Advanced Interventions for Headache

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Advisors Board:
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When all else fails...

• We all have so many patients for whom our meds fail, are inadequate, are contra-indicated, or are not tolerated

• These are patients with severe disability. Most have daily headaches, whether chronic migraine, TACs, or other primary headaches

• What else can we do?
Thoughts on Advanced Interventions for Headache

1. Detoxification. There is no substitute, and it must be absolute. Do not set out on a therapeutic quest without this first step.

2. This may require an intravenous bridge over several days, either in an IV unit or inpatient in a medical model, as noted by Dr. Krusz

3. Structured multidisciplinary headache program. This is for patients who require an interdisciplinary approach, and may be day-hospital or inpatient.

4. OnabotulinumtoxinA for chronic migraine. Do not proceed to #5 without having tried 3 & 4.

5. Blocks and stimulators
Is Wean Really Necessary?

- In 4 recent RCTs on rx of CDH with TPM and onabot, MOH patients were not completely excluded
- Post hoc, these studies were probed to see whether TPM and onabot could treat both primary CM, and MOH without detoxification
- Only one study showed benefit for TPM in MOH patients, and it worked 50% less well than in the non-rebound patients.
- Neither TPM study showed an improvement in decreasing acute medication intake
- In the onabot trials, most patients met criteria for baseline medication overuse (65.5%), and no between group differences were seen for acute medication intake

Problems with interpretation

• Benefits were established only by post-hoc analyses; the studies were not powered specifically and primarily to examine effectiveness of treatment without wean in MOH

• As noted, one study showed no benefit

• Opioid and barbiturate MOH patients were excluded, so the analysis excluded the most difficult of MOH patients

• Patients with continuous headache were excluded, so the analysis excluded the most difficult CM patients

• The studies did not examine whether the patients would have done better with TPM or onabot plus a wean
Always wean patients from rebound

- Wean alone can work in re-establishing EM, even with no prophylaxis
- Patients weaned, with prophylaxis and behavioral treatment, do better than with any one of these interventions alone, or no interventions
- Wean restores effectiveness of prevention and migraine-specific acute drugs
- Overuse leads to avoidable medical consequences, including gastrointestinal bleeds, analgesic nephropathy, barbiturate-worsened depression, etc.
- It is irresponsible to not address the wean up front, and disingenuous at best to hope that by adding a preventive agent or a stimulator, a habituated patient (such as one on methadone or mixed analgesics), is going to fortuitously self-detoxify
- MOH causes ongoing conflict with the care provider over prescriptive scheduled medications, interfering with therapeutic alliance

Detoxification or Wean

• Most wean can be done outpatient slowly or with an infusion suite

• Some requires inpatient infusion, medical model

• If there are a great deal of comorbid medical and psychiatric problems, it is time to refer to a structured headache program
Multidisciplinary Headache Programs for CM: Key Next Step in Advanced Interventions

• For high doses of rebound medications, with numerous overused drugs, or with long duration of CDH
• For excessive medical and psychiatric comorbidities
• Dangerous detoxification
• Can be Day Hospital (C. Besta, Milan; Cleveland Clinic IMATCH)
• Inpatient (Michigan Headpain and Neurological Institute, Diamond Headache Clinic, Cedars-Sinai Inpatient Headache Program, Houston Headache Center)
• Some patients clearly require inpatient treatment because of the risks during withdrawal and other needs for 24 hour monitoring
How do these programs operate?

• Multidisciplinary, e.g. Neurology, Internal Medicine, Psychology, Other medical disciplines, Skilled nursing, PT, Dietary

• Detoxify patients when appropriate intravenously

• Establish prevention with acute treatment and limits

• Provide education

• Provide behavioral evaluation and treatment

• All take weeks

• All have good outcome data
Blocks for headaches

• Greater occipital nerve blocks (GON)
  – E.g.: Gawel and Rothbart retrospective efficacy of lidocaine/methylpred GON block in refractory migraine
    – 54% “significantly better” after the blocks, with duration of rs lasted up to 6 months
    – With posttraumatic headache they reported a 72% response rate to GON
    – Multiple case reports on GON for CDH, CH, cervicogenic headache

• Other blocks: Supraorbital, Auriculotemoral, Trigeminal nerve

• Sphenopalatine ganglion blocks (SPG) for CH described since 1981, for migraine since 1999, & some think Dr. Maizel’s lidocaine drops worked here

• Majority of studies small and uncontrolled

• Results generally positive, but should be taken with reservation given the methodological limitations of the available studies.

