M I G R A I N E
Updates in Diagnosis & Treatment

Theresa Mallick-Searle, MS, RN-BC, APN-BC

Stanford Health Care

Division Pain Medicine

Tmallick@stanfordhealthcare.org

Disclosures:

Speakers bureau Allergan Pharmaceuticals

Speakers bureau Depomed Pharmaceuticals

Objectives

- Identify current diagnostic criteria for diagnosis of migraine headache.
- Based on current evidence, choose the most appropriate pharmacological treatments while evaluating side effects and efficacy.
- Evaluate non-pharmacological options available for treatment.

Migraine Defined

International Classification of Headache Disorders 3rd edition (beta version) (ICHD-3β)

Primary Headache Disorders
Migraine
Tension-type headache
Trigeminal autonomic (cephalalgias)
Other primary headache disorders

Cranial Neuralgias, Central & Primary Facial Pain, Other Headaches

Secondary Headache Disorders
Medication overuse headache
Post-traumatic headaches
Metabolic headaches (associated with hormonal/metabolic disorders)
Vascular/Infection/withdrawal/psychosomatic

Characteristics of common headache syndromes

Symptom	Migraine headache	Tension headache	Cluster headache
Location	Unilateral in 60 to 70 percent; bifrontal or global in 30 percent	Bilateral	Always unilateral, usually begins around the eye or temple
Characteristics	Gradual in onset, crescendo pattern; pulsating; moderate or severe intensity; aggravated by routine physical activity	Pressure or tightness which waxes and wanes	Pain begins quickly, reaches a crescendo within minutes; pain is deep, continuous, excruciating, and explosive in quality
Patient appearance	Patient prefers to rest in a dark, quiet room	Patient may remain active or may need to rest	Patient remains active
Duration	4 to 72 hours	Variable	30 minutes to 3 hours
Associated symptoms	Nausea, vomiting, photophobia, phonophobia; may have aura (usually visual, but can involve other senses or cause speech or motor deficits)	None	Ipsilateral lacrimation and redness of the eye; stuffy nose; rhinorrhea; pallor; sweating; Horner's syndrome; focal neurologic symptoms rare; sensitivity to alcohol

Headaches

Sinus:
pain is usually behind the forehead and/or cheekbones

Cluster:
pain is in and around one eye

Tension:
pain is like a band squeezing the head

Migraine:
pain, nausea and visual changes are typical of classic form

ICHD-III-β

I. Primary Headaches

Migraine

ICHD-IIIβ Cephalagia 2013:33:629-808

Chronic Migraine Defined

Headache frequency ≥15 days/month, for ≥3 months.

Lifetime history of ≥5 attacks migraine (w/without aura).

On ≥8 days per month for 3 months (fulfills criteria for migraine, w/without aura):

- Typical migraine pain characteristics & nausea/sensitivity (light/sound/movement).
- Headache considered migraine by patient and relieved by triptans/ ergots.

Practical Clinical Criteria

Headache ≥15 days/month.

On ≥8 days per month are migraine days.

Headaches last ≥ 4hr per day.

With or without medication overuse.

Pathophysiology

Migraine is an inherited, central nervous system disorder.

Neurogenic inflammation eventually leads to the pain associated with a migraine.

<u>Complex neuro-vascular contributing factors</u>:

- Cortical spreading depression.
- Reduction in brain electrical activity and decrease in blood flow.
- Release of K+ and H+ activates sensory fibers.
- Activation of trigeminal and brain stem neurons.
- Precipitation of vasodilation.

