EMERGING THERAPIES IN HEADACHE

Breakthroughs in Neurology

January 23–25, 2015 • Phoenix, AZ

POWERPOINT PRESENTATIONS

January 24, 2015
1:00 p.m. – 4:00 p.m.
Pointe Hilton Tapatio Cliffs Resort
Highland 3
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The Education and Science Committees meet each year to review and select the program for the next Regional Conference. Your evaluations are carefully reviewed and are critical for the selection process. Evaluation instructions are located in the syllabus. Please visit our website and follow the instructions to complete the online evaluation. We appreciate your assistance.

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Breakthroughs in Neurology Conference
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1. Enter your AAN ID. This can be found in the upper right-hand corner of your badge.
2. Select the programs you attended. You will be asked to complete an evaluation form for each program you attended.
3. Fill out the evaluation(s) and select the “Next” button.
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1. Enter your AAN ID. This can be found in the upper right-hand corner of your badge.
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3. Your evaluation has been submitted when you see the Thank You screen.

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- Attendees must be registered and badged to attend the individual programs.
- CME Category 1 Credit is awarded to persons registering for and participating in the AAN Regional Programs and submitting an evaluation form. Evaluation instructions are found at the beginning of each syllabus. Evaluations must be submitted online.
- CME Credits/Certificates of Attendance will be sent to attendees four to six weeks following the Regional Conference.

Program Director
Morris Levin, MD, FAAN
San Francisco, CA

Program Schedule and Faculty
1:00 p.m. – 1:15 p.m. Introduction and Overview of Challenges in HA Classification and Diagnosis
Morris Levin, MD, FAAN
San Francisco, CA

1:15 p.m. – 1:55 p.m. Comorbidities as Treatment Guides
Steven Baskin, PhD
Greenwich, CT

1:55 p.m. – 2:25 p.m. Pipeline Pharmacological Treatment for HA
Alan M. Rapoport, MD, FAAN
Woodside, CA

2:25 p.m. – 3:05 p.m. Injections and Surgical Options for HA
Carolyn Bernstein, MD
Brookline, MA

3:05 p.m. – 3:45 p.m. Neuromodulation for HA
Morris Levin, MD, FAAN
San Francisco, CA

3:45 p.m. – 4:00 p.m. Questions and Answers
Faculty

Program Description:
Headache, migraine in particular is the single most common neurological condition in the world, responsible for a huge degree of suffering and disability. A number of treatment options for migraine and its subtypes have emerged but sadly, numerous patients continue to be therapeutic challenges. Reasons for this include incorrect or partial diagnosis and failure to consider and treat important comorbid medical and psychiatric conditions. This program will provide participants information about current effective treatment options as well as newer proposed treatments.

Learning Objectives:
At the completion of this course, participants will:

1. Be able to review headache classification and diagnostic pitfalls to avoid
2. Be able to discuss common psychiatric and other headache and migraine comorbidities, as well as their treatment implications
3. Be conversant with new pharmacological developments in Headache Medicine
4. Have a better understanding of the use and benefits of anesthetic and toxin injections in headache medicine, as well as proposed surgical interventions for headache.
5. Be able to describe the various neuromodulation techniques that have been shown to be effective in headache disorders as well as some others that are being studied

Recommended Audience:
Practicing Neurologists; Neurology Residents; Pain Medicine Specialists

Accreditation
The American Academy of Neurology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.
AMA PRA Credit

The AAN designates these educational activities for a maximum number of hours in category 1 credit toward the AMA Physician’s Recognition Award. The number of credits assigned to each individual program is outlined in the program’s description. Each physician should only claim those hours of credit that he/she actually spent in the activity.

Certificates for Non-Physicians
Non-physician participating in the programs will receive a certificate of attendance indicating attendance at an activity designated for AMA PRA category 1 credit.

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Faculty Commercial Relationship Disclosures
- Dr. Levin has received personal compensation for activities with Nupathe, Allergan, Supernus, Depomed, and Transept as an advisory board member or consultant.
- Dr. Baskin has received personal compensation for activities with Allergan, NuPathe, and Depomed as an advisory board member and speaker.
- Dr. Rapoport has received personal compensation for activities with Pfizer Inc, Endo Pharmaceuticals, Nupathe, and MAP Pharmaceuticals.
- Dr. Bernstein has received personal compensation for activities with Forest Laboratories as a consultant.

Unlabeled Use of Product Disclosure
The AAN, as an ACCME accredited provider, requires all faculty members to disclose if a product is not labeled for the use being discussed or that the product is still investigational.

Faculty Unlabeled Use of Product Disclosures
- Dr. Levin will discuss a number of proposed neurostimulation and modulation devices that are generally experimental and thus not labeled for use in headache management.
- Dr. Baskin will not include any information on unlabeled use of products or investigational uses during the presentation.
- Dr. Rapoport will discuss pharmacological treatments for headache which are off label.
- Dr. Bernstein will not include any information on unlabeled use of products or investigational uses during the presentation.
Emerging Therapies in Headache
AAN Phoenix – 2015

Morris Levin, MD
Professor of Neurology
Director, Headache Center
UCSF Department of Neurology

AAN Emerging Therapies in Headache 2015:

• 1:00-1:15 Intro and Overview of Challenges in HA Classification and Diagnosis - Morris Levin, MD, FAAN
• 1:15-1:55 Comorbidities as treatment guides - Steven Baskin, PhD
• 1:55-2:25 Pipeline pharmacological treatment for HA - Alan Rapoport, MD
• 2:25-3:05 Injections and surgical options for HA – Carrie Bernstein
• 3:05-3:45 Neuromodulation for HA - Morris Levin, MD, FAAN
• 3:45-4:00 Q and A

• 40 min talks, Q&A at end
Emerging Therapies in Headache
AAN Phoenix – 2015

Issues of Headache Classification

Morris Levin, MD
Professor of Neurology
Director, Headache Center
UCSF Department of Neurology

History

- International classification of headache disorder, 1st edition (ICHD-1) in 1988
- ICHD-2 in 2004
- ICHD-3 beta in 2013
- ICHD-3 in 2016
Why a beta version?

• WHO plans field testing of ICD-11
• ICHD-3 will correspond
• An opportunity for broad input and detection of errors
• Research opportunities

Membership 3rd International Headache classification committee

• Jes Olesen, chair
• Lars Bendtsen
• David Dodick
• Anne Ducros
• Stefan Evers
• Michael First
• Peter J Goadsby
• Andrew Hershey
• Zaza Katsarava
• Morris Levin

• Julio Pasqual
• Michael B Russell
• Todd Schwedt
• Timothy Steiner (honoary secretary)
• Critina Tassorelli
• Gisela M Terwindt
• Maurice Vincent
• Shuu-Jiun Wang
ICHDI II – Basic Organization

Part 1: Primary headaches
Part 2: Secondary headaches
Part 3: Cranial Neuralgias, etc.
The Appendix

ICHDI 3 – Controversies and Challenges

- Tension type headache
- Migraine with aura
- Chronic Migraine
- Posttraumatic headaches
- Medication overuse HA
- Cervicogenic headaches
- Psychiatric headaches
What’s new in Primary HA

ICHDIII

Part 1: Primary headaches, chapters 1-4 (no other causative disorder)

1. Migraine
2. Tension-type Headache
3. Cluster and its relatives (TACs)
4. Other primary headaches – exertional, headaches associated with sexual activity, new daily persistent headaches, hypnic headache, etc.
Controversy 1: Is TTHA distinct from migraine or is there a continuum?

- Distinct: if one uses the criteria there is very little overlap
- Continuum: 40% of TTHA respond well to oral triptan. But cluster headache also responds, and there are many cases of subarachnoid hemorrhage, mass lesions, CO, poisoning, and posttraumatic HA have responded well to sumatriptan


ICHD 3 Migraine

- Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
- Headache has at least two of the following four characteristics:
  1. unilateral location
  2. pulsating quality
  3. moderate or severe pain intensity
  4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- During headache at least one of the following:
  1. nausea and/or vomiting
  2. photophobia and phonophobia
ICHD 3 Tension Type HA

• Lasting from 30 min to 7 days
• At least two of the following four characteristics:
  1. bilateral location
  2. pressing or tightening (non-pulsating) quality
  3. mild or moderate intensity
  4. not aggravated by routine physical activity such as walking or climbing stairs
• Both of the following:
  1. no nausea or vomiting
  2. no more than one of photophobia or phonophobia

Migraine and TTHA headaches can be seen as overlapping sets

• But this is true in many areas of medicine
• And diagnostic definitions are crucially important
Migraine classification

1.1 Migraine without aura
1.2 Migraine with aura
1.3 Chronic migraine
1.4 Complications of migraine
1.5 Probable migraine
1.6 Episodic syndromes that may be associated with migraine

1.2 Migraine with aura

1.2.1 Migraine with typical aura
   1.2.1.1 Typical aura with headache
   1.2.1.2 Typical aura without headache

1.2.2 Migraine with brainstem aura

1.2.3 Hemiplegic migraine
   1.2.3.1 Familial hemiplegic migraine (FHM)
   1.2.3.2 Sporadic hemiplegic migraine

1.2.4 Retinal migraine
1.2.1 Migraine with typical aura

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but **no motor, brainstem or retinal symptoms**
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes
   3. at least one aura symptom is unilateral
   4. the aura is accompanied, or followed within 60 minutes, by headache

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1.2.2 Migraine with brainstem aura

A. At least 2 attacks fulfilling criteria B and C below, and criteria C and D for 1.2.1 Migraine with typical aura
B. Aura of fully reversible visual, sensory and/or speech/language symptoms, but not motor or retinal
C. ≥2 of the following brainstem symptoms:

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<thead>
<tr>
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<th>Problems</th>
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<tbody>
<tr>
<td>1. dysarthria</td>
<td>1. Symptoms “clearly” emanating from the brainstem</td>
</tr>
<tr>
<td>2. vertigo</td>
<td>2. What to call migraine accompanied only by vertigo? Or vertigo without HA?</td>
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<tr>
<td>3. tinnitus</td>
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<td>4. hypacusis</td>
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<td>5. diplopia</td>
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<td>6. ataxia</td>
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<td>7. decr level of consc</td>
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Controversy 2 – What is Basilar Migraine?

- “Basilar Migraine" (ICHD 1)
- “Basilar Type Migraine” (ICHD 2)
- “Migraine with brainstem aura” (ICHD 3)

- One thing it is probably not: aura originating in the brainstem


Controversy 3 – Is vertigo a bona fide aura symptom? (and what is migrainous vertigo?)

