1. Migraine

2014

Recent Advances in Neurology
University of California, San Francisco

12th February 2012
Professor Peter J. Goadsby

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**International Classification of Headache Disorders-III**

I- Primary

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
   3.1 Cluster headache
   3.2 Paroxysmal hemicrania
   3.3 SUNCT/SUNA (SUNCT/SUNA)
4. Hemicrania continua
5. Cephalalgia
6. Other Primary Headaches
   4.1 Cough headache
   4.2 Exercise Headache
   4.3 Headache Medicated
   4.4 Thunderclap headache
   4.5 Cold stimulus: external/ingestion
   4.6 External pressure: compression/traction
   4.7 Stabbing Headache
   4.8 Nummular headache
   4.9 Hypnic headache
   4.10 New Daily Persistent Headache

II Secondary

- Infection
- Hemorrhage
- Trauma
- Tumour
- CSF pressure change

III Cranial neuralgias/facial pain

- Trigeminal neuralgia
- Glossopharyngeal neuralgia
- Occipital neuralgia

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**Cases**

European
**Nummular Headache**

4.8 Pain in a small area without a lesion

A. Continuous pain fulfilling B-C
B. Felt in a round or elliptical shape 1-6 cm in diameter
C. Lasting hours or days
D. Not better accounted for by another ICHD-III diagnosis

- **Case series** (Grosberg *et al.*, 2009)
  - Nine patients
  - PHx- Migraine (6)
  - Three had moderate to severe pain
  - Five continuous, three episodic, one evolved
  - Rx- amitriptyline

**Migraine - Update**

- Clinical Aspects
- Disorder mechanisms
- Treatment

**Migraine**

The Attacks & the Disorder

<table>
<thead>
<tr>
<th>Attacks</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premonitory symptoms</td>
<td>Repeated attacks</td>
</tr>
<tr>
<td>Pain</td>
<td>&lt; 15 days/month: Episodic</td>
</tr>
<tr>
<td>– unilateral</td>
<td>≥ 15 days/month: Chronic</td>
</tr>
<tr>
<td>– throbbing</td>
<td></td>
</tr>
<tr>
<td>– movement worse</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Family history</td>
</tr>
<tr>
<td>Sensory sensitivity</td>
<td>Triggers (biology)</td>
</tr>
<tr>
<td>– photophobia</td>
<td>– Sleep: missing/excess</td>
</tr>
<tr>
<td>– phonophobia</td>
<td>– Food: skipping meals</td>
</tr>
<tr>
<td>– osmophobia</td>
<td>– Chemical: alcohol or nitroglycerin</td>
</tr>
<tr>
<td>Aura</td>
<td>– Weather</td>
</tr>
</tbody>
</table>

"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
**Chronic Migraine ICHD-I**

Cephalalgia 1988;8 (suppl 7):1-96

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**Chronic Migraine ICHD-II**

A. Headache frequency ≥15 days for ≥3 months
B. Attacks fulfill criteria for migraine without aura
C. Not attributed to another disorder

Cephalalgia 2004;24 (suppl 1):1-160

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**Chronic Migraine ICHD-II-R**

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)

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**Chronic Migraine ICHD-IIIα**

A. Headache frequency ≥15 days for ≥3 months
B. Patient with at ≥5 attacks of migraine with aura (MwA) or without aura (MwoA) in the past
C. On ≥8 days per month for three months one of:
   1. MwoA: C. pain characteristics AND D. nausea/sensitivity
   2. MwA: typical aura (B & C)
   3. Attacks considered migraine by patient and relieved by triptans/ergots
D. Not better accounted for by another ICHD-III diagnosis

ICHD-IIIβ Cephalalgia 2013;33:629-808
**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

<table>
<thead>
<tr>
<th>Reduction in migraine/migraine days</th>
<th>Baseline, n =</th>
<th>12.7</th>
<th>11.5</th>
<th>19</th>
<th>19</th>
<th>17</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>338</td>
<td>341</td>
<td>358</td>
<td>347</td>
<td>153</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Botox-A</td>
<td>-6.1*</td>
<td>-6.3**</td>
<td>-4.7</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>-7.6</td>
<td>-6.4</td>
<td>-6.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aurora et al, Cephalalgia 2010;40:793
Dienes et al, 2010;40:904
Silberstein et al, Headache 2007;47:170

*Headache episode- Four hours headache bounded by no pain; * P = 0.002; ** P = 0.001; ; P = 0.01