Pathophysiology

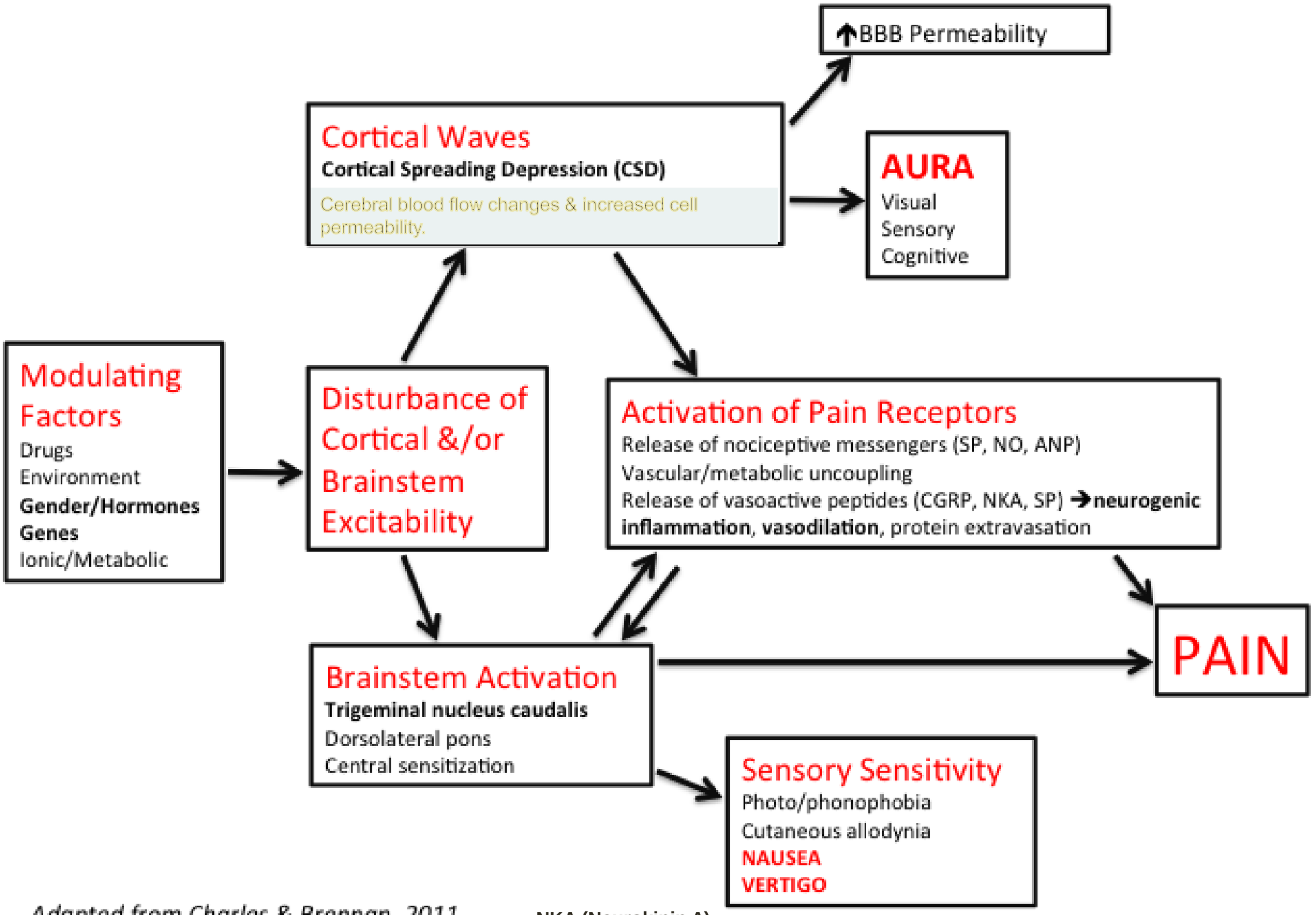
Migraineurs have hyper excitable brains.

<u>Migraine is progressive during an attack</u>

- Central sensitization.
- It has been hypothesized that migraineurs have an altered peripheral glutamate homeostasis & persistent neuronal hyper-excitability that becomes heightened during migraine attacks.

(Ramadan, 2003)

Hypothesized Sequence of Events in Migraine



Adapted from Charles & Brennan, 2011

NKA (Neurokinin A),
NO (nitric oxide), SP (Substance P), CGRP (Calcitonin Gene Related Peptide).

http://youtu.be/yZr9Joe85wg

Prevalence

It is estimated that 12-15% (>300 million) of the global population.

The American Migraine Study II (AMS II) estimated that 28 million Americans suffer from migraine—approximately 18% of women and 7% of men (Lipton et al, 2001a).