- Not classifiable if it is the only aura
- Many case reports of patients with episodic vertigo with headache or in isolation, who respond to migraine treatment
A1.6.5 Vestibular migraine

A. At least five episodes fulfilling criteria C and D
B. A current or past history of 1.1 Migraine without aura or 1.2 Migraine with aura
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 minutes and 72 hours
D. At least 50% of episodes are associated with at least one of the following three migrainous features:
   1. headache with at least two of the following four:
      a) unilat location b) pulsating quality c) moderate or severe intensity d) aggravation by routine activity
   2. photophobia and phonophobia
   3. visual aura

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1.4 Complications of migraine

1.4.1 Status migrainosus
1.4.2 Persistent aura without infarction
1.4.3 Migrainous infarction
1.4.4 Migraine aura-triggered seizure

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1.3 Chronic migraine

A. **Headache (TTH-like and/or migraine-like) on ≥15 d/mo** for >3 mo and fulfilling criteria B and C
B. In a patient who has had ≥5 attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. **On ≥8 d/mo** for >3 mo fulfilling any of the following:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. **believed by the patient to be migraine** at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

**Controversy – Why 15? Is a pt with 14/mo different from one with 16/mo?**

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**Controversy 4: Is Chronic migraine different than intermittent migraine?**

If so, where to draw the line? 15 days/mo? 20? 28?
And is daily migraine different from nearly daily migraine?
1.6 Episodic syndromes that may be associated with migraine

1.6.1 Recurrent gastrointestinal disturbance

1.6.1.1 Cyclical vomiting syndrome

1.6.1.2 Abdominal migraine

1.6.2 Benign paroxysmal vertigo

1.6.3 Benign paroxysmal torticollis

A 1.6.6 Vestibular migraine – or is there something like it without headaches?

What’s new in Secondary HA
**ICHD – Challenges with 2° HA**

- Morphology of headache is not necessarily diagnostic
- Location of pain is not necessarily diagnostic
- Presence of pathology in the face and head is not necessarily diagnostic
- Multiple sources of pain coexist in many patients
- Pain may not resolve when cause is gone

**ICHD III – 2° HA**

1) Resolution of headache after cause is removed – no longer a requirement
2) ICHD III criteria require two separate *evidential features* to be present in all cases, and allow up to four types of evidence
3) Diagnostic criteria restrict themselves to information reasonably available to the diagnosing physician in a typical clinical situation.
**ICHD III – 2° HA**

**What constitutes Evidence:**
- Pathology exists
- That pathology is capable of causing HA
- The features and timing of the headache seem consistent with the proposed cause

4) When a pre-existing headache disorder is clearly worsened by the occurrence of another disorder, conclude two problems – the initial primary headache and the secondary headache which represents the secondary “component”.

    Example: migraine + TBI → 1.1 and 5.2

5) If a headache is morphologically like migraine but arises as a result of a secondary cause, code as the secondary HA

6) No “Probable” secondary headaches – otherwise to inclusive
ICHD 3 - Post-traumatic headaches

*Headache attributed to trauma or injury to the head and/or neck*

1. Require headache following head or neck trauma within 7 days
2. Acute or Chronic: < or > 3 months
3. After mild or more severe trauma
4. Whiplash induced headaches

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**Controversy 5 – Timing of onset of Post-traumatic headaches**

- What to do with patients whose headaches began 8 days after the injury?
- What if the patient began having headaches but did not complain to medical personnel until weeks later?
ICHD 3 - Post-traumatic headache

– severity of trauma

5.1 Acute post-traumatic headache
   5.1.1 acute post-traumatic headache attributed to moderate or severe head injury
   5.1.2 acute post-traumatic headache attributed to mild head injury

5.2 Persistent post-traumatic headache
   5.2.1 mod or severe head injury
   5.2.2 mild head injury

5.3 Acute headache attributed to whiplash injury

5.4 Persistent headache attributed to whiplash injury

ICHD 3 - Headaches due to cranial, cervical, EENT, dental disorders

– broadened the cervicogenic category
– Appendix dx for cervical radiculopathy
– Ap dx for cervical myofascial pain induced HA
– Chronic rhinosinusitis
– Trochleitis
– Nasal contact point – Appendix
– TMD HA based on new TMD diagnostic criteria*

Cervicogenic Headache – ICHD III

A. Headache of any kind fulfilling criteria C and D
B. Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache, including tumors, fractures, infections, and significant upper cervical arthritic disease such as symptomatic spondylosis.

Controversy 6 – what can cause Cervicogenic Headache?

Innerv of face and head =
- Trigem for anterior
- C2,3 posterior

Upper cerv roots and Trigem afferents synapse with cells in spinal trigem nuc and dorsal horn
(which also carries afferents from VII, IX, X.)

This explains referral patterns of anterior nociception perceived as posterior and vice versa

Can a midcervical pain generator lead to headache?
A11.2.1.2 Headache attributed to myofascial pain in the cervical muscles

A. Headache of any type, generally posterior, fulfilling criteria C and D
B. Clinical evidence of a myofascial pain source in the muscle of the neck, including reproducible trigger points
C. Evidence that the pain can be attributed to the cervical myofascial pain disorder based on at least two of the following:
   1. Headache began or worsened in temporal relation to the onset of the cervical myofascial pain disorder
   2. Headache has improved in temporal relation to improvement or resolution of the cervical myofascial pain disorder
   3. Significant pressure-tenderness is elicited in cervical muscles corresponding to the pain perceived by the patient
   4. Abolition of headache and cervical pain occurs following placebo controlled anesthetic trigger point injections or trigger point massage

ICHD - Headaches due to psychiatric disease

- ICHD II – somatization or psychosis;
- “...the brevity ...is due to a paucity of evidence in this field, which will hopefully change in the future”
- It hasn’t
- ICHD III – somatization or psychosis
Controversy 7 – Do DSM 5 disorders cause or contribute to Headaches?

• Anxiety
• Depression
• Thought disorders
• PTSD
• Autism spectrum
• Confounding issues – medications, self injury, poor sleep, substance use

ICHDI III Appendix psych disorders

• A12.3 Headache attributed to Depressive Disorders
• A12.4 Headache attributed to Separation Anxiety Disorder
• A12.5 Headache attributed to Panic Disorder
• A12.6 Headache attributed to Specific Phobia
• A12.7 Headache attributed to Social Anxiety Disorder (Social Phobia)
• A12.8 Headache attributed to Generalized Anxiety Disorder
• A12.9 Headache attributed to Post-traumatic Stress Disorder
• A12.10 Headache attributed to Acute Stress Disorder
Why love the ICHD?

• It is a very effective tool for avoiding misdiagnosis
• It creates consistency
• Provides many fertile research questions
• Excellent bedtime reading material

Why hate the ICHD?

• It is full of arbitrary definitions not based on clear evidence
• It is long and wordy
• Many of the definitions may not fit with your observations
ICHD III – The Beta Version

• ICHD III published on line in March 2013, and in Cephalalgia April 2013
• Field testing began at that point with the aim of finalizing the ICHD by 2015
• Participate in assessing and commenting via www.i-h-s.org

ICHD 3 – Controversies and Challenges

• Tension-type headache
• Migraine with aura
• Chronic Migraine
• Posttraumatic headaches
• Medication overuse HA
• Cervicogenic and craniofacial headaches
• Psychiatric headaches
Migraine Comorbidities as Treatment Guides

Steven M. Baskin PhD
New England Institute for Neurology and Headache
Stamford, Connecticut

American Academy of Neurology
2015 Breakthroughs in Neurology Conference
January 24, 2015

Overview

• What is comorbidity?
• Medical and psychiatric comorbidities in migraine
• Comorbid anxiety as a driver of distress across medical and psychiatric disorders
• Can comorbidities inform care?
• Comorbidity and headache frequency
What is Comorbidity?

- When one disorder occurs with greater than chance frequency with another disorder, they are said to be comorbid.
- It is more than a coincidental association between two conditions.

Mechanisms of Comorbidity

- Chance
- One disorder causing another
  --diabetes leading to neuropathic pain
- Shared genetic or environmental risk factors
  --post-traumatic HA and post-traumatic SD
- Genetic and environmental factors may predispose to a brain state that may lead to both conditions (most likely the case in psychiatric comorbidity and migraine).
Why Study Comorbidity?

- May complicate differential diagnosis
- Could contribute to disease burden
- May affect treatment adherence
- Creates therapeutic opportunities and imposes therapeutic limitations
- Gives insight into mechanisms
- May alter the course of the index disease

Methodological Issues

- **Berkson’s bias** or paradox is the non-random co-occurrence of two conditions attributed to artifacts of the methodology employed
- Berkson’s bias arises because individuals with more than one disorder can seek treatment for any or all disorders and thus tend to be treated more often than those with only one disorder
- Individuals with two or more conditions may be over-represented in a clinical sample

Berkson J. Limitation of the application of the 4-fold table analysis to hospital data. *Biometrics*, 1946;2:47-53
Migraine: Comorbid Conditions

**Cardiovascular**
- Heart attack/angina
- Mitral valve prolapse
- PFO
- Hypertension, orthostasis
- Stroke
- Peripheral vascular disease

**CNS**
- Epilepsy
- Essential tremor

**Psychiatric disorders**
- Depression
- Bipolar Disorder
- Anxiety Disorders
- PTSD

**GI disorders**
- IBD
- Celiac disease
- IBS

**Allergy/Asthma**

**Musculoskeletal Disorders**

**Obesity**

**TMD**

Danish Population Study

### Danish Population Study

![Graph showing odds ratios for different conditions](image)

### Danish Study Comorbidities

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<td>3.1 F</td>
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<td>*</td>
<td>1.5 M</td>
<td>1.4 M</td>
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<td></td>
<td></td>
<td></td>
<td>1.8 F</td>
<td>1.5 F</td>
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<tr>
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Migraine and Coronary Heart Disease

- Women’s Health Study reported MI, angina, coronary revascularization, and ischemic CV death related to MA. MI associated with active MA in those with high Framingham score, particularly among women with high total cholesterol.
- Physicians Health Study men with migraine demonstrated a 42% increase in the risk of MI. No significant associations for risk of coronary revascularization, angina or ischemic CV death. No data on aura collected.
- AMPP sub-study showed that both MA and MO were associated with myocardial infarction.