• Procedures generally well tolerated

• Safer procedures worth a shot to buy time

Stimulators for headache

- Hypothalamic deep brain stimulation (DBS)
- Occipital Nerve Stimulation (ONS) St Jude device received CE in EU Sept 2011
- Vagal Nerve Stimulation (VNS)
- Transcranial magnetic stimulation (TMS)
- Sphenopalatine ganglion stimulation (SPG)
First CCH Patient with DBS

• The sentinel case was a 39-year old man who had 90% right side-locked refractory cluster, and:
  – Severe angioedema which closed his eye during attacks
  – Had thermal trigeminogangliorhizolysis X2
  – Developed vitreous hemorrhage and blindness OD

• Then developed severe chronic cluster on the other side
  – Every time he had an attack he was completely blind due to angioedema and closure of the good eye

Before the Operation

- Verapamil
- Lithium carbonate
- Methysergide
- Ergotamine
- Pizotifen
- Indomethacin
- Valproate
- Prednisone

- Dexamethasone
- Phenothiazines
- Tricyclic antidepressants
- Clonidine
- Propranolol
- Flunarizine
- and many others

Photo courtesy of Dr. D’Amenico D’Amico
## Table 1: Summary of results of hypothalamic stimulation in drug-resistant chronic cluster headache patients from various centers

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of implanted patients</th>
<th>Mean follow-up (years)</th>
<th>No. of improved patients*</th>
<th>Percentage improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoenen et al. (2005) (19)</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>D’Andrea et al. (2006) (20)</td>
<td>3</td>
<td>2.5</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>Leone et al. (2006) (18)</td>
<td>16</td>
<td>4</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Starr et al. (2007) (21)</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Bartsch et al. (2008) (22)</td>
<td>6</td>
<td>1.4</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Owen et al. (2007) (25)</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Benabid et al. (2006) (abstr) (23)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Mateos et al. (2007) (abstr) (24)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Lanteri-Minet et al.‡§</td>
<td>11</td>
<td>&gt;1</td>
<td>Not applicable</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Nikka et al.‡</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>50</strong></td>
<td><strong>23</strong></td>
<td></td>
<td><strong>59</strong></td>
</tr>
</tbody>
</table>

Total 61%

- Oculomotor disturbance & vertigo was the limiting factor for voltage increase in all patients
- Acute rx therefore does not work
- 42 days mean to effectiveness
- One death in Belgium; TIAs, hemorrhages described

Leone et al Cephalalgia 2008;28:787-97
## Deep Brain Stimulation

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Number treated</th>
<th>Efficacy</th>
<th>Significant adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leone et al.*</td>
<td>CH</td>
<td>16</td>
<td>81% had pain freedom or only sporadic attacks</td>
<td>1 sub-clinical hemorrhage</td>
</tr>
<tr>
<td>Schoenen et al.</td>
<td>CH</td>
<td>6</td>
<td>50% had pain freedom or &gt;50% decreased frequency</td>
<td>1 intra-operative hypertension followed by aneurysm rupture and death, 1 intra-operative panic attack with autonomic features</td>
</tr>
<tr>
<td>Black et al.</td>
<td>CH</td>
<td>2</td>
<td>100% had &gt;50% decreased frequency</td>
<td>None reported</td>
</tr>
<tr>
<td>Starr/Sillay et al.*</td>
<td>CH</td>
<td>5</td>
<td>60% &gt;50% decreased frequency or intensity</td>
<td>Intra-operative TIA</td>
</tr>
<tr>
<td>Bartsch et al.</td>
<td>CH</td>
<td>6</td>
<td>50% had &gt;50% decreased frequency</td>
<td>None reported</td>
</tr>
<tr>
<td>Fontaine et al.*</td>
<td>CH</td>
<td>11</td>
<td>55% had &gt;50% decreased frequency</td>
<td>1 subcutaneous infection, 1 transient loss of consciousness and hemiparesis with severe micturition syncope</td>
</tr>
<tr>
<td>Benabid et al.</td>
<td>CH</td>
<td>1</td>
<td>100% &quot;responded&quot;</td>
<td>Not reported</td>
</tr>
<tr>
<td>D'Andrea</td>
<td>CH</td>
<td>3</td>
<td>66% &quot;responded&quot;</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mateos et al.</td>
<td>CH</td>
<td>2</td>
<td>50% &quot;responded&quot;</td>
<td>Not reported</td>
</tr>
<tr>
<td>Leone et al.</td>
<td>CH</td>
<td>108 attacks</td>
<td>23% had &gt;50% decreased intensity of attacks</td>
<td>None reported</td>
</tr>
<tr>
<td>Walcott et al.</td>
<td>PH</td>
<td>1</td>
<td>Initial relief, follow-up pending</td>
<td>None reported</td>
</tr>
<tr>
<td>Leone et al.*</td>
<td>SUNCT</td>
<td>1</td>
<td>100% had pain freedom</td>
<td>None reported</td>
</tr>
<tr>
<td>Lyons et al.</td>
<td>SUNCT</td>
<td>1</td>
<td>100% had &gt;50% decreased frequency</td>
<td>Erectile dysfunction</td>
</tr>
</tbody>
</table>

| Total Number Treated Regardless of Condition | 55 |
| Number Responding | 36 |
| Percentage of Responders | 65% |
ONS: St Judes received CE in Sept 2011