Another study found a 1-year prevalence of 17% of women and 6% of men (Lipton et al, 2002).

Cost of Migraine

Migraine alone has been reported to cost the US economy billions of dollars, with **$13 billion a year** as a result of missed workdays and impaired work function.

The direct medical costs associated with migraine have been estimated at $9.5 billion.

Migraine sufferers use 2.5 times more prescription drugs than non migraine sufferers (Clouse & Osterhaus, 1994), at a cost of $2.7 billion annually in the US.

The reported cost of ED visits for migraine-related treatment in the US ranges from $>6 million - $2 billion annually.

Treatment

MEDICATIONS

- Abortive
- Preventative
- Infusions
- Steroids
- Oxygen therapy

INTERVENTIONS

- Nerve blocks
- Trigger point injections
- Implantable devices

COMPLEMENTARY

Cognitive/behavioral strategies, Manual therapies, Nutraceuticals

Predictors of Poor Treatment Outcomes

History of emotional, physical, sexual abuse.

Co-morbid Chronic disease history/chronic pain.

Multiple headache day a month.

High headache-related disability.

Poor treatment optimization.

Opioid/barbiturate use.

Persistent, frequent nausea w/headache.

Headache (2013) Mar;53(3):427-36

Medications

Preventative

Beta-blockers (Level A/B evidence)

Anticonvulsants (Level A evidence)

Calcium channel blockers
(Level U evidence)

Tricyclic antidepressants
(Level B evidence)

Onabotulinumtoxin A (Botox)™

Abortive

Non-specific effects

- NSAIDS – Level A evidence
- Anti-emetics – Level B evidence

Specific effects

- Triptans – Level A evidence
- Dihydroergotamine/ergotamines – Level A
- Opioid (butorphanol nasal spray) – Level A

Abortive Medications

Triptans

Almotriptan , Eletriptan, Frovatriptan*, Naratriptan, Rizatriptan, Sumatriptan (oral, injectable, intranasal, transdermal), Zolmitriptan (nasal spray).

Triptan/NSAID

Sumatriptan/naproxen: 85 mg/500mg at onset and repeat in 2 hrs prn.

Anti-inflammatory Drugs

Ibuprofen 600-800 mg q 4 hr prn, Ketorolac oral 10 mg, repeat once in 2 hrs prn, Ketorolac IV/IM 30 mg, repeat once in 1 to 2 hrs prn, Ketorolac, nasal 1 spray q6-8hr (maximum 4 sprays – 63mg/d), Naproxen sodium 550 mg, repeat once in 2 hrs prn. ■Corticosteroids: dexamethasone IV

Abortive Medications

Combination Drug

Acetaminophen/aspirin/caffeine 500/500/130 mg: Two capsules at onset, then one or two in 1 hr.

Butalbital/acetaminophen(aspirin)/caffeine (Fioicet/Fiorinal)

Ergot Alkaloids (dihydroergotamine, D.H.E.-45)

DHE mesylate, nasal 1 puff in each nostril, repeat in 15 min. This is the dose for 1 day.

DHE mesylate, IV, IM, and SC 0.5-1 mg, repeat in 1 hr. (Maximum dose is 3 mg in 24 hr).

Ergotamine tartrate/caffeine, oral 2 tabs at onset, repeat once every 0.5 hr up to a maximum of 5 tabs, Ergotamine tartrate/caffeine, suppository 1/2 to 1 at onset, repeat once in 1 hr, Ergotamine tartrate, sublingual 1 at onset, repeat once in 0.5 hr prn