Women’s Health Study


Cumulative CV disease in men

Driven by a 42% increased risk of MI

GEM Study of migraine and vascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Migraine With Aura (n = 192)</th>
<th>Migraine Without Aura (n = 396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>1.54 (1.1 – 2.1)</td>
<td>0.91 (0.7 – 1.1)</td>
</tr>
<tr>
<td>MD diagnosed HTN</td>
<td>1.73 (1.2 – 2.4)</td>
<td>1.09 (0.8 – 1.5)</td>
</tr>
<tr>
<td>FHx maternal MI (&lt;65)</td>
<td>1.86 (1.0 – 3.4)</td>
<td>1.64 (1.0 – 2.6)</td>
</tr>
<tr>
<td>Elevated Framingham Score¹</td>
<td>4.01 (1.1 – 15)</td>
<td>1.84 (0.7 – 5.0)</td>
</tr>
</tbody>
</table>

Scher et al, *Neurology*, 2005

HUNT Study

- Framingham risk score consistently increased with headache frequency.
- For non-migrainous HA and MO increased risk (OR 1.17) accounted for by lifestyle factors high BMI, smoking, and low physical activity.
- Lifestyle factors did not explain MA elevated risk (OR 1.54)

**Migraine and HTN, High Cholesterol**

- Two population based studies showed association between migraine and hypertension whereas two earlier population based studies showed negative relationship.
- Women’s Health Study showed relationship to total cholesterol and elevated SBP in women with prior migraine not active migraine. Women with active MA and high total cholesterol had significantly increased risk of MI.


**Migraine and Stroke**

- Highest risk in female migraineurs, those under age 45, and female smokers taking oral contraceptives. High frequency migraine greater risk than low frequency.
- Seems to be no clear cut association between migraineurs and the common vascular risk factors in a young adult population.
Migraine and Structural Brain Changes

- Population and clinic-based studies suggested that structural brain changes including white matter abnormalities, silent infarct-like lesions, and volumetric changes in GM and WM were more common in migraineurs than controls.
- Recent meta-analysis supports MA is associated with increased risk of WMA. Cumulative migraine exposure needs further investigation. Silent ILL’s data is strongest for MA with frequent attacks. Patients with ILL’s should be evaluated for stroke risk factors.
- Rist prospective study did not find any relationship between WMA's, ILL’s and cognitive decline although probably underpowered for these analyses.


Migraine and Obesity

- Obesity is comorbid with both episodic and chronic migraine. Risk of migraine increases with increasing weight gain. Obese episodic migraineurs have greater risk for headache chronification.
- Peterlin showed that in men and women 20-55, higher migraine prevalence was associated with both total and abdominal obesity.
- Some recent evidence that decreases in BMI are associated with headache reduction in obese migraineurs.

Migraine and Obesity

- Try to achieve and maintain normal BMI
- Because obesity is a risk factor for CM, it is important to treat obese episodic migraineurs with preventives to avoid progression.
- Physical exercise and bariatric surgery may modulate migraine frequency.
- Avoid preventives that have significant potential for weight gain.

Bariatric Surgery in Obese EM

- Bond et al (Neurology 2011)
  - 24 obese men and women with EM
  - 6 months post-surgery showed a 50% HA reduction

- Novak et al (Cephalalgia 2011)
  - 23 obese premenopausal women
  - low frequency EM (2-8 days per month)
  - mean HA frequency decreased from 4 to 1.6 months post-surgery

After Peterlin, 2014
# Weight and migraine preventatives

## Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>++</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>++</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+-</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+</td>
</tr>
</tbody>
</table>

## Anticonvulsants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex Sodium</td>
<td>+++</td>
</tr>
<tr>
<td>Gapapentin</td>
<td>+</td>
</tr>
<tr>
<td>Topiramate</td>
<td>-- --</td>
</tr>
</tbody>
</table>


---

## Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>+</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+</td>
</tr>
<tr>
<td>Timolol</td>
<td>+-</td>
</tr>
</tbody>
</table>

## Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunarizine</td>
<td>+++</td>
</tr>
<tr>
<td>Verapamil</td>
<td>+</td>
</tr>
</tbody>
</table>

## Serotonin antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyproheptadine</td>
<td>+</td>
</tr>
</tbody>
</table>

## Angiotensin II receptor blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>+</td>
</tr>
<tr>
<td>Telmesartan</td>
<td>-</td>
</tr>
</tbody>
</table>

## Ace inhibitor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>+ -</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>+-</td>
</tr>
</tbody>
</table>

**Migraine Treatments with CV disease**

- Any migraine treatment that constricts blood vessels, even temporarily, cannot be used in those with CV disease. In those with uncontrolled hypertension, high cholesterol or several risk factors, risk factors need to be treated and consideration given to cardiac testing before use of triptans or DHE.
- NSAIDS, increased risk of heart attack
- Migraine preventive strategies very important if acute options are limited. With HTN comorbidity consider candesartan and beta blockers.


---

**Migraine and Epilepsy**

- Most studies show bidirectional relationship between migraine and epilepsy, although some contradictory results. There was an overall 52% increase in the prevalence of migraine among PWE versus those without epilepsy. There was an overall 79% increase in the prevalence of epilepsy among migraineurs versus those without migraine in one recent study.
- Prevalence of interictal migraine in epileptic patients higher than in population at large.
- The prevalence of MA significantly increased with number of first degree relatives with SD.

Headache in Epilepsy

Cumulative Incidence of Migraine Headache by Age

EP: epileptic patients; PBDDS: population-based door-to-door survey

Cumulative Incidence of Migraine Headache by Age in Probands After and Before Epilepsy Onset

National Health and Nutrition Examination Survey (ages 4-18)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>W/O HA</th>
<th>W/HA</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>14.12%</td>
<td>21.83</td>
<td>1.7</td>
</tr>
<tr>
<td>Hay fever</td>
<td>10.48</td>
<td>20.05</td>
<td>2.14</td>
</tr>
<tr>
<td>Ear infection</td>
<td>4.14</td>
<td>9.30</td>
<td>2.37</td>
</tr>
<tr>
<td>Any 1 diagnosis</td>
<td>25.01</td>
<td>41.55</td>
<td>2.13</td>
</tr>
<tr>
<td>Any 2 diagnoses</td>
<td>3.51</td>
<td>10.65</td>
<td>3.28</td>
</tr>
</tbody>
</table>

Migraine and Asthma

• Women with a history of migraine have statistically higher odds of asthma (approx OR= 1.5) compared to nonmigraineurs.
• The odds of hypertensive disorders in pregnancy were found to be highest among women with migraine-asthma comorbidity.
• OR for migraine-asthma comorbidity and preeclampsia was 3.53 as compared to those who have neither disorder.


Migraine and “Sinus” Headache

• Schreiber, et al (2004) in neurology and primary care setting found that 80% of almost 3,000 “sinus headache” patients satisfied migraine diagnostic criteria.
• Eross, et al (2007) showed that 86% consecutive self-diagnosed “sinus headache” patient had migraine or probable migraine. Only 3 patients had rhino-sinusitis attributable headache.

Migraine and chronic pain

- Yoon et al (2013) in a large German population-based sample, the odd ratios were 2.7 for having frequent LBP with episodic migraine and 7.3 in CM controlling for BMI, smoking, drinking, education and frequent medication intake. With opioids, CM even more frequent.

- Clinical studies have shown that fibromyalgia affects approximately 10-20% of EM patients who present to tertiary care clinics and approximately 30-38% who present with CM.

Migraine and TMD

- Temporomandibular disorder symptoms are more common in migraine, ETTH, and CDH relative to individuals without headache. Magnitude of association is higher for migraine.
- Suggested as risk factor for increasing frequency of migraine
- Recent study showed better outcome in female migraineurs with TMD when treated with preventive medication plus stabilization splint.


Migraine associated with GI disorders

- Migraine is associated with people who regularly experience GI symptoms, IBS, IBD, infantile colic and celiac disease. A stronger association with increasing HA frequency.
- A few small studies suggest migraineurs have interictal delayed gastric emptying.
- TCA’s are constipating, SSRI/SNRI nausea, possible diarrhea, verapamil constipating, divalproex sodium nausea. May need different delivery systems because of gastroparesis. NSAID’s contraindicated ulcer, gastritis

**Psychiatric Comorbidity**

- May complicate differential diagnosis
- Non-adherence with treatment regimens 3 X more likely if depressed or anxious
- poorer drug tolerability
- Reduced response to pharm and behavioral Rx’s ???
- May increase risk of relapse
- May chronify the course of the migraine


---

**Nonadherence in Headache**

- 40% of patients don’t return for follow-up appointments
- 50%-70% of patients fail to optimally use medications
- 20% of triptan prescriptions and 25-50% of prescriptions for preventive agents are never filled
- More than half the population in a retrospective Dutch study had terminated treatment with migraine preventative within 3 months.
- Only 24% of headache patients use medications as instructed after 1 year
- Adherence with life style modification is poor

Edmeads, et al.,1993; Holroyd et al., 1988; Packard & Collins, 1986; Spierings et al., 1993; Evans and Linde, *Headache* 2009
Do clinical features influence adherence?

- Neither attack frequency, duration of attacks, nor cardinal symptoms during attacks were significantly associated with adherence.
- Even a problem with severe migraine


---

**Treatment Adherence**

**Assessment Basics**

- Does patient understand therapy rationale?
- Did patient receive adequate drug or behavioral Rx?
- Has patient adhered to past therapy regimens?
- Did medication overuse problems or psychiatric issues affect outcome?
- Ask open-ended questions. “How do you decide when to take your medication?”