**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

<table>
<thead>
<tr>
<th>(%) patients</th>
<th>Placebo</th>
<th>Levetiracetam 3g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache free rate</td>
<td>15.5</td>
<td>19</td>
</tr>
<tr>
<td>Loss of CDH criteria</td>
<td>8</td>
<td>18</td>
</tr>
</tbody>
</table>

Beran & Spira Cephalalgia 2011;41:530

**Lacosamide is ineffective in Episodic Migraine Prevention**

- Double-blind randomized placebo-controlled, parallel group
- Migraine: 2-8 attacks/month AND ≤ 15 days headache/month
- Stable acute treatment
- Primary endpoint: reduction in migraine rates in days

Placebo: -1.4, Lacosamide 100mg: -1.4, 300mg: -1.6

<table>
<thead>
<tr>
<th>(%) patients</th>
<th>Placebo</th>
<th>L-100mg</th>
<th>L-300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache free rate</td>
<td>27</td>
<td>27</td>
<td>33</td>
</tr>
</tbody>
</table>

Adverse event: - fatigue

(NCT00440518)
**Case 1**

**Landmark Study**
Migraine in Primary Care Offices

- Prospective, open-label study
- Patients tracked for three months or six attacks
- Assigned ICHD diagnoses by experts

<table>
<thead>
<tr>
<th>% Patients</th>
<th>Migraine</th>
<th>Migrainous</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td></td>
<td>18</td>
</tr>
</tbody>
</table>

(Tepper et al., Headache 2004;44:856-864)

**Tension-Type Headache**
*appendix*

- **Episodic**
  - lasts 30 mins to 7 days
  - Two of
    - pressing/tight pain
    - mild/moderate severity
    - bilateral
    - no aggravation by activity
  - Both of
    - No nausea
    - Photophobia or phonophobia, not both

- **Chronic**
  - ≥15 days/month
  - Two of
    - pressing/tight pain
    - mild/moderate severity
    - bilateral
    - no aggravation by activity
  - Both of
    - No vomiting
    - Only one of mild nausea, photophobia or phonophobia

**Relationship of Migraine and Tension-type headache**

<table>
<thead>
<tr>
<th>Attacks</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing</td>
<td>Family history</td>
</tr>
<tr>
<td>Movement worse</td>
<td>Triggers</td>
</tr>
<tr>
<td>Associations</td>
<td>Sleep: missing/excess</td>
</tr>
<tr>
<td>- Nausea</td>
<td>Eating: including alcohol</td>
</tr>
<tr>
<td>- Photophobia</td>
<td>Weather</td>
</tr>
<tr>
<td>- Phonophobia</td>
<td>Hormonal</td>
</tr>
<tr>
<td>- Aura</td>
<td>Stress- relaxation</td>
</tr>
<tr>
<td>- ? aura</td>
<td></td>
</tr>
</tbody>
</table>
Infantile Colic

A1.6.1.3 Infantile Colic
Description: Recurrent infantile attacks of irritability that are not predictable in duration or time occurring between birth and 4 months consistent with Wessel's criteria.

Diagnostic Criteria:
A. Recurrent episodes of irritability, fussing or crying from birth to 4 months of age fulfilling criteria B and C
B. Episodes lasting 3 or more hours per day
C. Episodes occurring at least 3 days per week for at least 3 week.
D. Not better accounted for by another ICHD-III diagnosis

Gelfand et al., Neurology 2012;79:1392

Migraine - Update

• Clinical Aspects
• Disease mechanisms
  ➢ Premonitory symptoms
• Treatment

Migraine: The Premonitory Phase

Giffin et al. Neurology 2003;60:935

Dose-dependent dopaminergic modulation of trigeminocervical complex neurons

Migraine - Update

- Clinical Aspects
- Disease mechanisms
  - Premonitory symptoms
- Treatment
Transdermal sumatriptan for migraine

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

% Patients

\[ n = \begin{array}{c} 228 \text{ Placebo} \\ 226 \text{ Sumatriptan-Id} \end{array} \]

Sustained pain relief 2-24 hr

(Goldstein et al., Headache 2012;52:1402)

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

Muscle

Skin

Injectate

(Brandes et al., Headache 2009;49:1435)

Ergot Alkaloid (tetracyclic ergolene) Family Tree

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

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

% Patients

<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>

(Anti-PPE compounds)

PNU142633

5HT1D agonists

CH₂₃H₂H₃

34.5

19.6

10.1

6.7

5.9

25.2

58.7

43.7

28.4

23.1

17.7

26.0

31.2

(Silberstein et al., Headache 2011;51:507)
DHE Receptor Binding and Headache Recurrence

- $K_{on/off}$ determined with in vitro binding methods
- Dissociation $t_{1/2}$ calculated (hr)