• St. Jude Medical received European CE Mark approval for the Genesis neurostimulator for ONS for the treatment of intractable CM

• Their CM study, an RCT was reported by Silberstein et al at IHC Berlin (not published in peer reviewed journal yet)

• NS for the primary FDA endpoint defined as a significant difference between active and pbo who reported a 50-percent reduction in pain as measured on VAS and a ≥10 point difference between the 95% confidence intervals comparing the active and placebo groups

• Statistical significance was demonstrated across most measures.

• There was a statistically significant difference between the active and placebo groups was observed at the 40-percent reduction in pain:
  – 157 patients demonstrated participants in the active group showed a 41% improvement after 12 weeks of stimulation, compared to a 13% improvement in the control group
## Occipital Nerve Stimulation

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Number treated</th>
<th>Efficacy</th>
<th>Significant adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popeney et al.</td>
<td>CM</td>
<td>25</td>
<td>88% had &gt;50% decreased frequency or severity</td>
<td>36% had lead migration/ 12% had infection</td>
</tr>
<tr>
<td>Schwedt et al.</td>
<td>CM</td>
<td>8</td>
<td>50% had &gt;50% decreased severity</td>
<td>20% had lead migration</td>
</tr>
<tr>
<td>Saper et al.</td>
<td>CM</td>
<td>29</td>
<td>39% had &gt;50% decreased frequency &gt;50% or a decreased severity over 3 points</td>
<td>24% had lead migration/ 14% had infection</td>
</tr>
<tr>
<td>Schwedt et al.</td>
<td>HC</td>
<td>2</td>
<td>100% had &gt;50% decreased frequency/severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Burns et al.</td>
<td>HC</td>
<td>6</td>
<td>66% had &gt;50% decreased severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Schwedt et al.</td>
<td>CCH</td>
<td>3</td>
<td>66% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Magnis et al.</td>
<td>CCH</td>
<td>8</td>
<td>63% had &gt;50% decreased frequency</td>
<td>12% had unbearable paresthesia</td>
</tr>
<tr>
<td>Burns et al.</td>
<td>CCH</td>
<td>8</td>
<td>37% had &gt;50% decreased frequency or severity</td>
<td>62% had lead migraine or power loss</td>
</tr>
<tr>
<td>de Quintana et al.</td>
<td>CCH</td>
<td>4</td>
<td>50% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Goadsby et al.</td>
<td>PH</td>
<td>3</td>
<td>66% responded well</td>
<td>None reported</td>
</tr>
<tr>
<td>Goadsby et al.</td>
<td>SUNCT</td>
<td>2</td>
<td>50% had near complete resolution</td>
<td>None reported</td>
</tr>
</tbody>
</table>

**Total Number Treated Regardless of Condition**: 98

**Number Responding**: 58

**Percentage of Responders**: 59%

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## Vagal Nerve Stimulation

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Number 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>Ceechini et al.</td>
<td>CM</td>
<td>4</td>
<td>50% had &gt;50% decreased frequency</td>
<td>None reported</td>
</tr>
<tr>
<td>Mauskop et al.</td>
<td>CCH</td>
<td>2</td>
<td>100% had significant MIDAS decrease</td>
<td>None reported</td>
</tr>
</tbody>
</table>

### Total Number Treated Regardless of Condition
- **14**

### Number Responding
- **8**

### Percentage of Responders
- **57%**

The vagus connects to pain and nausea pathways implicated in migraine

Figure 1 Schematic view of central projections of vagus nerve afferents. NTS, Nucleus and tractus solitarius; PB, parabrachial nucleus; HT, hypothalamus; AM, amygdala; ILC, infralimbic cortex; VP, ventroposterior thalamic complex; IC, insular area; ILT, intralaminar and midline thalamic nuclei; CTX, cerebral cortex (From Schachter et al., with permission (2)).