Migraine Progression
Modifiable Risk Factors

• Attack frequency
• Obesity
• Medication and caffeine overuse
• Stressful life events and psychiatric comorbidity
• Snoring and sleep apnea


Comorbid Psychiatric Disorders
Prognosis for Refractory Headache
8-year follow-up of adolescents & young adults
N=100

<table>
<thead>
<tr>
<th></th>
<th>Same or worse</th>
<th>Improved</th>
<th>HA-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple disorders</td>
<td>57%</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>Single disorder</td>
<td>15%</td>
<td>46%</td>
<td>39%</td>
</tr>
<tr>
<td>No psych disorder</td>
<td>7%</td>
<td>53%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Association Between Migraine and Depression: IHS- Based Community Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Association</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslau (1998)</td>
<td>Yes</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Migraine with aura</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Migraine without aura</td>
<td>2.2</td>
</tr>
<tr>
<td>Swartz et al (2000)</td>
<td>Yes</td>
<td>2.3</td>
</tr>
<tr>
<td>McWilliams (2004)</td>
<td>28.5% of migraineurs depressed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.3% of subjects without migraine</td>
<td></td>
</tr>
<tr>
<td>Patel (2004)</td>
<td>28.1% of migraine group depressed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19.5% of probable migraine group depressed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.3% of controls depressed</td>
<td></td>
</tr>
</tbody>
</table>

Depressed Patients Will Present With a Constellation of Symptoms

A major depressive episode includes the persistence of at least 5 of the following:

- Suicidal/Death Thoughts
- Slowed Thinking or Impaired Concentration
- Changes in Sleep
- Increased Fatigue
- Loss of Interest, Depressed Mood
- Changes in Appetite
- Feelings of Guilt/Worthlessness
- Psychomotor Retardation or Agitation
- Major Depression
Migraine and Mood Disorders

- There is about a 2.5 to three-fold higher relationship between migraine and bipolar spectrum disorders.
- Bipolar spectrum disorders, MDD, recurrent depression, suicide attempts exhibit a stronger relationship for migraine with aura than for migraine without aura.
- Greater in clinic than community; CM associated with higher levels than EM; higher prevalence in MOH.


---

### Association Between Migraine and Bipolar Disorder: Community Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IHS-Based</strong></td>
<td></td>
</tr>
<tr>
<td>Breslau (1998)</td>
<td></td>
</tr>
<tr>
<td>Bipolar I  Migraine with aura</td>
<td>7.3</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>2.4</td>
</tr>
<tr>
<td>Bipolar II Migraine with aura</td>
<td>5.2</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Non IHS-Based</strong></td>
<td></td>
</tr>
<tr>
<td>Merikangas et al (1990)</td>
<td></td>
</tr>
<tr>
<td>Bipolar spectrum</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Low & Merikangas, 2003
Migraine and Bipolar II disorder

- A comorbid migraine and depression group resembled bipolar II patients more than unipolar depressives.
- The comorbid group had higher number of depressive episodes, increased irritability, increased anxiety disorder.
- Migraine in depressed patients might be a bipolar spectrum trait.
- May be helpful to use a screening instrument, such as Mood Disorders Questionnaire.

Oedegaard and Fasmer, Journal of Affective Disorders, 2005

Association Between Migraine and Anxiety: Community Studies

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Panic</th>
<th>GAD</th>
<th>OCD</th>
<th>Phobia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslau (1998)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>migraine with aura</td>
<td>10.4</td>
<td>4.1</td>
<td>5.0</td>
<td>2.9</td>
</tr>
<tr>
<td>migraine w/o aura</td>
<td>3.0</td>
<td>5.5</td>
<td>4.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Swartz et al (2000)</td>
<td>3.4</td>
<td>--</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Breslau et al (2001)</td>
<td>3.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merikangas et al (1993)</td>
<td>3.3</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McWilliams (2004)</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saunders et al (2008)</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al (2007)</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Smitherman, TA et al. Headache 2013;53:23-45
Anxiety Disorders

- Onset of anxiety generally precedes the onset of episodic migraine, whereas the onset of major depression follows the onset of migraine. Anxiety may appear in childhood, followed by migraine then depression then by CM.
- The lifetime prevalence of anxiety disorders in migraineurs (ranging from 51-58%) is almost twice that of major depression.
- Anxiety disorders may complicate migraine more than depression with greater long-term persistence, greater headache-related disability, and reduced satisfaction with acute therapies. Anxiety is the driver of distress across most emotional disorders.


Anxiety Disorders

- Symptoms common to most all anxiety disorders:
  - Anxiety-related and danger-related cognitions (fear or worry)
  - Physical symptoms
  - Avoidance behaviors (some are very subtle)

- Assessment of physical symptoms and panic is of particular importance with migraine patients
  - As is fear of pain (anxiety about migraine). Overestimate the probability of migraine and perceive it as more unmanageable and threatening than objective reality. Very sensitive to medication side effects and somatic sensations.

Combined Mood and Anxiety Disorders

- Comorbid anxiety in bipolar disorder and MDD is associated with increased symptom severity, poorer treatment response, higher rates of suicidality and increased impulsivity.


Migraine with Anxiety Disorders

- Panic disorder is a chronic condition similar to migraine with episodic attacks of high impairment and interictal worry of future attacks.
- Headache patients with anxiety disorders may develop conditioned fear to somatic sensations that are similar to interoceptive conditioning in panic disorder
Anxiety Sensitivity

- Tendency to notice and fear benign physical sensations due to beliefs that these sensations will have harmful and possibly catastrophic consequences
- Predicts fear of pain and maladaptive avoidance behaviors in HA patients
- Associated with more frequent and disabling headaches as well as greater susceptibility to headache triggers


Psychiatric Disorders in MOH

<table>
<thead>
<tr>
<th>DSM-IV Dx</th>
<th>Precedes MOH</th>
<th>Follows MOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of MDD</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>79%</td>
<td>21%</td>
</tr>
<tr>
<td>GAD</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Social phobia</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>89%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Radat F et al *Cephalalgia* 2005;25:519-522
Headache and Psychiatric Comorbidity (multi-axial examples)

<table>
<thead>
<tr>
<th>Axis I</th>
<th>Axis I</th>
<th>Axis I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>Major Depression</td>
<td>Major Depression</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>Panic Disorder</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axis II</th>
<th>Axis II</th>
<th>Axis II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disorder</td>
<td>No disorder</td>
<td>Borderline personality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axis III</th>
<th>Axis III</th>
<th>Axis III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic migraine</td>
<td>Chronic migraine</td>
<td>Chronic migraine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MOH</td>
</tr>
</tbody>
</table>

Increasing Complexity and Difficulty


Borderline Personality Disorder

- 10% of all psychiatric outpatients and 15-25% of inpatients. There is no evidence that BPD is more common in women.
- In primary care, 4X the prevalence than in the general population, suggesting that individuals with BPD are frequent users of general medical care. PD’s affect 26% of inpatients with refractory CM (most BPD).
- Suicidal gestures, self-injury and unstable relationships most useful for correct diagnosis.
- Suicide risk 20-50X higher than general population.

Borderline Personality Disorder

- More likely to have more pervasive HA
- More HA-related disability
- Lower probability of responding to standard preventative pharmacological therapy
- More prone to medication overuse
Abuse Issues and Migraine

- Migraine appears to be related to childhood maltreatment.
- Headache in abused is more disabling and more likely to “transform” from episodic to chronic.
- Childhood maltreatment was more common in women with migraine and comorbid major depression than in those with migraine alone.
- There is also a growing body of literature supporting an association between migraine and PTSD. The presence of PTSD may increase disability substantially.

Managing Psychiatric Comorbidities

Monotherapy versus Polytherapy

- Idea is to use one drug to treat migraine and associated conditions whenever possible (“two-fer”)
- Simpler, less cost, less AE’s, eliminate potential drug interactions


Two-Fer

- Physicians often alter preferred choice for migraine prevention and comorbidity when both present together.
- There is risk of only treating one condition optimally.
- Emotional benefit of “treating two birds with one stone” often outweighs other factors.
- Physicians often sell value of “treating two conditions with one RX” more than controlling both conditions effectively.

Managing Headaches with Psychiatric Comorbidities

Combination treatment

**Depression**
- Cyclic antidepressants
- SNRI (duloxetine)

**Bipolar disorder** –
- Antiepileptics - Valproate (Depakote), Topiramate (Topamax), Lamotrigine (Lamictal)
- Lithium (Cluster HA)

**Psychosis** – neuroleptics (esp cluster headache)

**Anxiety** – Clonazepam (Klonipin)
Migraine and comorbid disease: Recommended Approach

- Select **best drug** to treat each disorder
- Do not treat migraine with drug contraindicated for other disorder
- Do not use drug for other condition that exacerbates migraine
- Beware of drug interactions
- Pay attention to women of child-bearing potential

“Therapeutic Independence”

- Adjusting a single drug to meet the dosing requirements of 2 separate conditions is tricky. For example, the maximum tolerated dose of a TCA may prove adequate for migraine but not for depression.
  - May require different doses and titration schedules. Anxious patients very sensitive to SE's
- May have better clinical benefit and less side effects if use a different medication for each condition.
- Therapeutic dosing of an SSRI combined with low dose TCA has not been studied in patients with migraine and depression nor has the treatment option of combining an SSRI with an anti convulsant been investigated.

Managing Headaches with Psychiatric Comorbidities

Major Obstacles

• Medication interactions
• Direct effects of medications
• Undertreatment of either can lead to failure of both
• Psychiatric symptoms lead to non-compliance, poor pt-MD relationship, anxiety and sensitivity to medication side effects.

PHQ-2 Screener

### PHQ-4

**Over the last 2 weeks, how often have you been bothered by the following problems?**

(Use “✓” to indicate your answer)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*(For office coding: Total Score I = ___ + ___ + ___)*

Cut score of 3 for first two items similar to full GAD-7

---

**Medication Interactions:**

Cytochrome P450-2D6 Isoenzyme

- Not very abundant but important for metabolism of many psychotropics including SSRI’s and SNRI’s (esp fluoxetine, paroxetine, sertraline) and TCA’s.
- Has limited capacity, and inhibition can render it functionally inoperative.
- Common interaction: TCA levels may increase two-fold after adding fluoxetine.