<table>
<thead>
<tr>
<th>5HT$_{1D}$</th>
<th>5HT$_{1B}$</th>
<th>DHE</th>
<th>Sumatriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.28</td>
<td>0.17</td>
<td>1.38</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Kori et al., Headache 2012;52:874

Lasmiditan, 5-HT$_{1F}$ receptor agonist, in acute migraine

- Double-blind parallel group randomised
- Placebo-controlled trial
- Migraine with/without aura; no preventives

Farkkila et al., Lancet Neurol 2012;11:405

Ergot Alkaloid (tetracyclic ergolene) Family Tree

Trigeminovascular System & Migraine

(Goadsby et al., NEJM 2002; 346:257-270)
Trigeminal Activation & CGRP

<table>
<thead>
<tr>
<th>Substance P</th>
<th>CGRP</th>
<th>Substance P</th>
<th>CGRP</th>
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<th>CGRP</th>
<th>Substance P</th>
<th>CGRP</th>
<th>Substance P</th>
<th>CGRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>12</td>
<td>Human</td>
<td>10</td>
<td>Cat</td>
<td>2</td>
<td>Human</td>
<td>4</td>
<td>Cat</td>
<td>0</td>
</tr>
</tbody>
</table>

Neuropeptides
Ann Neurol 1988;23:193
Ann Neurol 1990;16:69
Ann Neurol 1990;28;183

CGRP, Substance P, PPE & CGRP antagonists in Migraine
- Double-blind randomized parallel group single attack adult migraineurs

<table>
<thead>
<tr>
<th>Substance P</th>
<th>CGRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>

% patients

Oral CGRP receptor antagonists are effective in the treatment of acute migraine
- Double-blind parallel group randomised controlled trials
- Two hour pain free

<table>
<thead>
<tr>
<th>Ho et al., Lancet 2009;372:2115 Telcagepant</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diener et al., Cephalalgia 2011;37:515 BI-44270</td>
<td>70</td>
</tr>
<tr>
<td>Marcus et al., Cephalalgia 2014;34:114 BMS-92771</td>
<td>203</td>
</tr>
</tbody>
</table>

Biologic Approaches to Migraine
- Amgen
  - Human monoclonal IgG1 (AM338) receptor
  - CLR-RAMP1
  - Binding potency pM
  - Inhibited CGRP-stim cAMP Vmax 1-30nM
  - Fifty fold selectivity over other receptors in the class
  - Phase II: Episodic and Chronic Migraine
- Alder Biopharmaceuticals
  - ALD403: α and β CGRP antibody
  - Phase II: Episodic migraine prevention
- Arteaus Therapeutics
  - LBR-101 (RN-307 Rinat Pharmaceuticals/Pfizer) CGRP antibody
  - T1/2: 40 days
  - Phase II: to begin in (?) chronic migraine

1. Lu et al., Sh et al., Headache 2011;51[Suppl 1]:6,59
2. Smith IHC Boston 28th June 2013
3. De Hoorn et al., Cephalalgia 2013;33[Suppl 8]:247
4. Garzone et al., Cephalalgia 2013;33:596
Case

Primary Sex Headache

4.3 Primary headache associated with sexual activity
A. At least two episodes of pain in the head and/or neck fulfilling criteria B-D
B. Brought on by and occurring only during sexual activity
C. Either or both of the following:
   1. increasing in intensity with increasing sexual excitement
   2. abrupt explosive intensity just before or with orgasm
D. Lasting from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity
E. Not better accounted for by another ICHD-3 diagnosis

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/phono
- Blinding: Thought they got active, 67% Sham and 72% active

Transcranial magnetic stimulation blocks CSD not TCC in rat

(Lipton et al., Lancet Neurol 2010;9:973)
sTMS significantly modulates cortico-thalamic activation following CSD

Migraine
A brain systems disorder with many manifestations

- 5-HT1B/1D: triptans
- CGRP: gepants
- 5-HT1F: ditans
- Orexin 1 & 2: rexants
- mGluR5: glurants
- ASICs: mambalgins
- nNOS: NXN
- TRP: ?
- Neuromodulation

Case

Hypnic Headache

4.9 Attacks of headache that awaken the patient from sleep
A. Headache develops only during sleep, and awakens patient and fulfills criteria B-E
B. ≥10 days per month for at least 3 months
C. Lasting ≥ 15 minutes and < 4 hours after waking
D. No cranial autonomic symptoms or restlessness
E. Not better accounted for by another ICHD-III Dx