Transcranial Magnetic Stimulation (TMS)

- TMS blocks cortical spreading depression (CSD) and can terminate migraine with aura (MA)
- 164 patients with MA (≥30%) treated ≥ 1 attack with TMS (n=82) or sham stimulation (n=82)
- 2 h PF significantly higher with TMS (32/82 [39%]) than with sham stimulation(18/82 [22%])
- No device-related serious adverse
- Has not worked in migraine wo aura (MO)

Background to sphenopalatine ganglion stimulator (SPG) studies

• Parasympathetic outflow may account for:
  — Ptosis, scleral injection, lacrimation, rhinorrhea, nasal stuffiness, and vasodilation causing pain in cluster headache attacks
  — Activation of meningeal neurogenic inflammation and vasodilation as peripheral pain mechanisms in migraine

• Parasympathetic outflow from the brainstem traverses the sphenopalatine ganglion (SPG)

• SPG blocks and ablation can be useful in treating cluster, and perhaps migraine, by interrupting efferent pathways

• Oxygen works in cluster at neurons in the parasympathetic facial/greater superficial petrosal nerve pathways to SPG and out

SPG Anatomy: the key to physiologic response
# Sphenopalatine Ganglion Stimulation

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Number treated</th>
<th>Efficacy</th>
<th>Significant adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibarra et al.*</td>
<td>CCH</td>
<td>1</td>
<td>Complete resolution</td>
<td>Stimulation failure</td>
</tr>
<tr>
<td>Ansarinia et al.</td>
<td>CCH</td>
<td>6</td>
<td>Aborted 14 or 18 attacks</td>
<td>None reported</td>
</tr>
<tr>
<td>Tepper et al.*</td>
<td>Migraine</td>
<td>10</td>
<td>20% had abolition of attack</td>
<td>None reported</td>
</tr>
</tbody>
</table>

* Double blinded placebo controlled.
+Stimulation interruption resulted in recurrence

Autonomic Technologies Inc (ATI) Neurostimulation System

Programmer Software
Physician sets stimulation parameters including frequency, pulse width, patient amplitude limits and active electrodes

Neurostimulator

Physician Programmer

Remote Controller
Telemetric activation and transmission

Controller Use
Hold the controller near the neurostimulator to apply therapy
ATI Neurostimulation System: Neurostimulator

- Angled Lead
- Six Electrodes
- Titanium Bone Fixation Plate
The Future?

SPG Stimulation for the Acute Treatment of Chronic Cluster Headache

Pathway CH-1 Study - Initial Results Presented at IHC Berlin, 2011

• Multi-center, randomized, controlled, dose range finding, prospective study

• Subjects chronic cluster headache, minimum 4 attacks/week and be dissatisfied with current treatment

• Each headache treated independently with random insertion of placebo

Pathway CH-1 Design

Design: Pre-implant Baseline: 4 weeks
Post-implant Stabilization: 3 weeks
Experimental: 3 weeks minimum or shortest time to 30 uses or 8 weeks maximum
Open label: 1 year

• Primary endpoints:
  – Acute pain relief by 15 minutes
  – Device-related SAE rate

• Secondary endpoints:
  – Acute pain free by 15 minutes
  – Rescue medication use
  – Acute Pain Relief at 30, 60, 90 minutes
  – Reduction in headache frequency

Preliminary SPG results

• Implants performed under general anesthesia, average 80 min

Preliminary Surgical Procedure Assessment

• No unanticipated adverse device effects

• 1 SAE: Neurostimulator explanted (lead migration)

• Most subjects experienced non-serious transient post surgical related AEs typical for oral surgery:

  • Sensory Dysfunction: paresthesias, numbness, allodynia and pain

  • Autonomic Dysfunction: dry eye and tearing

Preliminary SPG Stimulation Assessment

• Well tolerated with occasional mild uncomfortable paresthesias

• Uncomfortable paresthesias can be eliminated with programming
Preliminary Acute Stimulation Efficacy

Cluster Attack Response with up to 15 minutes of SPG Stimulation

<table>
<thead>
<tr>
<th>% of Attacks</th>
<th>T15</th>
<th>T90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>52%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>27%</td>
</tr>
</tbody>
</table>

**Pain Freedom**
Drop in Categorical Pain Scale from ≥2 (≥moderate) to 0 (none)

**Pain Relief**
Drop in Categorical Pain Scale from ≥2 (≥moderate) to 0 (none) or 1 (mild)

**48 Attacks Analyzed**
Attacks with only both 15 and 90 minute diary responses completed were included

Reduction in Attack Frequency

Conclusions on Advanced Interventions for Headache

1. Detoxification. There is not substitute, and it must be absolute. Do not set out on a therapeutic quest without this first step.

2. This may require an intravenous bridge over several days, either in an IV unit or inpatient in a medical model.

3. Structured multidisciplinary headache program. This is for patients who require an interdisciplinary approach, and may be day-hospital or inpatient.

4. OnabotulinumtoxinA for chronic migraine. Do not proceed to #5 without having tried 3 & 4.

5. Blocks and stimulators- will the future be SPG and ONS?
Thank you!