*Neuropsychobiology 1992;25:202*
### Medication interactions in HA tx

#### CYP2D6 Affected Drugs and Inhibitors

<table>
<thead>
<tr>
<th>Affected Drugs</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic</td>
<td>SSRIs, especially paroxetine and fluoxetine</td>
</tr>
<tr>
<td>Antidepressants (TCA)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
</tr>
<tr>
<td>Narcotics (eg. codeine)</td>
<td></td>
</tr>
</tbody>
</table>

#### CYP3A Affected Drugs, Inducers, and Inhibitors

<table>
<thead>
<tr>
<th>Affected Drugs</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletriptan, ergots</td>
<td>Phenobarbital</td>
<td>Cardizem, verapamil</td>
</tr>
<tr>
<td>Methadone</td>
<td>Phenytoin</td>
<td>Nefazodone</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td>Rifampin</td>
<td>Valproate</td>
</tr>
<tr>
<td>AEDs</td>
<td>Topiramate</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Cyclophosphamide</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Tamoxifen</td>
<td>Azole antifungals, esp. ketoconazole and itraconazole</td>
</tr>
<tr>
<td>Calcium Channel Bl</td>
<td>Dexamethasone</td>
<td>Cimetadine</td>
</tr>
<tr>
<td>Cisapride (Propulsid)</td>
<td></td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td></td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
<td>Protease Inhibitors</td>
</tr>
<tr>
<td>Terfenadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Levin*
Medication interactions in HA tx

**CYP1A2 Affected Drugs, Inducers, and Inhibitors**

<table>
<thead>
<tr>
<th>Affected Drugs</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>Carbamazepine</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Omeprazole (Prilosec)</td>
<td>Quinolone antibiotics, esp.</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Phenobarbital</td>
<td>Cipro</td>
</tr>
<tr>
<td>F-Warfarin</td>
<td>Phenytoin</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Theophylline Antipsychotics</td>
<td>Rifampin</td>
<td>Smoking</td>
</tr>
<tr>
<td>Frova</td>
<td>Char-broiled meats</td>
<td></td>
</tr>
</tbody>
</table>

**CYP2C9 Affected Drugs, Inducers, and Inhibitors**

<table>
<thead>
<tr>
<th>Affected Drugs</th>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>AEDs</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Rifampin</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td></td>
<td>Azole antifungals</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td>Ritonavir (Norvir)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# QT interval prolongation

Meds with tendency to prolong QT interval:

- Neuroleptics – chlorpromazine, droperidol, quetiapine, ziprasidone
- Tricyclic antidepressants- venlafaxine
- Lithium
- Methadone
- Tizanidine
- Diuretics, antiarrhythmics, antibiotics

---

## Antidepressants

<table>
<thead>
<tr>
<th>First generation</th>
<th>Second-generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Tricyclic and tetracyclic antidepressants</td>
<td>-SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, vilazodone (5-HT 1A partial agonist)</td>
</tr>
<tr>
<td>-Monoamine oxidase inhibitors (MAOIs)</td>
<td>-NDRI’s: bupropion</td>
</tr>
</tbody>
</table>

- SNRI’s: venlafaxine, duloxetine, desvenlafaxine, levomilnacipran
- SARI: nefazodone, trazodone
- NaSSA: mirtazapine;
- NRI’s: atomoxetine, reboxetine
- Other: vortioxetine

NaSSA = noradrenaline and specific serotonergic agent; alpha 2 antagonist
SARI = serotonin 2 antagonist/reuptake inhibitor (blocks 5-HT and NE reuptake pumps)
Clinical Tips for Comorbid Depression and Anxiety

- Initiate treatment with agent that is shown to be effective for comorbid anxiety.
- Start with very low dose to minimize anxiety to optimize adherence as these pts. are very sensitive to AE’s.
- Watch for antidepressant induced increase in anxiety symptoms in short run.
- Only use benzos for short-term at treatment initiation and behavioral relaxation-based therapies important.
- Treatment resistance common, higher doses often needed with slow titration, longer time to reach remission, and OFTEN NEED mood and anxiety specific psychological therapies.

After Ravindran, *Psychiatric Times*, 2013
Meta-analysis of new-generation AD’s

Sertraline and escitalopram exhibited the best balance of efficacy and acceptability.

Sertraline, escitalopram, venlafaxine, mirtazapine most effective. **Magnitude of benefit increases with severity and may be minimal with mild-moderate symptoms**

Second-generation not shown to be effective for migraine prevention. TCA’s (amitriptyline) effective in both (off-label for migraine) but many more side effects. Difficult to use TCA’s to meet dosing requirements of both disorders.


**Depression-specific psychotherapies**

There is evidence that their effects may be more enduring than medications. They can be combined with antidepressants to delay time to relapse, help prevent recurrence and improve medication adherence. Cuts the risk of depression relapse by about 50%.

Key skills in psychological therapy for depression

• Increase pleasurable and productive activities ("behavioral activation") from maximizing adherence to exercise to scheduling activities with the potential for enjoyment.
• Counter negative and self-defeating thinking patterns ("cognitive restructuring")
• Enhance interpersonal effectiveness and problem solving skills

Driessen E, Hollon SD *Psychiatr Clin North Am* 2010;33:537-555

Predictors of Bipolarity in Depressed Patients

• Psychotic symptoms
• Family history of bipolar disorder
• Early age of onset and high frequency of depressive episodes
• High frequency of suicidal thoughts
• High rates of divorce, job changes
• History of erratic, impulsive behavior
• A quicker onset or improvement of symptoms
• Pharmacologic-induced mania or hypomania
• Hypersomnia, psychomotor retardation, profound fatigue, overeating more common

Bowden, 2001; Judd, et al, 2002; Frye et al, 2004
Managing Anxiety Disorder

- Exposure treatment to feared stimuli is a hallmark of treating anxiety. Treatment requires a gradual limiting of the avoidance response, tolerating some distress and more prolonged exposure to the feared event which can be external or internal (panic disorder or anticipatory migraine anxiety). Relaxation training may help.
- Cognitive treatment also helps modify danger and vulnerability thoughts to more rational alternatives.

Conclusions

- Numerous medical and psychiatric comorbidities are comorbid with migraine
- Comorbidities are increased with HA frequency.
- Comorbid psychiatric disorders may heighten distress, increase impairment and RX refractoriness and contribute to headache progression and nonadherence to therapies.
- Anxiety confers greater negative impact than depression
- Both migraine and comorbid conditions need to be assessed and treated. Therapeutic independence may be necessary.
Pipeline Pharmacological Treatment for Headache

AAN Emerging Therapies in Headache 2015
Phoenix - January 24, 2015

ALAN M. RAPOPORT, M.D.

Clinical Professor of Neurology
The David Geffen School of Medicine at UCLA
Los Angeles, California

President
The International Headache Society

Founder and Director-Emeritus
The New England Center for Headache
Stamford, Connecticut

---

DR. RAPOPORT'S DISCLOSURES

SPEAKERS BUREAU

- Depomed

ADVISORY BOARD

- Avanir
- Depomed
- Dr. Reddy's
- ElectroCore
- Impax
- Merck
- Teva
- Winston

December 18, 2014
Overview of Future Headache Treatments

- CGRP Receptor Antagonists (olecegepant, telcagepant + BMS, BI)
- Monoclonal antibodies to CGRP or its receptor
  - The re-launch of Zomig in the US; Zolmitriptan oral film
- Sumatriptan Optinose
- Sumatriptan iontophoretic patch
  - Sumatriptan needle-free injection and Auto-Injection
- Inhalers: prochlorperazine, loxapine and DHE
  - Diclofenac K in sachet

Glutamate Receptor Modulators

- Tezampanel, an AMPA/KA antagonists (Glu Inhibitor)
- Perampanel, an AMPA receptor antagonist for prevention
- ADX10059, an mGluR5 modulator or negative allosteric modulator
- LY-466195, a GluK5 receptor antagonist
- Memantine (Glutamate inhibitor) for intractable headache

Overview of Future Headache Treatments

- Botulinum Type A (onabotulinumtoxinA)
- New Preventives (tonabersat and XP13512)

Devices:
  - DBS, ONS, PFO closure, TMS, TNS, SPG STIM, VNS (non-invasive)

- Serotonin_{1F} receptor agonist (COL-144)
  - Large conductance calcium-activated potassium channels (BK_{Ca})
- Glial Activators, attenuators and resolvins

Emerging Targets

- Transient receptor potential vanilloid (TRPV1) receptor modulators
- Nitric oxide antagonism (NOS Inhibitors)
- Gap junction modulators
- Orexin receptor antagonists
- Prostanoid receptor antagonists
- Pannexin1 megachannel opening blockade
- ASIC-3 (acid sensitive ion channel blocker) – amilioride 2
Rationale for CGRP modulation

- Released from trigeminovascular afferents
- Potent vasodilator
- Causes perivascular plasma protein extravasation and nociceptive pain
- CGRP levels elevated in migraineurs
  - Migraine-specific triptans block CGRP release
- CGRP induces migraine-like headache in susceptible individuals
- CGRP enhances transmission of pain signals in the CNS

**BIBN4096BS (Olcegepant)**

*Phase II Trial*

- One phase-II trial (iv preparation)
- Effective in acute migraine vs. placebo
  - 2.5 mg iv
  - 66% 2 hour headache response vs 25% PI
- AEs: mild paresthesia
- Does not constrict blood vessels

Olesen J, Cephalalgia 2003. also NEJM


---

**MK-0974 (telcagepant) phase 3 clinical data**

*Primary outcomes @ 2h*

![Graph showing pain relief, pain freedom, and associated symptoms for Placebo, Telcagepant 150 mg, Telcagepant 300 mg, and Zolmitriptan 5 mg.](image)

- Pain Relief
  - Placebo: 37.7
  - Telcagepant 150 mg: 48.8
  - Telcagepant 300 mg: 65.0
  - Zolmitriptan 5 mg: 96.4

- Pain Freedom
  - Placebo: 9.6
  - Telcagepant 150 mg: 17.2
  - Telcagepant 300 mg: 35.0
  - Zolmitriptan 5 mg: 31.3

- Associated Symptoms
  - Phonophobia: Placebo: 53.8, Telcagepant 150 mg: 65.3, Telcagepant 300 mg: 40.0, Zolmitriptan 5 mg: 67.0
  - Photophobia: Placebo: 51.9, Telcagepant 150 mg: 62.0, Telcagepant 300 mg: 55.3, Zolmitriptan 5 mg: 65.1
  - Nausea: Placebo: 45.3, Telcagepant 150 mg: 51.1, Telcagepant 300 mg: 71.3

*p <0.010, ***p <0.001 for telcagepant-placebo pairwise comparison.
#p <0.001 for telcagepant 150 mg-zolmitriptan pairwise comparison*

CGRP
Monoclonal Antibodies

Four mAbs are being actively developed for the preventive treatment of episodic or chronic migraine
Diagram of sequence for monoclonal antibody production
Key Properties of Antibodies Relevant to Therapy

- **Binding function**
  - Exquisite specificity
  - High avidity from two binding sites
- **Long half life**
  - Weeks to months
  - Liver FcRn receptor
  - Carrier function for other drugs
- **Large size**
  - Unique biological activities
  - Restricted tissue distribution (does not cross the BBB)
- **Effector functions (when killing cells desired)**
  - Complement
  - Fc receptors (ADCC)