Triptan	Formulation	Doses	Max daily	Notes
Sumatriptan (Imitrex)	Tablets Nasal spray SC injections Suppositories	25, 50, 100 mg 5, 20 mg 4, 6 mg 25 mg	200 mg 40 mg 12 mg 50 mg	Maximum recommended monthly dose: 18 (50mg) tabs/equivalent.
Zolmitriptan (Zomig)	Tablets Oral dissolving (ZMT) Nasal spray	2.5, 5 mg 2.5, 5 mg 2.5, 5 mg	10 mg 10 mg	
Rizatriptan (Maxalt)	Tablets Orally dissolving (MLT)	5, 10 mg 5, 10 mg	30 mg 30 mg	Propranolol increases serum concentration of rizatriptan.
Naritriptan (Amerge)	Tablet	1, 2.5 mg	5 mg	Only triptan NOT contraindicated with MAOI, slower onset.
Almotriptan (Axert)	Tablet	12.5 mg	25 mg	
Frovatriptan (Frova)	Tablet	12.5 mg	25 mg	Longest half life: 25 hours, slow onset.
Eletriptan (Relpax)	Tablet	20, 40 mg	80 mg	

Preventatives

Beta Blockers

Atenolol 50-100 mg , Metoprolol succcinate/tartrate 50-150 mg, Nadolol 20-160 mg , Propranolol 80-240 mg, Timolol maleate 10-20 mg

Antiepileptic Drugs

Divalproex Sodium 250-1500 mg, Topiramate 25-150 mg, Valproic Acid 250-500 mg, Carbamazepine 200-400 mg bid

Calcium Channel Blockers

Verapamil 180-480 mg

ACE Inhibitor

Lisinopril 10-80 mg

Preventatives

Antidepressants

Amitriptyline 25-150 mg, Venlafaxine 37.5-150 mg

Nonsteroidal Anti-inflammatory Drugs

Naproxen sodium 500-1000 mg, Ketoprofen 100-200 mg.

Petasites

Butterbur

Other – Level C evidence (possibly effective)

