Migraine Research Update
Clinical and Scientific Highlights

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Objective

Discuss some of the important advances in clinical and basic research in migraine and other headache disorders over the past year as presented in the literature and at International Congresses.
Overview

- Burden of illness
- Genetics
- Pathophysiology
- Clinical insights
- Treatment
  - Drugs
  - Devices
Tension-type headache and migraine are the 2nd and 3rd most prevalent medical disorders on the planet.

Migraine accounts for 30% of the global burden and more than 50% of the disability burden attributable to all neurological disease worldwide.

Overall, it is the 4th ranking cause among women and the 7th ranking cause of all disease-associated disability worldwide.
Migraine Genetics: Monogenetic Mendelian Disease

Increase glutamate, $K^+_E$

Tottene et al. PNAS 2002; JBC 2005
Suzuki M, et al. PNAS 2010

De Fusco et al. Nat. Genet. 2003
Kahlig et al. PNAS 2008
Progress in Migraine Genetics

Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1


Genome-wide association study reveals three susceptibility loci for common migraine in the general population

Daniel I Chasman, Markus Schürks, Verneri Anttila, Bouke de Vries, Ulf Schminke, Lenore J Launer, Gisela M Terwindt, Arn M J M van den Maagdenberg, Konstanze Hendrich, Henry Völzke, Florian Ernst, Lyn R Griffith, Paul M Ridker, Aarno Palotie, Tobias Kurth

Genome-wide association analysis identifies susceptibility loci for migraine without aura

Genes for Common Migraine Subtypes

Migraine with aura
(Anttila et al) 2,731 cases vs. 10,747 controls

Migraine
(Chasman et al) 5,122 cases vs. 18,108 controls

Migraine without aura
(Freilinger et al) 2,455 cases vs. 4,611 controls

Vascular integrity and function

Glutamatergic pathways

Pain signalling pathway

MTDH

LRP1

TRPM8

PRDM16

TGFB2

ASTN2

PHACTR1

MEF2D
Overview

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  - Drugs
  - Devices
Midbrain Activation in the Premonitory Phase of Migraine: A $\text{H}_2\text{^15O}$-Positron Emission Tomography Study

Till Sprenger, Farooq H. Maniyar, Teshamae Monteith, Christoph Schankin, Peter J Goadsby

American Headache Society
Los Angeles, CA, 2012
Migraine Phases – Premonitory Phase as a Clue to Migraine Genesis

- Premonitory Symptoms
- Aura
- Headache

- Migraine with Aura
- Migraine without Aura
- Aura Alone
Brain activation during early premonitory phase

Cortical activations in:
- Prefrontal cortex
- Temporal cortex
- Parietal/precuneus
- ACC
- Bilateral occipital cortex
- Cerebellum

Late premonitory phase - additional activation of:
- Thalamus
- Putamen

P<0.05 FDR corr.
Conclusions

• Midbrain, hypothalamic, and pontine activations occur early on during an attack BEFORE pain onset
• Pontine, but not midbrain or hypothalamic activation persists well into the headache phase
• Hypothalamic activation may explain premonitory symptoms
• Areas of early activation involved in the modulation of sensory perception and their activation during early attack phases suggests malfunction of modulatory circuits as an important mechanism of migraine attack generation
Migraine With Aura: CSD (Aura) Activates Peripheral and Central Trigeminal Sensory Neurons

Lambert GA et al. Cephalalgia 2011;31:1439-1451
Spreading Depression Triggers Headache by Activating Neuronal Panx1 Channels

Hulya Karatas,1,2 Sefik Evren Erdener,1,2 Yasemin Gursoy-Ozdemir,1,2 Sevda Lule,1 Emine Eren-Koçak,1,3 Zümrüt Duygu Sen,1,3 Turgay Dalkara1,2*

The initial phase in the development of a migraine is still poorly understood. Here, we describe a previously unknown signaling pathway between stressed neurons and trigeminal afferents during cortical spreading depression (CSD), the putative cause of migraine aura and headache. CSD caused neuronal Pannexin1 (Panx1) megachannel opening and caspase-1 activation followed by high-mobility group box 1 (HMGB1) release from neurons and nuclear factor κB activation in astrocytes. Suppression of this cascade abolished CSD-induced trigeminovascular activation, dural mast cell degranulation, and headache. CSD-induced neuronal megachannel opening may promote sustained activation of trigeminal afferents via parenchymal inflammatory cascades reaching glia limitans. This pathway may function to alarm an organism with headache when neurons are stressed.