### Future Drugs: Preventive Drugs for Migraine
Four injectable monoclonal antibodies to CGRP

<table>
<thead>
<tr>
<th></th>
<th>Amgen</th>
<th>Alder ALD403</th>
<th>Arteaus/Lilly LY2951742</th>
<th>Labrys/Teva LBR101-102</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodic vs Chronic Migraine</strong></td>
<td>Episodic</td>
<td>Chronic</td>
<td>Episodic</td>
<td>Episodic Chronic</td>
</tr>
<tr>
<td><strong>Phase 2 Dosing</strong></td>
<td>Multidose, dose-ranging with OLE</td>
<td>Single dose level</td>
<td>Single dose level</td>
<td>Multi-dose, Dose-ranging</td>
</tr>
<tr>
<td><strong>Phase 2 Administration</strong></td>
<td>Subcutaneous</td>
<td>Intravenous</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Phase 2 Dosing Frequency</strong></td>
<td>Once/month</td>
<td>One treatment</td>
<td>Twice/month</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Target (peripheral)</strong></td>
<td>CGRP receptor</td>
<td>CGRP peptide</td>
<td>CGRP peptide</td>
<td>CGRP peptide</td>
</tr>
</tbody>
</table>
ALD463 Phase 2 Data: Reduction in migraine days in patients with 5-14 migraine days at baseline

Improvement LS Mean Change from Baseline

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo (N=110)</th>
<th>LY2951742 (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-3.0</td>
<td>-4.2</td>
</tr>
<tr>
<td>1</td>
<td>-3.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-2.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-2.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-1.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

LY2951742 Primary Endpoint Phase 2
Reduction in migraine days (patients had 4-14 migraine days/month at baseline)
Everything Old is Back
New Drug Delivery Systems

- DHE
  - Allergan {MAP} Tempo™ inhaler
- Sumatriptan
  - GSK Suma + Naproxen Na (Treximet tablet)
  - Avanir Suma Nasal Powder (Optinose)
  - Zogenix Needle-free Injection (Sumavel DP)
  - Pfizer pen injector (Alsuma)
  - Teva Iontophoretic Patch system (Zecuity)
**OptiNose** technology targets sites in the nose

**Breath powered, Bi-directional Delivery**

- The device consists of a mouthpiece and a sealing nozzle.
- Using the natural function of a patient’s breath enables the soft palate to close, isolating the nasal cavity.
- As the patient continues to blow, the device is triggered, releasing drug into the air flow and carrying it deep into the nasal cavity.
- This positive pressure delivery causes the narrow nasal passages to expand and helps more effectively and reliably carry medication beyond the nasal valve to targeted sites.

---

**OptiNose Phase III**

The Phase 3 regulatory pivotal study on the AVP-825 22 mg is the TARGET study. It is a MC, R, DB, PC, PG single attack study. There were 223 subjects randomized who received treatment (112 AVP-825 and 111 device loaded with placebo).

The primary outcome measure was 2-hour headache relief, which occurred in 67.6% of subjects in the AVP-825 group vs 45.2% in the placebo group ($P < .01$). For headache relief, AVP-825 reached statistically significant separation from placebo earlier than in the Phase 2 trial, this time at 30 minutes (41.7% vs 26.9%; $P < .05$).

Pain freedom at 2 hours occurred with 34% of AVP-825 subjects compared with 17% for placebo ($P < .01$).

Adverse events occurring >5% included abnormal taste (22%), nasal discomfort (13%), and rhinitis (6%). No serious adverse events occurred in the pivotal trial.

Tepper SJ. *Headache* 2013;53:1341-49.
**OptiNose 2-h HA Relief**

![Graph showing percentage of subjects with headache relief over time](image)

* P<.0.05

Adapted from Tepper SJ. Headache 2013;53:1341-49.

---

**Novel Drug Delivery System:**

**Iontophoretic Patch for Sumatriptan Transdermal Delivery**

- **Nupathe NP101** {Teva} **(ZECUITY)** uses iontophoresis or low level electric current to drive sumatriptan across skin in a controlled fashion
- Linear relationship between applied current and drug delivery
- Patches delivering 6 and 12 mA/hr can maintain sumatriptan plasma levels above target level of \( \geq 10 \text{ ng/ml} \) for greater than 7 hours
- AEs include: localized sensations and patch site reactions *no triptan AEs*
NP101 patch (study 005)
Sumatriptan plasma concentration profiles

6 mg sumatriptan subcutaneous injection (n = 23)
20 mg sumatriptan nasal spray (n = 23)
100 mg sumatriptan oral tablet (n = 23)
NP101-I (n = 17)
NP101-II (n = 17)

Zecuity (sumatriptan transdermal patch) Phase III
Efficacy Results

Data presented at 14th Congress of the International Headache Society September 10-13, 2009 (Philadelphia, USA)
Optimized use of DHE with a Proprietary Inhaler from MAP (Allergan)

- Dihydroergotamine Inhalation Aerosol (MAP0004) - Levadex
  - DHE suspended in hydrofluoroalkane (HFA) propellants
  - Orally inhaled with the Tempo® inhaler
    • Proprietary, novel, breath-actuated
    • Expected to deliver most of the drug to the deep lung
    • Minimizes oropharyngeal deposition – lessens cough
  - Phase 2 data suggests an onset of action comparable to IV administration of DHE, with relief that is both rapid and sustained
  - Well tolerated in Phase 2 studies

Phase 1 pK Shows Rapid Uptake of DHE and Similar AUC Versus IV

- Tmax ~ 10 min
- Cmax about 10-13 times lower

Levadex Pain Relief

Proportion of Subjects with Pain Relief

<table>
<thead>
<tr>
<th>Time to Pain Relief</th>
<th>Placebo</th>
<th>LEVADEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>10min</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>30min</td>
<td>22%</td>
<td>29%</td>
</tr>
<tr>
<td>60min</td>
<td>28%</td>
<td>35%</td>
</tr>
<tr>
<td>2hrs</td>
<td>35%</td>
<td>59%</td>
</tr>
<tr>
<td>4hrs</td>
<td>37%</td>
<td>65%</td>
</tr>
<tr>
<td>2-24hrs</td>
<td>20%</td>
<td>44%</td>
</tr>
<tr>
<td>2-48hrs</td>
<td>17%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Primary and secondary endpoints marked in red
+ p=0.0245, * p<0.0001

Note: p-values from exploratory endpoints not adjusted for multiplicity

Levadex Adverse Event Profile

<table>
<thead>
<tr>
<th>Adverse Events ≥ 2% in Any Group</th>
<th>Run-In Period (N=805)</th>
<th>Double-Blind Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=401)</td>
<td>LEVADEX (N=404)</td>
</tr>
<tr>
<td>Number (%) of Patients Reporting at Least 1 AE</td>
<td>140 (17.4%)</td>
<td>101 (25.2%)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>22 (2.7%)</td>
<td>12 (3.0%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 (1.7%)</td>
<td>14 (3.5%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>16 (2.0%)</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.1%)</td>
<td>8 (2.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.1%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4 (0.5%)</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>Social Circumstances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharma Product Complaint (Indication of Taste)</td>
<td>0 (0.0%)</td>
<td>7 (1.7%)</td>
</tr>
</tbody>
</table>

* Symptoms and sensitivities typically associated with triptans, such as chest discomfort (1%), chest pain (0%) and paresthesia (0.5%), were rare and comparable to placebo
* No decrease in pulmonary function (spirometry) compared to placebo group
5-HT$_{1F}$ Agonist COL-144
in the acute treatment of migraine

- NAAMA: Neurally acting anti-migraine agents
- Does not constrict blood vessels
- Phase II trial: **intravenous** COL-144 (2.5 – 30 mg)
- Randomised, single-blind placebo-controlled adaptive design
  - Significant pain relief and pain freedom from 2 hours
  - Significant sustained response
  - No significant AEs
  - Oral solution and tablet forms also effective

Reuter et al. Cephalalgia 2009;29:122

Acute treatment of migraine with the selective 5-HT$_{1F}$ receptor agonist lasmiditan –
A randomised proof-of-concept trial

- **Conclusions:**
  At intravenous doses of 20 mg and higher, lasmiditan proved effective in the acute treatment of migraine. Further studies to assess the optimal oral dose and full efficacy and tolerability profile are completed. The non-vascular, neural mechanism of action of lasmiditan may offer an alternative means to treat migraine especially in patients who have contra-indications for agents with vasoconstrictor activity. The clinicaltrials.gov identifier for this study is NCT00384774.

COLUCID = COL-144

Glial Activator AV411 (ibudilast)

Ibudilast (current development codes: AV-411 or MN-166) is an antiinflammatory drug used mainly in Japan, which acts as a phosphodiesterase inhibitor, inhibiting the PDE-4 subtype to the greatest extent, but also showing significant inhibition of other PDE subtypes. Ibudilast crosses the blood-brain barrier and suppresses glial cell activation. This activity has been shown to make ibudilast useful in the treatment of neuropathic pain and it not only enhances analgesia produced by opioid drugs, but also reduces the development of tolerance.


Glial Activator AV411 (ibudilast)

In phase II trials

- Suppresses the production of pro-inflammatory cytokines (IL-1beta), TNF-alpha, and IL-6
- Enhances the production of the anti-inflammatory cytokine IL-10
- Upregulates the release of neurotrophic factors (i.e. glial-derived neurotrophic factor and nerve growth factor)
- It appears to suppress neuropathic pain
- Developed by Avigen, Inc, recently acquired by MediciNova, Inc.
Welcome to Valencia

IHC 2015
Valencia, Spain

May 14-17, 2015
Spanish Headache Society

(2017 – Brazil, Vancouver, Istanbul ??)

Thanks for your attention!
Injections and Surgical Options for Headache

Carolyn Bernstein MD, FAHS
Clinical Director,
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Attending physician, Departments of Anesthesia and Neurology,
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Assistant Professor of Anesthesia (Neurology),
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• Dr. Bernstein has no disclosures.
The International Classification of Headache Disorders, 3rd edition (beta version)

- Specific guidelines for classification of headaches
- Will use this as framework for discussing therapies
- Should be used in diagnosis
- Available online

Headaches for discussion

- Migraine-episodic and chronic
- Occipital neuralgia
- Tension-type headache
- Cervicogenic headache
- Cluster
• Ona-botulinum toxin A—BoNT-A
• Nerve blocks
• Trigger point injections
• De-activation surgery for migraine

AAN Classification of Evidence

• All studies rated Class I, II, III, or IV
• Five different classification systems
  – Therapeutic
    • Randomization, control, blinding
  – Diagnostic
    • Comparison to gold standard
  – Prognostic
  – Screening
  – Causation
AAN Classification of Evidence for Therapeutic Intervention

- Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Part One—BoNT-A

- Anecdotal: people receiving cosmetic injections were experiencing fewer headaches.
  Patients paying out of pocket, receiving arbitrary injection paradigms.

