NEUROSCIENCE PEARLS

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Migraines

Welcome to **Neuroscience Pearls**: A publication from the UW Medicine Neurosciences Institute. In this issue we bring you key points related to migraines including diagnosis, work-up and treatment as well as current understanding on mechanisms thought to cause migraines and investigational and emerging treatments for this disease. Our goal is to provide useful information in a readable format that is easy to digest and pertinent to your practice.

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WHAT IS A MIGRAINE?: A migraine is a severe one-sided headache with nausea, light and sound sensitivity. Migraines are number 19 among all diseases causing worldwide disability as defined by the World Health Organization. It is estimated that about 16% of women and 5% of men suffer from migraines. Any recurrent headache that is disabling to the point where the sufferer is unable to function might be a migraine. Migraines have high personal and socioeconomic costs.

DIAGNOSIS: We diagnose migraines using International Headache Society (IHS) criteria[1]. Migraines are divided into two major sub-types. Migraines without an aura are the most common, characterized by a headache with severe unilateral pain, photophobia, phonophobia and functional impairment. Migraines with an aura are primarily characterized by the aura: focal neurological symp- toms such as visual loss that precede or sometimes accompany the headache. The first step in assessment is always to diagnose the patient with a specific type of headache. This requires careful assessment of history, as many patients who diagnose themselves with a migraine actually have a sinus headache or other condition. The success of headache treatment depends on making the cor- rect diagnosis.

WORK-UP: In most patients, the diagnosis is made using their history and IHS criteria[1]. If they have a normal neurological examina- tion with no "red flags", then no further work-up is required. Patients with "red flags" such as abnormalities during the neurological examination, fever, unintentional weight loss, history of cancer, transplant or immunodeficiency, need further work-up with neuro- imaging, such as Magnetic Resonance Imaging (MRI) of the brain. In rare cases, patients may also require lumbar puncture or other tests to rule our secondary causes of headaches.

MECHANISMS THOUGHT TO CAUSE MIGRAINES: The initial conception of a migraine as a purely vascular pain disorder is giv- ing way to a new understanding of migraines as a genetic brain disorder and as a neurovascular disorder that occurs in genetically susceptible people. "Once considered exclusively a disorder of blood vessels, compelling evidence has led to the realization that a migraine represents a highly choreographed interaction between major inputs from both the peripheral and central nervous systems, with the trigeminovascular system and the cerebral cortex among the main players."[2] Some studies suggest that the hypothalamus and the thalamus are also involved. Abnormalities of long-term cortical plasticity, which have been observed between migraine epi- sodes, could be related to altered thalamic control. [3]

TREATMENT: The treatment strategy for migraines has shifted dramatically, from using non-specific pain medications such as aspirin and acetaminophen to migraine-specific therapies such as triptans and BOTOX. There is a new emphasis on prevention of migraine attacks. Migraine treatment is divided into acute and preventive treatments. Acute treatments, also called abortive treat- ments, are used to stop a migraine attack that has already begun. Preventive medications are taken daily to reduce the severity and frequency of migraines before they start. Patients should be considered for preventive therapy based on the frequency and severity of migraine attacks, the degree of disability they cause, and other medical conditions. Preventive treatment should be considered for patients who are very disabled by their migraines, those who are missing work, using the emergency room for headache treatment, having 5 or more migraine days a month or overusing acute medications. Patients with other significant medical disorders such as heart disease or stroke that preclude acute treatments should also be considered for preventive therapy.

INVESTIGATIONAL AND EMERGING TREATMENT OF MIGRAINES:[4] Patients with chronic forms of migraines are especially dif- ficult to treat. Despite recent developments, there is a huge unmet need for better migraine-specific

treatments. While many new agents with promise for migraine treatment are still investigational, a number of new treatments have become available which use approved medications with innovative delivery mechanisms. These new routes of administration are designed to improve delivery, speed onset of relief, minimize adverse reactions and improve tolerability. The most recent advances that have been or will be brought to the US market have not been novel drugs, but rather innovative delivery mechanisms with the goal of enhancing delivery, shortening time to reach maximum plasma concentration, and improv- ing tolerability and efficacy of already existing medications. Four novel delivery mechanisms have been granted US FDA approval: Cambia, Sumavel Dose Pro, Alsuma, and Zecuity. Emerging potential anti-migraine strategies include: Calcitonin gene-related pep- tide (CGRP) receptor antagonists, 5-hydroxytrypamine (F-HT)(1F) receptor agonists, nitric oxide antagonists. Tonabersat, a cortical spreading depression inhibitor, has shown efficacy in the prophylaxis of migraines with aura.[4] The future targets include nitric oxide synthase, the 5-HT(1D) receptor, the prostanoid receptors EP(2) and EP(4) and the pituitary adenylate cyclase receptor PAC1.[5] The table summarizes information about recently developed migraine treatments, both approved and investigational.