Raskin Headache 1988;28:534
ICHD-III-beta
**Trigeminal Autonomic Cephalalgias (TACs)**

3.1 Cluster Headache
- Episodic
- Chronic

3.2 Paroxysmal Hemicrania
- Episodic
- Chronic

3.3 SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing)/SUNA

3.4 Hemicrania continua

3.4 TAC- not otherwise classified

*Goadsby & Lipton Brain 1997;120:193
Cephalalgia 2004; 24[Suppl 1]: 1-160
ICHD-III-beta

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**Oxygen for Acute Cluster Headache**

- Randomised, double-blind, placebo controlled, four attack study
- Two period each with paired air/oxygen
- n = 76 patients, reporting n = 276 attacks

**Cohen et al., JAMA 2009;302:2451; **P < 0.001

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**Oxygen inhibits trigeminal neurons activated by Superior Salivatory Nucleus (SuS) stimulation**

O$_2$ inhibits lacrimal sac blood flow

O$_2$ inhibits SuS V neurons

Akerman et al., Brain 2012;135:3664

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**Trigeminal Autonomic Cephalalgias**

*trigeminal-autonomic activation facilitated by the brain*
Hemicrania continua

A. Headache occurring > three months with B-E
B. Unilateral headache with moderate or greater severity
C. Headache is accompanied by either one of
   1. One or more cranial autonomic features
      a. Conjunctival injection, or lacrimation, or both
      b. Nasal congestion, or rhinorrhea, or both
      c. Eyelid oedema
      d. Forehead or facial sweating
      e. Forehead and facial flushing
      f. Sense of aural fullness
      g. Miosis, or ptosis, or both
   2. Sense of restlessness, or aggravation of pain with movement, or both
D. Headache is prevented completely by indomethacin
E. Not better accounted for by another ICHD-III diagnosis

(Cittadini et al., Brain 2010;173:1973 and ICHD-III-beta)

Indomethacin-sensitive headache
ventrolateral midbrain activation in PET studies

Hemicrania continua
Matharu et al., Headache 2004;44:747

Paroxysmal hemicrania
Matharu et al., Ann Neurol 2006;59:535

Does indometacin work through Nitric Oxide?
Effect of NSAIDs on neurogenic dural vasodilation
Indometacin blocks SNP meningeal dilation

Summ et al., J Head Face Pain 2010;11:477
Botulinum toxin and the Sphenopalatine Ganglion

- Dogs ($n=4$): botulinum toxin type A soaked gauze applied to nasal cavity
- SPG stimulation for ten minutes (50 Hz)
- Collected nasal secretion
- Reduced in three of four

Ozcan et al., Am J Otolaryngol 2006;27:314

Botulinum toxin and vasomotor rhinitis

- Patients with vasomotor rhinitis
- Random: Control ($n=5$), BTX-A 10U ($n=15$), 20U ($n=10$)
- BTX-A or control injected into inferior and middle turbinates
- Results
  - Total symptom score reduced for 20U vs control
  - Total symptom score no effect for 10U vs control

Intravenous Dihydroergotamine (DHE) and Migraine

- Intravenous DHE is effective in acute migraine
  (Winner et al., Arch Neurol 1996;53:188)
- Repetitive intravenous DHE: 1g 8hrly prn
  - Medically refractory chronic migraine ($n=326→114$)
  - Follow-up: 11±2 months
  - Efficacy
    - Headache free in hospital: 69%; at one month: 83%
    - Comparable effect: females, migraine type, age, triptan or opioid overuse
    - Predictors of good outcome
      - Increase dose from 7 to 11mg
      - Absence of nausea
  - Adverse events
    - Nausea
    - Leg cramps
    - IV site pain/discomfort
    - Limb pain
    - Diarrhea/abdominal cramps/constipation
    - Chest pain ($n=5$): normal ECG
  (Nagy et al., Neurology 2011;77:1827)

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)

-Adverse event: non-target sensory symptoms
Occipital nerve stimulation in chronic migraine

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

![Graph showing reduction in headache days and 50% responder rate](image)

**St Jude**
- Double-blind randomized parallel group sham stimulation controlled study
- Chronic migraine or probable chronic migraine
- Occipital pain, failed two preventives; Successful trial 250% reduction in pain or paresthesia
- **Results:** Implanted (n = 177); **Primary endpoint - Failed**

![Graph showing response rates and adverse events](image)

(Saper et al., Cephalalgia 2011:31:271)

*Adverse event: lead migration in 24%

(Silberstein et al., Cephalalgia 2012:32:1165)

*P = 0.032; **P = 0.003

#### Acute Medication Overuse

**Definition**
- Headache ≥ 15 days/month for > three months
- **Overuse of**:
  - Triptan ≥ 10 days/month
  - Opioid ≥ 10 days/month
  - Paracetamol or NSAID ≥ 15 days/month
  - Is this a receptor agonist problem?