- FDA approval for migraine—2010
  First medication approved specifically to treat chronic migraine.
Chronic Migraine

- Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

Diagnostic criteria:
A. Headache (tension-type-like and/or migraine-like) on 15 days per month for >3 months and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On 8 days per month for >3 months, fulfilling any of the following:
   1. criteria C and D for 1.1 Migraine without aura
   2. criteria B and C for 1.2 Migraine with aura
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis
What about episodic migraine?

- At this time, no evidence to support efficacy.
- Not evidenced for other headaches although interest exists.

Medication Overuse Headache (MOH)

Description:
Headache occurring on 15 or more days per month:
- developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped.
WHAT CAUSES EPISODIC MIGRAINE TO BECOME CHRONIC MIGRAINE?

Central sensitization

- Mechanism by which episodic migraine becomes chronic
- Both peripheral and central hyperexcitation
- Sensitization of nociceptors results in spontaneous neuronal discharges—change in nociceptive threshold
- Headache. 2011 Jul-Aug;51 Suppl 2:77-83. (Lipton)
• Release of peripheral peptides and glutamate may cause release in CNS.
• Peripheral hyperexcitability leads to allodynia, hyperalgesia.
• Headache transformation becomes increasingly refractory to treatment.
• Migraine can not be explained by one single initiating factor.
• What is mechanism for BoNT-A?

• Semin Neurol. 2010 Apr;30(2):120-30 (Cutrer)

• PREEMPT [Phase III REsearch Evaluating Migraine]
• PREEMPT 1—1384 patients, double blind, 24 weeks
• PREEMPT 2—607 continued into 36 week open label phase
• Multiple variables: days of headache, days of migraine, acute events, improvement in overall disability
results

• Statistical reduction in headache-day frequency at week 56 (-11.7 to -10.6 in placebo)
• Also decrease in headache days, severity and headache hours
• Headache. 2011 Oct;51(9):1358-73 (pooled analysis)

• Set template, 155 units, up to 195, administered every 90 days up to and including 5 cycles (56 weeks)
• Patients treated with BoNT-A had significantly fewer migraine and headache days, decreased disability, less likely to use triptans
• Relatively few side effects (neck pain and muscle weakness)
• PREEMT 2 achieved primary end-point: reduction of headache days
• Significant improvement for all secondary end-points (migraine days, headache days, hours of headache, severe HIT-6 scores.)
• Patients with MOH did better than those without—difficulties of managing chronic migraine without abortive medications.

• Difference small but statistically significant.
• Few options for these patients.
• Generally safe and well-tolerated.
Patient selection—Imploding vs. Exploding Pain

- Described by Rami Burstein PhD
- Is the pain pressure building inside of skull—exploding?
- Or outside of head—crushing sensation
- Eye-popping pain

- The exploders are less likely to be BoNT-A responders.


Proposed mechanism

- BoNT-A blocks acetylcholine release at neuromuscular junction—but this is unlikely to be only mechanism in treating chronic migraine.
- BoNT-A likely prevents release of inflammatory mediators including substance P, glutamate and CGRP.
- Toxin may work due to both decreasing motor activation and hyperexcitability and has both central and peripheral mechanism that suppress sensitization.
FPP and FTP

• BoNT-A is diluted and injected in 0.1 mL amounts (5 units per injection).
• Standardized template of 31 sites—fixed point protocol.
• Occipitalis/cervical paraspinals/trapezius/temporalis/frontalis/corrugator/procerus.
• Addition 40 units may be injected in “follow the pain pathway” up to 195 total units.
• May be injected every 90 days/12 weeks.

exclusions

• myasthenia gravis, Lambert-Eaton, trouble swallowing
• Pregnancy—class c
• Allergies to albumin

Relatively small dose, serious side effects rare
Logistics of obtaining approval

• Arbitrary, varies by health insurance
• Little else, other than topiramate
• Trials of other medications or justification why not used
• Must meet chronic migraine diagnostic criteria

Practical elements

• Physical location
• Average time 10-15 minutes per patient
• Data collection, some insurers require
• Approval, time to obtain
• How long to treat—at 8-12 rounds, evaluating for when to stop
• Intervals between treatments
• Concluding the treatment—conversion back to episodic migraine
• Reduction/elimination of MOH

Nerve blocks
• Regional injection of anesthesia in order to block transmission of pain
• Bupivacaine, with or without steroids
• Bridge technique until preventive therapy demonstrates efficacy
• May be abortive treatment
• Pain specialist or neurologist
cluster

- At least five attacks fulfilling criteria B–D
- Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
- Either or both of the following:
  - 1. at least one of the following symptoms or signs, ipsilateral to the headache:
    - a) conjunctival injection and/or lacrimation
    - b) nasal congestion and/or rhinorrhea
    - c) eyelid oedema
    - d) forehead and facial sweating
    - e) forehead and facial flushing
    - f) sensation of fullness in the ear
    - g) miosis and/or ptosis
  - 2. a sense of restlessness or agitation. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
- Not better accounted for by another ICHD-3 diagnosis.

Occipital neuralgia

- Unilateral or bilateral pain fulfilling these criteria
- Pain is located in the distribution of the greater, lesser and/or third occipital nerves
  Pain has two of the following three characteristics:
  1. recurring in paroxysmal attacks lasting from a few seconds to minutes
  2. severe intensity
  3. shooting, stabbing or sharp in quality
- Pain is associated with both of the following:
  1. dysesthesia and/or allodynia apparent during innocuous stimulation of the scalp and/or hair
  2. either or both of the following: a) tenderness over the affected nerve
  3. trigger points at the emergence of the greater occipital nerve or in the area of distribution of C2
- Pain is eased temporarily by local anaesthetic block of the affected nerve
- Not better accounted for by another ICHD-3 diagnosis.
Indications and types of headache

• Cluster headache—data exists: two double-blind, placebo-controlled studies supporting efficacy and safety for occipital nerve blocks.
• Consensus statement 2012, AHS
• Migraine, Chronic tension-type headache, cervicogenic headaches, occipital neuralgia—studies going forward

• Occipital
• Auriculo-temporal
• Supra-orbital

• May last hours/days/weeks
• Safe, well-tolerated, may be painful
• More data needed for subgroups to properly evidence

Trigger point injections

- Three types—anesthetic/steroid/needle only
- Performed at palpable “trigger point”, bands of tight muscle
- Well-tolerated, generally safe during pregnancy
- Lack of specific evidence

- Multiple types of headache including chronic migraine, cervicogenic, tension-type
Migraine de-activation surgery

• Initially reported by Dr. Bahman Guyuron, plastic surgeon—patients noting fewer migraines after cosmetic facial surgery
• Surgery removes muscle or a piece of the trigeminal nerve.
• Few studies, questions about selection, randomization.
• Study design and methodology flawed.
• Plast Reconstr Surg. 2011;127:603-608 (five year data)

• Patients evaluated for diagnosis
• Treated with 25 units of BoNT-A at the site of pain to decrease the muscle spasm
• Responders had actual surgery vs. sham surgery with exploration only for 12 year study.
• Five year study looked at responders to BoNT-A plus surgery to saline injections only.
• How might the surgery work?
  – Decreasing entrapment of nerve which has triggered migraine
  – Placebo effect
  – Treating other pain processes then migraine

• Debate at 2013 AHS scientific session
• Headache: The Journal of Head and Face Pain
  Volume 54, Issue 1, pages 142–152, January 2014
Moving forward with non-medication therapies for headaches

- Proper study design
- Consistent end points
- Use ICHD 3 diagnoses
- Factor in MOH
- Translational research
Emerging Therapies in Headache
AAN Phoenix – 2015

Neuromodulation

Morris Levin, MD
Professor of Neurology
Director, Headache Center
UCSF Department of Neurology

AAN Emerging Therapies in Headache 2015:

• 1:00-1:15 Intro and Overview of Challenges in HA Classification and Diagnosis - Morris Levin, MD, FAAN
• 1:15-1:55 Comorbidities as treatment guides - Steven Baskin, PhD
• 1:55-2:25 Pipeline pharmacological treatment for HA - Alan Rapoport, MD
• 2:25-3:05 Injections and surgical options for HA – Carrie Bernstein
• 3:05-3:45 Neuromodulation for HA - Morris Levin, MD, FAAN
• 3:45-4:00 Q and A
• 40 min talks, Q&A at end
Stimulation for HA

- Occipital nerve
- Sphenopalatine ganglion
- Vagal nerve
- Deep brain stimulation
- Transcranial magnetic

Occipital n stim

- Rationale – occipital nerve blockade seems to help migraine, cluster and other headaches
- Mechanism may involve an alteration in nociceptive traffic in the trigeminocervical system
Occip n stim in migraine

3 studies, none reached primary endpoint, all had methodological issues,
– Lipton PRISM, only available in abstract form: 1 endpoint reduction in migraine days/month not significant @ 12 weeks versus sham
– Saper ONSTIM2: no primary endpoint pre-specified; adjustable stimulation, no sham group (vs medical management), 39% had 50% drop in frequency or 50% drop in severity
– Silberstein et al, 20123, St Judes Genesis system: no blinding and negative for the 1 endpoint, a difference in responder % of a 50% drop in mean daily VAS at 12 weeks; There was a drop of 30%, HA days, disability, & pain relief


Occip n stim in Cluster

4 studies, none reached primary endpoint, all had methodological issues
• Schwedt CCH 3 patients 2 had >50% decr in freq or severity
• Magnis CCH 8 pts 5 had >50% decr freq
• Burns CCH 8 pts 3 had “ “
• de Quintana CCH 4 pts, 2 had “ “

Occip n stim

• ICON study – a prospective multi-center international DBRCT to follow attack freq in CCH patients with high and low amp stim.
• Hypothesis – there is a dose response relationship
• Design is aimed at avoiding unblinding of sham – subjects cannot distinguish between low and high amplitude stimulation.
• Primary outcome measure is the mean number of attacks over the last four weeks.


Occip n stim - Summary

• Primary barrier to establishing evidence:
  Sham control almost impossible to construct so the effect is confounding
• Complications
  – Surgical complications – Intraoperative hypotension etc; incision site complications – abscesses etc
  – Electrode migration, lead erosion
  – Uncomfortable paresthesias
  – Lead Infection
  – Neck stiffness
  – Hemorrhage around pulse generator (e.g. abd)
  – Battery failure, lead breakage/failure
Sphenopalatine ganglion stim

The sphenopalatine ganglion (aka pterygopalatine ganglion) contains sensory fibers that contribute to the maxillary branch of the trigeminal nerve, as well as both parasympathetic and sympathetic fibers.