Science 339, 1092 (2013);
Dural afferents express acid-sensing ion channels: a role for decreased meningeal pH in migraine headache

Jin Yan¹, Rebecca M. Edelmayer¹, Xiaomei Wei¹, Milena De Felice¹, Frank Porreca¹, and Gregory Dussor¹,*

A

\[
P_{\text{H}6.0} \quad \text{Amiloride} \quad 5 \text{nA} \quad 1 \text{s}
\]

B

\[
P_{\text{H}6.0} \quad \text{CZP} \quad 5 \text{nA} \quad 1 \text{s}
\]

C

\[
P_{\text{H}6.0} \quad \text{AMG} \quad 5 \text{nA} \quad 2 \text{s}
\]

D

\[
\begin{array}{c}
\text{Peak Current Block (\%)} \\
10 \mu \text{M} \quad 1 \text{mM} \quad \text{CZP} \quad \text{AMG}
\end{array}
\]

Pain 2011;152:106-113
ASIC-3 Antagonist Blocks CSD and Inhibits Trigeminal Activation

Holland PR, et al. ANN NEUROL 2012;72:559–563
Attack Frequency Dependent Functional and Structural Remodeling of Pain Matrix

Maleki et al. Cephalalgia 2012; 32(8) 607–620
Attack Frequency Dependent Functional and Remodeling of Pain Matrix

Significant increase in connectivity between PAG and nociceptive and somatosensory processing; significant decrease between PAG and brain regions involved in inhibitory pain modulation. Both findings strengthened by attack frequency and presence of allodynia.
Overview

- Burden of illness
- Genetics
- Pathophysiology
- Clinical insights
- Treatment
  - Drugs
  - Devices
• Prospective cohort study of 27,860 women aged ≥45 participating in the Women's Health
• Migraine (5130) with aura (40%)
• 15 year follow-up (528 total strokes (430 ischemic)
• The incidence rate was 4.3 (3.0-6.0) for total, 3.4 (2.3-5.0) for ischemic and 0.8 (0.3-1.8) for hemorrhagic stroke.
• Migraine with aura was strongest single contributor relative to other vascular risk factors followed by diabetes and hypertension

Kurth et al. American Academy of Neurology, San Diego, CA 2013
Structural Brain Lesions in Migraine

Women with migraine had higher volumes and greater progression of deep white matter hyperintense lesions. Lesion load not related to type or frequency of attacks and no evidence of impaired cognitive performance. Non-significant progression in brainstem WMHLs and posterior circulation infarctions.
Does Transverse Sinus Stenosis Influence the Clinical Course of IIH


American Headache Society, Los Angeles CA, 2012
Does Transverse Sinus Stenosis (TSS) Influence the Clinical Course of IIH

- Quantitative measurements of TVS (51 patients with IIH)
- All patients had some degree of stenosis (median 56%; 71% had > 50% stenosis)
- 16% of patients had “poor” clinical courses.
- No association between the degree of TSS and either the clinical course (0.44) or the visual field outcome (p=0.98).
- There was no correlation between the degree of TSS stenosis and CSF opening pressure (p=0.28).

Conclusions

- TSS is very common in IIH
- No association between the severity of TSS and the clinical course or the visual field outcomes
- The degree of TSS does not predict prognosis and stenting should not be pursued without clinical correlation
Overview

- Burden of illness
- Genetics
- Pathophysiology
- Clinical insights
- Treatment
  - Devices (Neurostimulation)
  - Drugs
# Neurostimulation for Headache

## Peripheral neurostimulation
- Occipital Nerve Stimulation
- Sphenopalatine ganglion
- Vagal nerve (VNS)
- Auriculotemporal (ANS)

## Central neurostimulation
- sTMS
- hDBS
- rTMS (high/low frequency)
- tDCS (cathodal/anodal)
- High spinal cord stimulation
Peripheral Neurostimulation: Occipital Nerve (Field) Stimulation
Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study

Joel R Saper¹, David W Dodick², Stephen D Silberstein³, Sally McCarville⁴, Mark Sun⁴ and Peter J Goadsby⁵ for the ONSTIM Investigators
ONSTIM: Mean Percent Reduction in Headache Days Per Month From Baseline to Month 3

- Adjustable stim: 27% ± 45%, P=0.132
- Preset stim: 9% ± 29%, P=0.058
- Medical Mgt: 4% ± 19%
- Ancillary: 40% ± 51%, P=0.566

N=75

Saper, JR et al. Cephalalgia 2010;31(3) 271–285
ONSTIM: Responder Rate

Responder rate = ≥ 50% reduction in headache days/mo or ≥3 point reduction in overall pain intensity (VAS)

P=0.032* P=0.003*

<table>
<thead>
<tr>
<th></th>
<th>N=75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustable stim</td>
<td>39%</td>
</tr>
<tr>
<td>Preset stim</td>
<td>6%</td>
</tr>
<tr>
<td>Medical Mgt</td>
<td>0%</td>
</tr>
<tr>
<td>Ancillary</td>
<td>40%</td>
</tr>
</tbody>
</table>