Candesartan, Clonidine, Guanfacine

Migraine diagnosis

Patient Education
Assessment of Severity

Mild to Moderate

Simple Analgesics:
aspirin, acetaminphen
± antiemetic

Combination analgesics & caffeine

Inadequate response

Manage as severe migraine

Associated w/ nausea, vomiting, diarrhea

Add an antiemetic

Inadequate response

Consider preventive therapy

Severe

Triptans

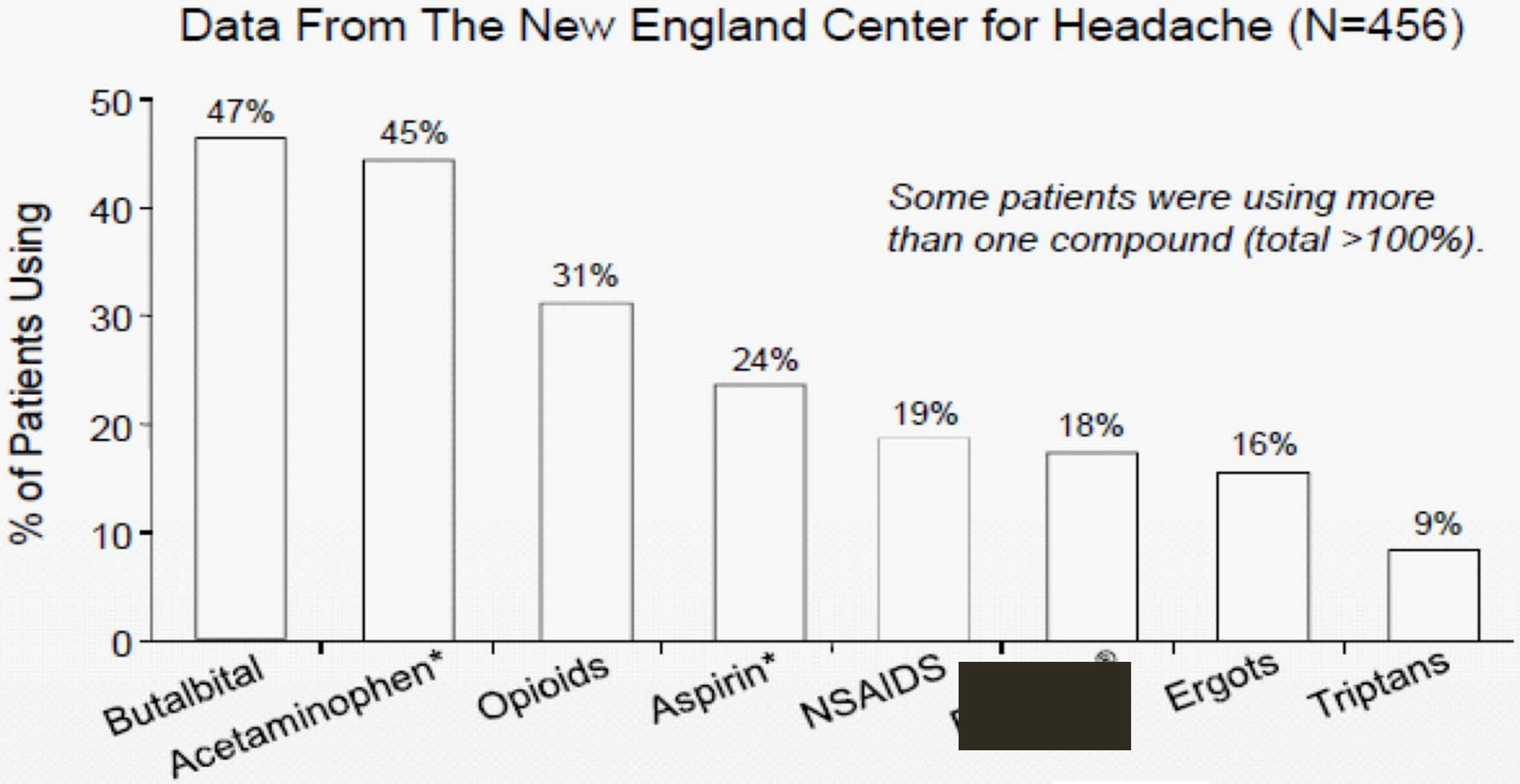
DHE nasal spray

Butorphanol nasal spray

Corticosteroids i.v.

Adapted from Silberstein SD et al., 2000

Medication Overuse Headache



*Aspirin and acetaminophen alone or in compounds except for [redacted], which was considered separately.

acetaminophen/aspirin/caffeine (Excedrin)

Bigal ME et al. *Cephalalgia*. 2004;6:483-90.

Interventions

Nerve Blocks

- Occipital
- Cervical spine
- Cervical medial branch
- Peripheral nerve block

Trigger point Injections

- Onabotulimuntoxin A via PREEMPT
- Other myofascial TP injections

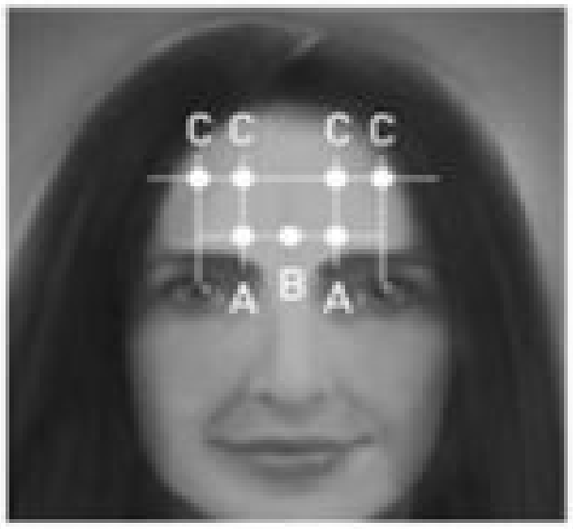
Infusions

Dihydroergotamine, lidocaine, divalproex, magnesium, ketamine, propofol.

Implantable Devices

Occipital nerve stimulator, deep brain stimulator, IT infusion pump, ganglion sphenopalatinum stimulation, dorsal column stimulator – cervical.