SPG stim proposed for Migraine and Cluster

SPG modulation rationale in Cluster

- The parasympathetic outflow from the superior salivatory nucleus to the sphenopalatine (pterygopalatine) ganglion (SPG) and from there, after synapsing, to target organs of eye and sinuses is felt to be the pathway for most of the autonomic features of cluster.
- Sympathetic fibers transit the SPG (without synapsing), and some cluster attacks manifest a partial Horner’s, suggesting sympathetic paresis.
- Sphenopalatine ganglion blocks and even ablation have been used to treat refractory cluster.
- Stimulation of the SPG has been tried in the hopes of creating an inhibitory information block or reproducing the effects of ablation, but with reversibility.
SPG modulation rationale in migraine

• Parasympathetic outflow through the SPG may also be a target - efferents from the SPG innervate the dura and meninges, and initiate peripheral pain mechanisms of migraine, including neurogenic inflammation and vasodilation
• SPG blockade has been used to terminate migraine clinically

SPG Stimulation

• Miniaturized implant
• No battery or software
• Powered and controlled externally by patient
• No need to recharge or replace the implant
• Allows physician to set and quickly adjust therapy as needed using laptop
SPG Stimulation

• Trans-oral implantation with remote controller

![Image of SPG stimulation implantation]

SPG stim for migraine

• 10 patients with migraine: temporary SPG stimulator placed. Migraines or exacerbations of migraine off baseline were triggered with alcohol or odors. Then, SPG stimulation or sham was administered.

• Two of the studied patients had episodic migraine, while 8 had MOH and secondary CM. One patient responded to sham stimulation, making interpretation of response difficult. Two patients had complete abolition of their induced headaches within 3 minutes of SPG stimulation, 1 each with episodic migraine and MOH. Three had reduction in pain, and 5 had no response. Reduction and elimination of pain were accompanied by reduction in nausea and photophobia to the same extent. Five patients had no pain relief.

• Studies on whether acute SPG stimulation can terminate episodic migraine attacks reliably are underway at the time of this writing.

SPG stim for migraine

- Tepper in 2009: 10 patients with migraine had temporary SPG placed
- Migraine induced by a trigger, then had sham or stim
- 2 patients had complete abolition of HA within 3 minutes
- 3 had reduction in pain, and 5 had no response.
- 1 responded to sham


SPG stim for Chronic Cluster HA

Randomized, controlled, blinded, prospective multi-center study
- Minimum 4 attacks/week, dissatisfied with current treatment
- Random insertion of placebo study design
- Initial 28 patient results published this year in Cephalalgia, another 11 recruited subsequently
- Final N = 38 patients; 769 cluster attacks treated presented at IHC Boston June 2013

Results of SPG stim for Cluster

- Pain Relief at 15 minutes (T15) was achieved in 55% of full stimulation treated attacks (vs. 6% sham p<0.0001) (n = 566 CH attacks)
- Acute medications were used less often with stimulation vs. sham
- 42% (16) of patients had 89% reduction in attack
- frequency vs. baseline


Results of SPG stim for Cluster

High amplitude stim v. low amp stim
- Low frequency neurostimulation of the SPG induces immediate cluster-like headache attacks with autonomic symptoms: it activates stimulation
- High frequency neurostimulation of SPG can terminate cluster attacks or prevent cluster headache: it depletes activation, causes an information block, or somehow inhibits outflow

Results of SPG stim for Cluster

Conclusions:
• Good evidence for SPG to abort a cluster HA
• Fair evidence that it can be effective prophylactically


SPG stim AEs

• Adverse events are similar to those reported in other oral procedures
• 81% transient, mild/moderate loss of sensation in maxillary nerve regions;
• 65% of events resolved within 3 months
Vagal nerve stimulation

• Rationale – central projections of the vagus include nucleus and tractus solitarias, parabrachial nucleus, hypothalamus, amygdala, intralimbic cortex, ventroposterior thalamic complex, insula, thalamic nuclei, and other cortical areas.
• Many involved in the production of migraine

Vagal nerve stim

• ElectroCore
Open label Acute treatment of Migraine pilot study, nVNS

- 2h headache relief/attack: 58% (46/79)
- 2h pain free: 28% (22/79)
- Of 26 patients 20 (77%) responded for at least one treated headache
- Among this subset of 20 patients 47/61 (77%) of their treated headaches responded.
- Treatment related adverse effects:
  - Transient muscle or local tissue irritation
  - 2 reports of light headedness
  - Most resolved immediately after treatment, and all within two hours of treatment


Open label studies VNS in Migraine

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th># treated</th>
<th>Efficacy</th>
<th>Significant adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hord et al.</td>
<td>EM</td>
<td>4</td>
<td>75% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Mauskop et al.</td>
<td>CM</td>
<td>4</td>
<td>25% had &gt;50% decreased frequency</td>
<td>25% could not tolerate</td>
</tr>
<tr>
<td>Ceccini et al.</td>
<td>CM</td>
<td>4</td>
<td>50% had &gt;50% decreased frequency</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Total Number Treated for Migraine: 12
Number Responding: 6
Percentage of Responders: 50%
Open label Treatment of Cluster

**Acute Use: 21 pts Abortive Effect**
About 64% of attacks treated with nVNS
Estimated mean of 47% *terminated within 15 min*
About 27% improved within 15 min
Persistent effect in those followed 6 & 12 mos
4 (2 chronic) able to stop all acute meds
2 stopped O2; 10 reduced it by an about
55%, 3 used the same amount; 1 started O2
4 stopped triptans; 10 reduced triptan use by an estimated 48%


---

Open label Treatment of Cluster pilot study, nVNS

**Preventive Use: Frequency Reduction**
20/21 patients had full frequency data available for analysis
Significant in 24-hour attack frequency
Pre-nVNS mean: 4.68 (SD 2.36)
(F1,18 = 20.137, *p < 0.0005, two-way mixed ANOVA)
With-nVNS mean: 2.54 (SD 2.12)

Open label Treatment of Cluster pilot study, nVNS

Subjective Summary
- 9/21 Very Satisfied
- 9/21 Satisfied
- 2/21 Equivocally Satisfied
- 1/21 Dissatisfied
- All would recommend nVNS to other cluster headache patients


VNS AEs

Adverse events reported include:
- Local discomfort
- Mild skin reaction to gel
- Worsening of pain – rare

- 4 RCTs are underway, for acute and preventive treatment of Cluster, and prevention of Chronic Migraine
- CE mark in Europe for ElectroCore device, approved in Canada
DBS for cluster HA

Rationale (Leone) – A positron emission tomography (PET) study has shown that the posterior hypothalamus is activated during CH attacks, suggesting that hypothalamic hyperactivity plays a key role in CH pathophysiology. On this basis, stimulation of the ipsilateral posterior hypothalamus was hypothesized to counteract such hyperactivity to prevent intractable Cluster headache.

Evidence – only uncontrolled cases or series


DBS for Cluster

• Ten years after its introduction, hypothalamic stimulation has successfully prevented attacks in more than 61% of 59 hypothalamic implanted drug-resistant chronic CH patients. Turning it off without pt knowing seems to lead to attacks
• Oculomotor disturbance & vertigo was the limiting factor for voltage increase in all patients
• 42 days mean to effectiveness
• One death (Belgium); TIAs, strokes, hemorrhages described

DBS for TAC

- One case report, 2009, for PH1
- Two case reports for SUNCT (2005, 2009) 2, 3

Transcranial Magnetic Stim (TMS)

- Rationale – disrupting the wave of CSD
TMS for Migraine

Misra 2013 – preventive treatment of migraine
- TMS vs sham, n=100, episodic migraine, with or without aura >4 attacks/month, no prevention
- outcome measures: HA frequency and severity drop of 50 % by Visual Analogue Scale (VAS), functional disability, use of rescue meds, HA severity, and AEs
  - At 1 month:
    - HA frequency (78.7 vs. 33.3 %; P = 0.0001)
    - VAS score (76.6 vs. 27.1 %; P = 0.0001)
    - Functional disability & HA severity also improved
  - 1 patient withdrawn due to drowsiness, 2 lost to follow-up
Misra et al. J Neurol. 2013

TMS for Migraine

Lipton 2010 - acute migraine with aura treatment, n=164:
- MA treated 1 attack with TMS (n=82) or sham (n=82)
- 2 h pain free significantly higher with TMS (32/82 [39%]) than with sham stimulation(18/82 [22%]), no significant AEs
- Effects seemed sustained
- No apparent acute response for migraine without aura
- 71% of sham group and 67% of TMS group believed it was the active tx
- AEs rare – aphasia, vertigo
TMS for Migraine

• N=42, open label, two brief pulses, 5 sec apart
• Pain levels were recorded pre-stimulation, and at poststimulation at 5-min intervals for 20 minutes
• 69% showed improvement by 1 point on a 1-5 scale in 1 trial
• Mean ↓ pain intensity 75%
• “In individuals with an aura, relief was 100% and immediate”
• Mean time to improvement ~10-20 min
• 32% pain-free at 24 hours


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TMS for Migraine

• 123 patients (MO and MA) sTMS for ≥3 months, 69 completed ≥1 survey, and 42 completed 2–3 surveys
• Pain reduction maintained or improved over the treatment period in 74% of patients.
• Associated symptoms were improved in 63% of patients or for some, did not develop after treatment
• 58% (40 of 69) reported ↓ attack duration, and these patients reported a 63% ↓ in headache days over the 12-week treatment period- preventive effect?
• Well tolerated with no serious adverse events reported

Bhola et al. (Goadsby). *Cephalalgia* 2013, 33:973
TMS for depression

• Neuronetics NeuroStar ® TMS system approved in 2012 by FDA for major depression
• 1 hour daily
• HF can → Seizure

Supraorbital nerve stimulation

Schoenen 2013
“Double blind, randomized, sham controlled”
67 patients, 5 Belgian HA clinics
20 min daily for 3 months verum and sham
50% improvement found in 38% v. sham 12%
Therapeutic gain similar to oral proph meds but questions about blinding

Supraorbital nerve stimulation


Neurostimulation in HA

- **ONS**
- **SPG**
- **VNS**
- **TMS**
- **DBS**

- Some suggestive evidence supporting Occipital Nerve stimulation in migraine and cluster headache, SPG stim in acute cluster, and TMS in migraine
- Further blinded, sham-controlled studies are needed