Migraine

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Recent Advances in Neurology
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Headache
International Classification of Headache Disorders-II

I- Primary
1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
   3.1 Cluster headache
   3.2 Paroxysmal hemicrania
   3.3 SUNCT
4. Other Headaches
   4.1 Primary Stabbing
   4.2 Cough Headache
   4.3 Exertional headache
   4.4 Sex headache
   4.5 Hypnic headache
   4.6 Primary Thunderclap Headache
   4.7 Hemicrania continua

II Secondary

- infection
- hemorrhage
- trauma
- tumour
- CSF pressure change

III Cranial neuralgias/facial pain

- trigeminal neuralgia
- glosopharyngeal neuralgia
- occipital neuralgia

Migraine
Age Specific Prevalence in the United States

(Lipton et al., Headache 2001; 41:646-657)

Headache Group, UCSF
Disclosure- by proportion*

• Sandler Family Trust
• UCSF Medical Center
• Governments: California, Germany, Australia
  • Industry: MSD/GSK/Medtronic/Boston Scientific/MAP
  • Consulting/reviews: Amgen, Almirall, ATI, Belgian Research Council, BMS, B-l, Générix, Cipla, E- Lilly, European Space Agency, Fidelity Foundation, Medical Research Council UK, Migraine Research Foundation, Migraine Trust, Minister, Netherlands Research Council, Neuralee, Neuraxon, NHMRC, NINDS, NTP, OUCH-UK, Pfizer

*Font scale for direct contributions in proportion to contribution Q1-10 to Q4-10
(Font ~ {Contribution/Total Group Income} * 100)
**Migraine**

The Attacks & the Disorder

**Attacks**
- Premonitory symptoms
- Pain
  - unilateral
  - throbbing
  - movement worse
- Nausea
- Sensory sensitivity
  - photophobia
  - phonophobia
  - osmophobia
- Aura

**Disorder**
- Repeated attacks
  - < 15 days/month: Episodic
  - ≥ 15 days/month: Chronic
- Family history
- Triggers (biology)
  - Sleep: missing/excess
  - Food: skipping meals
  - Chemical: alcohol or nitroglycerin
  - Weather
  - Sensory: light, smells
  - Hormonal
  - Stress - relaxation

“The simple headaches have the same characters, and occur under the same causal conditions of heredity &c, as those in which there are additional other sensory symptoms”

Gowers 1893

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**Migraine - Update**

- Genetics
- Disorder mechanisms
- Treatment

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**Genetics of Migraine**

Familial Hemiplegic Migraine: an ionopathy

- FHM-I CACNA1A:
  - P/Q voltage-gated Ca$^{2+}$ channel chr 19
  - Ophoff et al. Cell 1996; 87:515

- FHM-II ATP1A2:
  - Na$^{+}$/K$^{+}$ ATPase chr 1q23
  - De Fusco et al. Nat Gen 2003;33:192

- FHM-III SCN1A:
  - Voltage-gated Na$^{+}$ channel chr 2

- New migraine genes
  - Anttila et al., Nat Gen 2010: online

- Migraine
  - GWAS - cases: 3202; controls: 40062
  - Flanking genes around allele (8q22.1) involved in glutamate homeostasis

- Sporadic Hemiplegic Migraine
  - 11 yr male with hemiplegic migraine
  - SLC1A3 - glial glutamate transporter EAAT1

- Freilinger et al., J Headache Pain 2010;11[1]:90
**TRESK mutation & familial migraine with aura**

- Two-pore domain (K2P), *TWIK*-related spinal cord K channel- TRESK (KCNK18)
- TRESK K2P: CNS channel target by volatile anesthetics & neuroprotective agents
- Activated by calcineurin after Gqα stimulation and increased Ca2+

*TWIK- tandem of P domains in a weak inwardly rectifying K+ channel*

**Migraine frequency and CVS risk in females**

- Meta-analysis
- Risk adjusted for BP, age, smoking, BMI, cholesterol, family history
- Highest risk for stroke: females, migraine with aura, <45, smoke & O/C

(Schurks et al., BMJ 2009;339:b3419)

**Changes (lesions) in the Migrainous Brain?**

**CAMERA-I**

- Follow-up
  - 8.5 (7.9-9.2) years
  - Controls (n=83/140)
  - MwA (114/162)
  - MwoA (89/134)