Saper, JR et al. Cephalalgia 2010;31(3) 271–285
Silberstein SD, et al. Cephalalgia 2012;32(16) 1165–1179:

Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Results from a randomized, multicenter, double-blinded, controlled study

Stephen D Silberstein¹, David W Dodick², Joel Saper³, Billy Huh⁴, Konstantin V Slavin⁵, Ashwini Sharan¹, Ken Reed⁶, Samer Narouze⁷, Alon Mogilner⁸, Jerome Goldstein⁹, Terrence Trentman², Julien Vaisma¹⁰, Joseph Ordia¹⁰, Peter Weber¹¹, Timothy Deer¹², Robert Levy¹³, Roni L Diaz¹⁴, Stephanie N Washburn¹⁴ and Nagy Mekhail¹⁵
**Primary Endpoint: Significant difference at 50% reduction in pain AND 10% differential at the 95% CI**

<table>
<thead>
<tr>
<th>% reduction from baseline</th>
<th>Control Group % responders (n=52)</th>
<th>Active Group % responders (n=105)</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
<th>met protocol objective (&gt;10% dif.)&lt;sup&gt;2&lt;/sup&gt;</th>
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<tbody>
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<td>10,0%</td>
<td>30,8%</td>
<td>56,2%</td>
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<tr>
<td>20,0%</td>
<td>19,2%</td>
<td>40,0%</td>
<td>0,009</td>
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<td>30,0%</td>
<td>17,3%</td>
<td>35,2%</td>
<td>0,020</td>
<td>Yes</td>
</tr>
<tr>
<td>40,0%</td>
<td>15,4%</td>
<td>25,7%</td>
<td>0,0143</td>
<td>No</td>
</tr>
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<td>50,0%</td>
<td>13,5%</td>
<td>17,1%</td>
<td>0,553</td>
<td>No</td>
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<td>60,0%</td>
<td>9,6%</td>
<td>11,4%</td>
<td>0,731</td>
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<tr>
<td>70,0%</td>
<td>1,9%</td>
<td>4,8%</td>
<td>0,664</td>
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<td>80,0%</td>
<td>1,9%</td>
<td>3,8%</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>90,0%</td>
<td>0,0%</td>
<td>1,0%</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>100,0%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>No</td>
</tr>
</tbody>
</table>

Silberstein SD, et al. Cephalalgia 2012;32(16) 1165–1179:
## Headache Days: 12-Week Control Phase

<table>
<thead>
<tr>
<th>Visit</th>
<th>Control Group (n=52)</th>
<th>Active Group (n=105)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± std)</td>
<td>20,1 (± 7,2)</td>
<td>22,4 (± 6,9)</td>
<td>0,049</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change¹</td>
<td>-3,0 (14,9%)</td>
<td>-6,1 (27,2%)</td>
<td>0,008</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-3,1 (-5,4, -0,8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Silberstein SD, et al. Cephalalgia 2012;32(16) 1165–1179:
PRISM: Primary Endpoint: No Significant Change From Baseline in Migraine Days/Month at 12 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Intent-to-Treat (n=139)</th>
<th>Modified ITT (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine days/month</td>
<td>18.9 ± 8.0</td>
<td>19.2 ± 7.9</td>
</tr>
<tr>
<td><strong>12-Week Outcome</strong></td>
<td>-3.6 ± 8.3</td>
<td>-3.9 ± 8.2</td>
</tr>
<tr>
<td>P</td>
<td>0.26</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Lipton RB, et al. Presented at IHC 2009
Response to Percutaneous Trial Stimulation May Predict 12-Week Outcome

Active percutaneous trial followed by 12-weeks active stimulation

<table>
<thead>
<tr>
<th>Positive Trial*</th>
<th>Negative Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.7 ± 6.9</td>
<td></td>
</tr>
<tr>
<td>-8.8 ± 8.4</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Response to Percutaneous Trial Stimulation (Active Group)

12-Week Outcome % Reduction at 12-Weeks†

<table>
<thead>
<tr>
<th></th>
<th>≥50%</th>
<th>&lt;50%</th>
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</thead>
<tbody>
<tr>
<td>Positive* Trial</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Negative Trial</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Positive* Trial</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Negative Trial</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

* Subjects with ≥20% reduction in the % migraine days from baseline during percutaneous trial stimulation.
† Subjects with 50% reduction in migraine days/month from baseline at 12 weeks.

Lipton RB, et al. Presented at IHC 2009
ONS May Restores Central Descending Opioidergic Tone But Does Not Deactivate Generator

Perigenual ACC selectively activated in responders

Magis et al. BMC Neurology 2011, 11:25
Migraine prevention with a supraorbital transcutaneous stimulator

A randomized controlled trial

ABSTRACT

Objective: To assess efficacy and safety of trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med, Herstal, Belgium) in migraine prevention.