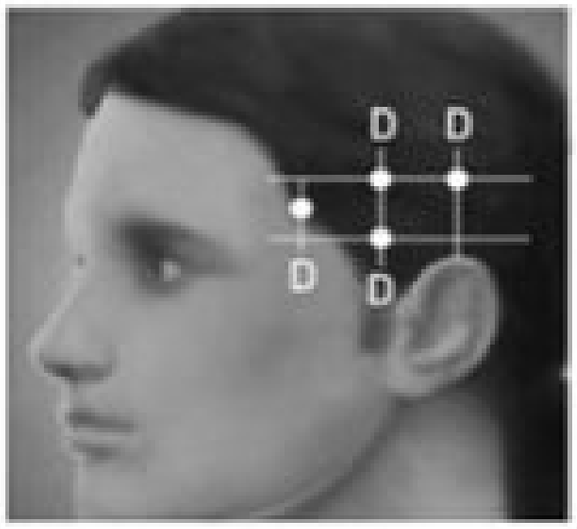
Recommended injection sites for chronic migraine:



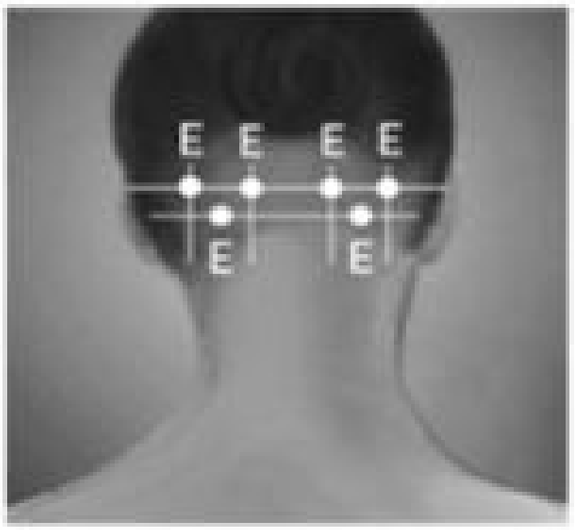
A. Corrugator: 5 U each side

B. Procerus: 5 U (one site)

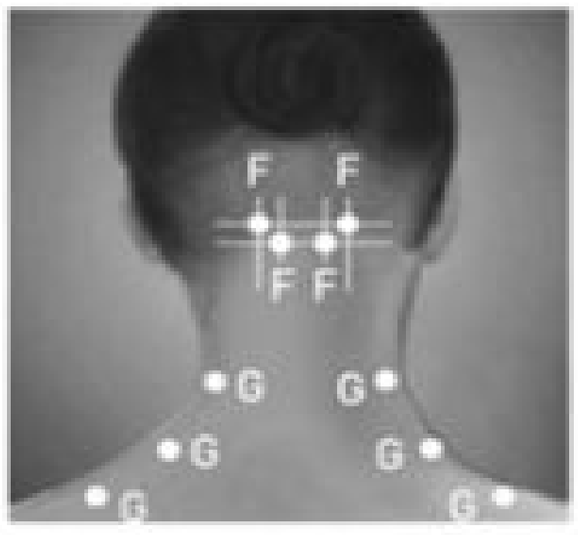
C. Frontalis: 10 U each side



D. Temporalis: 20 U each side



E. Occipitalis: 15 U each side



F. Cervical paraspinal: 10 U each side

G. Trapezius: 15 U each side

Onabotulinumtoxin A **Dosing by Muscle for Chronic Migraine**

Head/Neck Area	Recommended Dose (Number of Sites[a])
Frontalis[b]	20 Units divided in 4 sites
Corrugator[b]	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis[b]	30 Units divided in 6 sites
Temporalis[b]	40 Units divided in 8 sites
Trapezius[b]	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
Total Dose:	**155 Units** divided **in 31 sites**

[a] **Each IM injection site = 0.1 mL = 5 Units**

[b] **Dose distributed bilaterally**

Interventions

Occipital Nerve Stimulator

(Paemeleire, 2010)

Deep Brain Stimulator

(Leone, 2010)

Interventions

Ganglion Sphenopalatinum Stimulation

Cervical Dorsal Column Stimulator

(Schoenen, 2013)

Interventions

First FDA approval transcutaneous electrical nerve stimulation (TENS) system OK'd for migraine prevention.

http://youtu.be/0Rh3btp7Rxw

Complementary

- Acupuncture/acupressure
- Aromatherapy
- Biofeedback
- Meditation
- Massage
- Herbs, vitamins & minerals
- Nutrition
- Exercise/stress reduction/trigger identification (avoidance)

Acupuncture for recurrent headaches: a systematic review of randomized controlled trials

Melchart, D., Linde, K., Fischer, P. et al. – Dept. of Internal Medicine II, Klinikum rechts der Isar, Technische Universitat, Germany

Cephalalgia 2000 Oct; 20(8):762-3

Design:
Systematic Review using electronic databases (Medline, Embase, Cochrane Field for Complementary Medicine, Cochrane Controlled Trials Register), personal communications & bibliographies.