- “Lesions”
  - None vanished
  - Anterior circulation: no change
  - Posterior circulation:
    - Ctrl: no new changes
    - Migraine: in females only, deep white matter volume increase of 2.1 (1.1-4.2) ml greater risk in MwoA
  - Cognitive testing
    - No significant change cf controls

**CAMERA-II**

Kruit et al., Brain 2005;128:2068

**Migraine - Update**

- Genetics
- Disease mechanisms
  - Premonitory symptoms
    - The neck
    - Functional neuroimaging
- Treatment
**Migraine**

*The Premonitory Phase*

![Graph showing time course of symptoms in migraine premonitory phase](image)

- premonitory
- headache
- postdrome

(Tiedtke et al., Neurology 2003;60:935-940)

**Dose-dependent dopaminergic modulation of trigeminocervical complex neurons**

![Graph showing dose-dependent modulation](image)

**A11 Modulation of Trigeminocervical Neurons**

- Stimulation
- Lesion

![Images of neuronal firing](image)

**A11 facilitation of trigeminocervical neurons can be reversed by a triptan, 5-HT\_1B/1D receptor agonist**

![Images of neuronal modulation](image)

(Charbit et al., J Headache Pain 2010;11[S1]:20)
Migraine - *Update*

- Genetics
- **Disease mechanisms**
  - Premonitory symptoms
  - The neck
  - Functional neuroimaging
- Treatment

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Migraine and the Neck

Reflected Pain in the Trigeminocephalocervical Complex (TCC)

Bartsch & Goadsby
Current Pain and Headache Reports 2003;7:371-376

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Migraine and the pons

Nitroglycerin-triggered

Spontaneous

Bahra *et al.*
Lancet 2001;357:1016-1017

Afridi *et al.*
Arch Neurol 2005;62:1270-1275
Brainstem activations in right and left-sided headache with PET

Afridi et al., Brain 2005; 128:932-939

Motor cortex activation versus functional connectivity

Biswal et al. 1995

Connectivity networks identified by ICA

Sensorimotor network

Visual network

Auditory network

Salience network = affective pain network

Default mode network

Sprenger et al., 2010

Results: Migraineurs ≠ Controls

Sensorimotor network

Visual network

Auditory network

Salience network = affective pain network

Default mode network
Migraine - Update

- Genetics
- Disease mechanisms
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Trigeminovascular System & Migraine

(Goadsby et al., NEJM 2002; 346:257-270)

Ergot Alkaloid (tetracyclic ergoline) Family Tree

Acute Treatment of Migraine with Sumatriptan and Naproxen

- Double-blind randomized parallel group single attack adult migraineurs

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Naproxen 500 mg</th>
<th>SumaRT 85 mg</th>
<th>SUMA+Npx</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>15</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>16</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>9</td>
<td>17</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

- pain free 2hr

Brassard et al, JAMA 2007;297:1443
SumaRT+Nap

Ferri et al, Lancet 2001;358:1668
sumatriptan
**Acute Treatment of Migraine with Sumatriptan and Naproxen**

- Double-blind randomized parallel group single attack adult migraineurs
- Placebo, Naproxen 500 mg, SumaRT 85 mg, SUMA+Npx

**AEs**
- Nausea
- Somnolence
- Dizziness
- Paresthesia
- Dyspepsia

**Acute Treatment of Migraine with Oral diclofenac potassium in acute migraine**

- Double-blind parallel group randomised placebo-controlled trial
- Migraine with/without aura; preventive ok; 1-6 attacks/month

**Oral diclofenac potassium in acute migraine**

- Placebo, 50 mg
- Nausea, Dizziness, Dyspepsia

**Transdermal sumatriptan for migraine**

- Randomised double-blind placebo controlled study
- Subjects: migraine with & without aura
- Primary endpoint: 2 hr pain free

**Needle-free sumatriptan injection**

- Needle-free injection: powered by N₂
- Bioequivalent: when injected onto abdomen/thigh not arm
- Delivers: sumatriptan 6mg s/c not IMI
**Ergot Alkaloid (tetracyclic ergolene) Family Tree**

- Ergotamine
- Dihydroergotamine
- Sumatriptan
- Erglina
- Ergotamine analogs
- Erglina analogs

