]. External stimulators such as cephaly, peripheral nerve blocks, and behavioral therapy have also been developed and refined to help the migraine treatment [Table 4]. These developments are expected to improve the outcomes and reduce disabilities related to migraine.

Table 3: Newer pharmacological therapy of migraine

Class of molecules	Dose and administration	Side effect profile
CGRP monoclonal antibodies: FDA approved (2018) for preventive treatment of episodic migraine[5]		
Erenumab target: CGRP receptor	S/C prefilled injections – 70 or 140 mg every 28 days	Respiratory tract infections, back pain Not to be used in IHD, stroke, PVD
Fremanezumab target: CGRP ligand	S/C prefilled syringe – 225 mg every 28 days or 675 mg every 3 month	M/c injection site reaction
Galcanezumab target: CGRP ligand	S/C prefilled autoinjector/syringe – 240 mg loading f/b 120 mg every 28 days	
Eptinizumab target: CGRP ligand	IV infusion	Ongoing phase 3 trial (not yet approved)
CGRP receptor antagonists: FDA approved for acute treatment of migraine (2019)[6]		
Ubrogepant	50 or 100 mg oral tablets	CNS depression; sedation, dizziness, fatigue, paresthesias
Rimegepant	Oral disintegrating tablet 75 mg	S/E: Hypersensitivity
Ditans (5HT1F agonist): FDA approved for acute treatment of migraine (2019)		
Lasmiditan	50–100 mg oral tablet	Dizziness, drowsiness paresthesias No CVS adverse effects of triptans
Botox: FDA approved for preventive treatment of chronic migraine (2010)		
Onabotulinum toxin A	155 units every 12 weeks	Neck pain, ptosis, muscle weakness

Table 4: Non-pharmacological therapies

Neuromodulation
External trigeminal nerve stimulation device (Cephaly): FDA approved for prevention of episodic migraine (2014) Mechanism – transcutaneously stimulates the upper divisions of trigeminal nerve, modulates the activity in brain regions such as ACC – which provide descending pain regulation to the trigeminovascular nociceptors
Invasive single-pulse transcranial magnetic stimulator device (SpringTMS): FDA approved for acute and preventive treatment (2017) Mechanism – inhibits cortical spreading depression, also has thalamocortical modulatory effect
Peripheral nerve blocks: Greater occipital, supratrochlear, supraorbital – for acute migraine Relative lack of evidence, but safe and well tolerated Provides long-lasting benefits
Behavioral therapy
Relaxation training, thermal/electromyographic biofeedback Cognitive behavioral therapy

Table 5: Treatment options: Conventional and newer agents

	First line	But often I face situations where my patients –	I give them options of –
Acute treatment	NSAIDs Triptans	• Have failed multiple treatments • Have cardiovascular risk factors (which are now equally prevalent in younger age) • Are already overusing NSAIDs (medication overuse headache)	Gepants Ditans Neuromodulation devices, for example, Cephaly
Chronic migraine	Beta-blockers Antidepressants (TCA/SNRI) Antiepileptics ACE/ARB	• Non-compliant for regular medications • Inadequate or slow pain relief • Have issues with tolerability and side effect profile – liver or renal diseases • Multiple drug interactions • Willing to try innovative therapies	CGRP monoclonal Abs Botox injections Neuromodulation devices

NSAIDs: Nonsteroidal anti-inflammatory drugs, TCA/SNRI: Tricyclic antidepressants/Serotonin–norepinephrine reuptake inhibitors, CGRP: Calcitonin gene-related peptide

CONCLUSION: HOW HAS MY PRACTICE CHANGED?

With the changes that have come about in the recent years, more options have been available to us for treating migraines. While the foundations remain same, newer options can be carefully considered in situations where response is inadequate or there are limitations to the use of conventional agents. Table 5 documents the current options.

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