Question:
To assess whether there is evidence that acupuncture is effective in the treatment of recurrent headaches.

Acupuncture for recurrent headaches: a systematic review of randomized controlled trials

Findings:

- Twenty-two trials, including a total of 1042 patients, met criteria.
- Fifteen trials were in migraine patients, six in tension-ha patients, & in one trial patients with various headaches were included.
- The majority of the 14 trials comparing true and sham acupuncture showed at least a trend in favor of true acupuncture.
- The eight trials comparing acupuncture and other treatment forms had contradictory results.
- Overall, the existing evidence suggests that acupuncture has a role in the treatment of recurrent headaches.

Alternative headache treatments: nutraceuticals, behavioral & physical treatments

Sun-Edelstein, C., Mauskop, A. - Department of Clinical Neurosciences, St Vincent's Hospital, Melbourne, Vic., Australia.

Headache. 2011 Mar;51(3):469-83

Design:
Systematic Review of the available scientific literature.

Question:
Review body of literature that explored the evidence supporting the efficacy of various complementary & alternative medicine approaches in the management of headache disorders.

Alternative headache treatments: nutraceuticals, behavioral & physical treatments

Findings:

- Vitamins & Supplements (magnesium, riboflavin, coenzyme Q(10), and alpha lipoic acid).

- Herbal Preparations (feverfew, and butterbur).

- Cognitive behavioral therapy & Bio-behavioral training (biofeedback, relaxation training).

- Physical Treatments, were not well defined in the literature

(acupuncture, oxygen therapy, transcutaneous electrical nerve stimulation, occipital adjustment, cervical manipulation, physical therapy, massage, chiropractic therapy, and osteopathic manipulation).

Behavioral & non-pharmacological treatments of headache

Lake, A.E. – Michigan Head-Pain & Neurological Institute, Ann Arbor, Michigan, USA.

Med Clin North Am. 2001 Jul;85(4):1055-75.

Design:
Systematic Review (standard medical/scientific literature databases 1977-2011).

Question: Apply a cognitive-behavioral analysis & assessment to the following behavioral domains:

1) **Headache frequency & severity**
2) **Analgesic & abortive medication use/overuse,**
3) **Behavioral & stress risk factors**
4) **Co-morbid psychiatric disorders**
5) **Degree of overall disability.**

Behavioral & non-pharmacological treatments of headache

Findings:

- CBTs for migraine have a prophylactic efficacy of about 50%, roughly equivalent to propranolol.
- The combination of behavioral therapies with prophylactic medication creates a synergistic effect, increasing efficacy beyond either type of treatment alone.
- Overuse of abortive medications impedes the effectiveness of behavioral & prophylactic medication therapies.
- Behavioral therapies can help sustain improvement after analgesic withdrawal.
- Cognitive factors (an enhanced sense of self-efficacy & internal locus of control), appear to be important mediators of successful behavioral treatment.

Nutraceuticals

Feverfew 50-100 mg daily

Butterbur 50-100 mg twice daily

Riboflavin 400 mg daily

Magnesium dicitrate 600 mg daily

CoQ10 100 mg three times daily

- Some evidence exists that the herbs feverfew and butterbur may prevent migraines or reduce their severity.
- A high dose of riboflavin also may prevent migraines by correcting tiny deficiencies in brain cells.
- Coenzyme Q10 supplements may be helpful in some individuals.
- Oral magnesium sulfate supplements may reduce the frequency of headaches in some people

The Keeler Migraine Method

The Keeler Migraine Method

Three Part Individualized Treatment Plan

Lifestyle Modification

- Sleep hygiene
- Exercise
- Dietary habits
- Trigger management
- Stress management
- Hormonal influences (menstruation/pregnancy)

Prevention

Medication options, mind-body therapies, hormone adjustment, nutraceuticals.