**Dihydroergotamine by inhalation (MAP0004) in the treatment of acute migraine**

- Randomised double-blind placebo controlled study
- Primary endpoint: 2 hr pain relief

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo</th>
<th>DHE - 0.5mg (actual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Cough</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Taste</td>
<td>1.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

(Silberstein et al., Cephalalgia 2009:29)

**Lasmiditan, 5-HT1F receptor agonist, in the acute treatment of migraine**

- Randomised, single-blind placebo-controlled adaptive design
- Specific agonist: 500 fold less affinity at 5-HT1D than 5-HT1F receptors
- No detectable 5-HT1B receptor agonist activity in vivo, e.g., rabbit saphenous vein

Ferrari et al., Cephalalgia 2010:30:1170
Trigeminovascular System & Migraine

5-HT\textsubscript{1D} and CGRP

Hou et al., Brain Res 2001;909:112-120

Trigeminal Activation & CGRP

Trigeminal ganglion

Superior Sagittal Sinus

Cat

Human

Ann Neurol 1988;23:193

Neuropeptides 1990;16:69

Calcitonin Gene-Related Peptide (CGRP) and Migraine

- CGRP is released in the cranial circulation in migraine\textsuperscript{1}
- BIBN4096BS (olecegepant), a CGRP receptor antagonist, is effective in migraine\textsuperscript{2}

Calcitonin/Calcitonin gene-related peptide (CGRP) Receptor Family

<table>
<thead>
<tr>
<th>Ramp</th>
<th>Agonist</th>
<th>Telcagepant nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLR</td>
<td>CGRP</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>adrenomedullin</td>
<td>100,000</td>
</tr>
<tr>
<td></td>
<td>adrenomedullin</td>
<td>29,000</td>
</tr>
<tr>
<td>CTR</td>
<td>amylin</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>amylin</td>
<td>100,000</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Goadsby et al., Ann Neurol 1990;28:183
\textsuperscript{2}Olesen et al NEJM 2004;350:1104
CGRP receptor antagonist telcagepant is effective in the treatment of acute migraine

- Double-blind parallel group randomised controlled trials
- Two hour pain free

Ho et al., Lancet 2008;372:2115
Connor et al., Neurology 2009;73:970
Ho et al., IHC 2009

CGRP receptor antagonist BI44370 is effective in the treatment of acute migraine

- Double-blind parallel group randomised placebo-controlled trial
- Migraine with/without aura; no preventives; 2-8 attacks/month

Diener et al., Cephalalgia 2011;41

Trigeminocervical nociceptive transmission is inhibited by Triptans & CGRP receptor antagonists

Periaqueductal Gray Matter (PAG)
Ergot, Triptan, CGRP and P/Q Ca²⁺ channel actions converge
### Chronic Daily Headache*

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chronic migraine</td>
<td>• Intracranial lesions</td>
</tr>
<tr>
<td>2. Chronic tension-type headache</td>
<td>• Post-traumatic</td>
</tr>
<tr>
<td>3. Chronic TACs</td>
<td></td>
</tr>
<tr>
<td>3.1 Chronic Cluster Headache</td>
<td></td>
</tr>
<tr>
<td>3.2 Chronic Paroxysmal Hemicrania</td>
<td>• Inflammatory</td>
</tr>
<tr>
<td>3.3 Chronic SUNCT</td>
<td></td>
</tr>
<tr>
<td>4. Chronic Other</td>
<td>• Dural irritation</td>
</tr>
<tr>
<td>4.5 Hyptic headache</td>
<td></td>
</tr>
<tr>
<td>4.7 Hemicrania continua</td>
<td>• CSF pressure changes</td>
</tr>
<tr>
<td>(* ≥15 days/month of headache)</td>
<td>• Trigeminal neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Chronic Migraine

A. Headache frequency ≥15 days for ≥3 months
B. Patient with at ≥5 attacks of migraine without aura (MWoA) in the past
C. On ≥8 days per month for three months has
  1. typical MWoA
  2. Attacks treated and relieved by triptans/ergots
D. Not attributed to another disorder, particularly no medication overuse

(Olesen *et al.*, *Cephalalgia* 2006;26:742-746)

### Migraine Classification

- **Feature full headache**
  - Throbbing, unilateral, photophobia, phonophobia, movement effect

- **Is there Medication Overuse?**
  - Analgesics ten days or more per month

- **Is there headache on 15 days or more per month?**

- **Episodic Migraine**
- **Chronic Migraine**
  - (15+ days/month)

### Levetiracetam in Chronic Daily Headache

- Double-blind randomised placebo-controlled crossover trial
- CDH: migraine (74%) and tension-type headache (37%)
- **Issues**: drop-out and ordering effects

![Graph showing headache free rate and loss of CDH criteria](Beran & Spira Cephalalgia 2011:41)
Can preventive treatment stop the development of chronic migraine?