Methods: This was a double-blinded, randomized, sham-controlled trial conducted at 5 Belgian tertiary headache clinics. After a 1-month run-in, patients with at least 2 migraine attacks/month were randomized 1:1 to verum or sham stimulation, and applied the stimulator daily for 20 minutes during 3 months. Primary outcome measures were change in monthly migraine days and 50% responder rate.

Results: Sixty-seven patients were randomized and included in the intention-to-treat analysis. Between run-in and third month of treatment, the mean number of migraine days decreased significantly in the verum (6.94 vs 4.88; p = 0.023), but not in the sham group (6.54 vs 6.22; p = 0.608). The 50% responder rate was significantly greater (p = 0.023) in the verum (38.1%) than in the sham group (12.1%). Monthly migraine attacks (p = 0.044), monthly headache days (p = 0.041), and monthly acute antimigraine drug intake (p = 0.007) were also significantly reduced in the verum but not in the sham group. There were no adverse events in either group.

Conclusions: Supraorbital transcutaneous stimulation with the device used in this trial is effective and safe as a preventive therapy for migraine. The therapeutic gain (26%) is within the range of those reported for other preventive drug and nondrug antimigraine treatments.

Classification of evidence: This study provides Class III evidence that treatment with a supraorbital transcutaneous stimulator is effective and safe as a preventive therapy for migraine. Neurology 2013;80:1-8
Supraorbital Transcutaneous Stimulation: PREMICE Study (Cefaly® device)

Responder rate: 38.2 vs 12.1; p=0.023

Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study

Jean Schoenen¹, Rigmor Højland Jensen², Michel Lantéri-Minet³, Miguel JA Láinez⁴, Charly Gaul⁵, Amy M Goodman⁶, Anthony Caparso⁶ and Arne May⁷
Cranial Parasympathetic Pathways
Sphenopalatine Ganglion Stimulation for Acute Treatment of Cluster Headache
Pathway CH-1 Study: Stimulation of the SPG Stimulation for Cluster Headache: A randomized, Sham-Controlled Study

Responders: 67.1% (FS) vs 7.4% (sham) vs 7.3% (SP) (p<0.0001)

43%

>50% reduction in frequency

Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial

Richard B Lipton, David W Dodick, Stephen D Silberstein, Joel R Saper, Sheena K Aurora, Starr H Pearlman, Robert E Fischell, Patricia L Ruppel, Peter J Goadsby
Single Pulse Transcranial Magnetic Stimulation

(Holland et al., Neurology 2009;72-Suppl 3:A250)
Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial

Richard B Lipton, David W Dodick, Stephen D Silberstein, Joel R Saper, Sheena K Aurora, Starr H Pearlman, Robert E Fischell, Patricia L Ruppel, Peter J Goadsby

Pain-free 2 hours after treatment

ITT

PP

SPF 24 and 48 hours after treatment

24h

48h

*T M P<0.018

* P<0.040

** P<0.033

UK Pilot: Preliminary Efficacy Results (Open Label)

- Reduction or alleviation of pain in 74% of patients
- 63% of patients reported reduced attack duration
- These patients reported a 64% reduction in headache days over the 3 month period

SpringTMS Effectiveness on Migraine Pain

- 11% Excellent
- 23% Very good
- 40% Good

74% of patients surveyed reported device was effective in reducing or alleviating migraine pain.

# of Patients
- Month 1 N = 44
- Month 2 N = 35
- Month 3 N = 23
High Value Drug Targets

- CGRP receptor
- NMDA (mGluR2; GluA3) receptor
- ASIC-3
- δ opioid receptor
- Monoclonal antibodies
- OR1
- 5HT₁F
- nNOS
- CGRP receptor
Lasmiditan (5HT-1F) Agonist: Pooled Analysis of Two Randomized Placebo-Controlled Trials

Headache Response: Reduction of a moderate or severe headache at baseline to mild or none 2 hours after dosing

* p < 0.05 vs PBO

Novel Human Monoclonal Antibodies Against CGRP or CGRP Receptor Complex
CGRP Antagonists and Monoclonal Antibodies

- CGRP small molecule receptor antagonists for acute migraine treatment
  - Merck and BMS
- CGRP monoclonal antibodies (Mab) for prevention (episodic and chronic migraine)
  - Anti-CGRP Mab (Arteaus, Alder, Labrys)
  - Anti-CGRP receptor Mab (Amgen)
Example: ALD403

- High affinity: <50 pM
- Long $T_{1/2}$: ~28 days
- CGRP selective (no off target biology)
- Compatible with current abortive therapy (triptans)
- Aglycosylated IgG1
  - Improved infusion profile and reduced immunogenicity
- Ongoing proof of concept study in frequent episodic migraine

With permission, Jeff Smith, (Alder Biopharmaceuticals Inc)