Rescue “plan your plan”

Rescue environment, organize resources, abortive medications.

The Keeler Migraine Method

Eating

- Omega-3 fatty acids, instead of omega-6
- Anti-inflammatory foods
- Consistency/timing/”healthy diet”
- Avoid triggers (red wine, cheese, chocolate)

Exercise

- Pacing, variety, start with physical therapist
- Higher endorphin levels
- Higher pain thresholds
- Improved sleep

The Keeler Migraine Method

Sleep

•Good sleep hygiene (behavioral modification)

•Avoid habitual use of sleep medications

•Natural remedies (melatonin, chamomile tea, valerian root)

•Limit caffeine

Work

•Minimize workplace triggers (stress, computers, physical strain, shift work, lighting).

•Rescue in the workplace (medications, space, ride home).

Highlights from American Headache Society Annual Conference

Acute Migraine Treatment:

Allodynia & Timing of Triptan Therapy:

Patients who never develop cutaneous allodynia can be successfully treated with triptans at any time during their migraine attack, whereas those who develop cutaneous allodynia must be treated early, before central sensitization can be established.

COX-2 Inhibitor for Migraine:

A long-acting selective cyclooxygenase-2 (COX-2) inhibitor, may be as effective as nonselective NSAIDs and opioid analgesics in the treatment of acute pain.

acetaminophen/aspirin/caffeine (*Excedrin* Migraine) versus Sumatriptan:

acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg (*Excedrin* Migraine) has been shown to be effective in the acute treatment of migraine.

http://www.medscape.org/viewarticle/453289

Highlights from American Headache Society Annual Conference

Preventive Treatment:

Menstrual Migraine:

For intermittent prophylaxis of menstrual migraine, naratriptan 1 mg twice daily was well tolerated and more effective than placebo but appears to be less effective than frovatriptan 2.5 mg twice daily (38.4% vs 50%).

Migraine Prophylaxis with Anticonvulsant Drugs:

Anticonvulsant medication is increasingly recommended for migraine prevention because of placebo-controlled, double-blind trials that prove them effective. Topiramate has demonstrated efficacy in migraine prevention in several open-label studies and pilot trials. MOA could either directly inhibit the trigemino-cervical complex or influence the neural network that controls sensory input.

http://www.medscape.org/viewarticle/453289

Hot off the presses …

Monoclonal antibodies for Migraine prevention

Dr. David Dodick of the Mayo Clinic in AZ, an author of two studies looking at drugs that target the calcitonin gene-related peptide, which is thought to be important in migraine pathogenesis.

The study participants had migraine 4-14 days a month. On one medication participants had 5.6 fewer migraines per month (a decrease of 66%); on the other, 4.2 fewer migraines per month (63% decrease).

“While we’ve moved from the blood vessel to the space between the blood vessel & from the nerve to the brain, we are now focused on molecular targets within the brain.”

Hot off the presses …

Use of Social Media by patients

A study recently published in *The Journal of Medical Internet Research* found that Twitter proved to be a powerful source of knowledge in migraine research.

This study reveals the modern characteristics and broad impact of migraine headache suffering on patients' lives as it is spontaneously shared via social media.

The researchers also noted that the growth of social media has facilitated a trend toward the cathartic sharing of physical, as well as emotional pain.

The study also showed that people are willing to use social media to communicate about their migraines during an attack, provided that they can do it quickly.

May help Practitioners to develop new tools to interact with migraine patients and identify headache patterns.

Resources

American Academy of Neurology: http://www.aan.com/

American Headache Society: http://www.americanheadachesociety.org/

Cleveland Clinic Headache Center
International Headache Society: http://www.ihs-classification.org/en/

Johns Hopkins Medical Center:
http://www.hopkinsmedicine.org/neurology_neurosurgery/specialty_areas/headache/

Mayo Clinic Headache Center

National Headache Foundation: http://www.headaches.org/

Stanford Headache Center

World Health Organization: http://www.who.int/topics/headache_disorders/en

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