- Double-blind randomised placebo-controlled parallel-group trial
- Recruited patients with high frequency episodic migraine (9-14 days)
- Treated for six months

![Graph showing reduction in migraine days and headache days for Placebo and Topiramate 100mg/day](Lipton et al., Cephalalgia 2011;31:18-30)

Botulinum Toxin A (Botox-A) in the preventive management of chronic migraine… in context

- 18-65 yrs, baseline one month/ 50% days migraine/probable migraine
- **Primary endpoint**: headache episodes baseline vs last four weeks (20-24)
- **Result**: I- NS, II- significant; I/II Headache days/migraine days- significant

![Graph showing reduction in migraine days for Botox-A and Topiramate](Aurora et al., Cephalalgia 2010;40:793; Diener et al., 2010;40:804; Silberstein et al., Headache 2007;47:170)

Migraine a systems disorder

![Diagram showing the brain structures involved in migraine (after Goadsby et al., NEJM 2002; 346:257-270)]

Botulinum Toxin A (Botox-A) in the preventive management of chronic migraine

50% responder rates

![Bar chart showing 50% responder rates for Placebo, Botox-A, and Topiramate](Aurora et al., Cephalalgia 2009;29 *P < 0.05; IHC 2009)
Valproate but not Gabapentin inhibits thalamic trigeminovascular transmission


Occipital nerve stimulation in chronic migraine

ONSTIM

• Double-blind randomized parallel group sham stimulation controlled study
• Note: occipital pain, fail 2 preventives, exclude MOH

(Saper et al., Cephalalgia 2011; in press)

P = 0.032; **P = 0.003

Occipital nerve stimulation in migraine & chronic migraine- PRISM

• Double-blind randomized parallel group sham stimulation controlled study
• Migraine ≥6 days/month or chronic migraine (ICHD-II)
• Failed two preventives/two attack treatments

(Lipton et al., Cephalalgia 2009;29:30)

Effect of ONS on Chronic Migraine

Brain 2004;127:220-230

-Adverse event: non-target sensory symptoms
Transcranial magnetic stimulation for Migraine

- Randomised double-blind placebo controlled study
- Include: 30% aura episodes, aura leads to headache 90%
- Exclude: Prolonged aura, MOH
- TMS: 0.9T for 180 µs; Sham: click and vibrate
- Primary endpoint: 2 hr pain free plus non-inferiority for nausea/photo/phonophobia
- Blinding: Thought they got active, 67% Sham and 72% active

% Patients

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain free 2 hr</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>Sustained pain free 2-24 hr</td>
<td>16</td>
<td>29</td>
</tr>
</tbody>
</table>

n = 82, 82

(Lipton et al., Lancet Neurol 2010;9:973)

Transcranial magnetic stimulation blocks CSD not TCC in rat

Holland et al., Cephalalgia 2009:29; Andreou et al., JHFP 2010;

CGRP receptor antagonist telcagepant is effective in the treatment of acute migraine

Placebo T-150 T-300 Z5

(% patients)

<table>
<thead>
<tr>
<th>Aes</th>
<th>Placebo</th>
<th>T-150</th>
<th>T-300</th>
<th>Z5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32.1</td>
<td>31.4</td>
<td>50.7</td>
<td></td>
</tr>
<tr>
<td>Triptan-like Aes</td>
<td></td>
<td></td>
<td>3.2</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.3</td>
<td>10.4</td>
</tr>
</tbody>
</table>

?Gepant-class AEs- dry mouth, fatigue

(Lancet 2008;372:2115)

Trigeminocervical nociceptive transmission is blocked by anti-migraine compounds

Goadsby & Hoskin Pain 1996;67:385

Storer and Goadsby, Brain 1997; 120:2171