Especially for refractory patients, when adequate trials of specific medications failed in improving their headache or quality of life, further therapies are needed. More invasive modalities (such as neurostimulation) and rTMS should be considered in their migraine therapy. Limited studies of repetitive transcranial magnetic stimulation (rTMS) as an emerging treatment for migraines show that rTMS appears to be effective and safe in migraine prophylaxis.[6]

• Current and Prospective Migraine Treatments •

Treatment	Generic name	Mechanism	Dose	Advantage	Adverse Effect(AEs)/ Problems	FDA approval status and date
CAMBIA	Diclofenac potassium powder	NSAID	50 mg dissolve in water	Faster than tablet Tmax 15 min	Anise taste	FDA JUNE 2009
SUMAVEL	Sumatriptan injection	Triptan 5-HT1B 5-HT1D	6 mg injection	Needle-free injection Tmax of 12 min	Single device	FDA JULY 2009
ZECUITY	Sumatriptan transdermal patch	Triptan 5-HT1B 5-HT1D	6.5 mg/4-hour	Acts despite GI dysfunction, well tolerated	Single use device, a triptan with few AEs	FDA JAN 2013
ALSUMA	Sumatriptan injection device	Triptan 5-HT1B 5-HT1D	6.5 mg trans-dermal patch	Easy and quick use, rapid onset	Single use, injection site discomfort	FDA JAN 2010
LEVADEX	Dihydroergotamie mesylate; ergot alkaloid	5-HT1Dα 5-HT1DB	One-time inhaler	Rapid onset, works for a long time	Contraindicated in Pregnancy	FDA rejected 2013
Optinose	Sumatriptan intranasal	Triptan 5-HT1B 5-HT1D	20 mg single use inhaler	Faster than oral tablets; bypasses GI	Single use	Studies ongoing
cGRP-R antagonist ("gepants")	BI44370A BMS-927711		2.5 mg IV over 10 min	Novel target, No vasoconstriction	Several "gepants" have caused liver toxicity	Studies ongoing
Antibodies to CGRP and CGRP-R			One to two times a month injection	Novel target, No vasoconstriction	No expectation of significant AEs	Studies ongoing
Lasmitidan		5 HT1F antagonist		Novel target, No vasoconstriction	High rate of AEs	Studies ongoing
Dolorac	Ciyamide	TRPV1 modulator		Novel target	Burning in the nose, No systemic AEs	Studies ongoing
Orexin Antagonists	MK-6096	Orexin antagonist		Novel target	Sleepiness	Studies ongoing
Ibudilast		Glial cell modulator, phosphodies terase inhibitor		Rapidly crosses BBB; suppresses glia		Studies ongoing
Neuro-stimulation	**Name of Device**	**Mechanism**	**Usage**	**Advantages**	**Adverse Effects/ Problems**	
Occipital Stimulation		Neuromodulation of trigeminocervical system	Implanted, continuous	For refractory Chronic migraine	Invasive; Leads can be dislodged	Approved in Europe; Approved in US for occipital neuralgia
Transcranial Magnetic Stimulation	Cerena device	Stimulation of occipital cortex	Once a day PRN	Non-invasive	Dizziness	FDA December 2013

ESSENTIAL CITATIONS

1. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition. (beta version). *Cephalalgia: An International Journal of Headache. Jul 2013;33(9):629-808.*

2. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annual Review of Physiology. 2013;75:365-391.*

3. Pierelli F, Iacovelli E, Bracaglia M, Serrao M, Coppola G. Abnormal sensorimotor plasticity in migraine without aura patients. *Pain. 2013.*

4. Vollbracht S, Rapoport AM. The Pipeline in Headache Therapy.*CNS Drugs. 2013:1-13.*

5. Olesen J, Ashina M. Emerging migraine treatments and drug targets. *Trends in Pharmacological Sciences. 2011;32(6):352-359.*

6. Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial mag- netic stimulation in migraine prophylaxis: a randomized, placebo-con- trolled study. *J Neurol. 2013:1-9.*

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