**Consequences**
- General Medical issues: CVS, GI, Psychiatric
- Rebound headache: headache returns when medicine effect dissipates
- Inhibition of effect of preventives

**Management**
- Withdraw offending substance
- Offer symptomatic support
- Consider infusion center or in-patient approaches
- Start a preventive when appropriate

#### Genetics of Migraine

**Familial Hemiplegic Migraine - an ionopathy**

- **FHM-I CACNA1A:**
  - P/Q voltage-gated Ca^{2+} channel chr 19
  - Optoff et al. Cell 1996; 87:582

- **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

- van den Maagdenberg et al., Neuron 2004;41:701-710
Migraine Genes

- Two GWAS’s
- Migraine without aura
- Findings
  - Transient receptor potential cation channel subfamily M member 8: TRPM8, aka cold and menthol receptor
  - Lipoprotein receptor related protein 1: LRP1, glutamate signaling

Chasman et al., Nat Gen 2011;43:695
Freilinger et al., Nat Gen 2012;42:869

Transient Receptor Potential Channels

- TRPV (vanilloid)
  - Cation channel
  - Low pH (protons or acid)
  - Heat: >43°C
  - Capsaicin, endocannabinoids
- TRPA (ankyrin repeats)
  - Located in trigeminal ganglion
  - Colocalized with CGRP
  - Mustard oil, wasabi, cinnamon
- TRPM (melastatin)
  - Na+/Ca2+ channel
  - Cold: < 20°C
  - Menthol

Albrecht et al., EHMTIC 2012

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

Odds ratios

- Stroke: 2.16
- CVS disease: 1.73
- MI: 1.03

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

Does Migraine “hurt” the brain?

CAMERA-I

- French population based vascular risk study
- Patients born between 1922-32
- Interviewed/diagnosis probable migraine or non-migraine
- Results
  - Supratentorial: increased deep white matter hyperintensities by 0.11 [0.01-0.26] ml females with MwoA- new changes
  - Not related to BP or diabetes
  - Infratentorial: no change in hyperintensities
  - Progression unrelated to headache frequency
  - No effect of hyperintensities on cognition

Kruit et al., Brain 2005;128:2068

CAMERA-II

- Population-based, 9 year follow-up
- Ctrl 83/140 and Migraine 203/295
- Adjust: age, sex, BP, diabetes, education
- Results
  - Supratentorial: increased deep white matter hyperintensities by 0.11 [0.01-0.26] ml females with MwoA- new changes
  - Not related to BP or diabetes
  - Infratentorial: no change in hyperintensities
  - Progression unrelated to headache frequency
  - No effect of hyperintensities on cognition

Kurth et al., BMJ 2010;341

EVA Study

- Dutch population based vascular risk study
- Patients born between 1922-32
- Interviewed/diagnosis probable migraine or non-migraine
- Cohort n = 1170/migraine (166)/+aura (24)
- Results
  - Battery of ten cognitive tests showed no difference between migraine and non-migraine;
  - Average scores decline
  - No effect of migraine status on rate of decline
  - No effect of presence of brain changes on MRI on decline

(Palm-Meinders et al., JAMA 2012;308:1889) (Kurth et al., BMJ 2010;341)
Is glutamate involved in human aura?

- Randomized double-blind active control parallel group multiple attack crossover
- Migraine with prolonged aura (ICHD-I)/hemiplegic migraine
- Ketamine/placebo versus Midazolam/placebo (intranasal) (2 x 3 attacks/arm)
- Primary Endpoint: reduced length or severity of attack

<table>
<thead>
<tr>
<th>Change</th>
<th>Length</th>
<th>Severity</th>
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<tbody>
<tr>
<td></td>
<td>3</td>
<td>1.5</td>
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<td>-0.05</td>
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Afridi et al., Neurology 2013; in press

* P = 0.032

Glurants, allosteric modulators of mGluR5 receptors

- ADX10059, randomised, double-blind placebo-controlled parallel group
- Migraine with or without aura (n = 129)
- Primary endpoint: pain free at two hours (p = 0.039)

CGRP is not necessary for plasma protein extravasation (PPE)

- Dural PPE not present in NK1 knock-out mice
- Histamine not necessary for PPE
- CGRP does not produce PPE in isolation

Grant et al., Eur J Pharmacol 2005;507:273-280