Neuromodulation Approaches to Migraine Treatment

Learning Objective

- Differentiate neuromodulation approaches to migraine treatment
Neuromodulation Approaches to Migraine

- Noninvasive neuromodulation represents a new therapeutic approach for acute and preventive treatment of migraine
- The FDA has approved 4 noninvasive non-significant risk neuromodulation devices
- For Acute Treatment of Migraine:
  - Transcutaneous Supraorbital Neurostimulation, External Trigeminal Nerve Stimulation (tSNS, eTNS)
  - Single-pulse Transcranial Magnetic Stimulation (sTMS)
  - Noninvasive Vagal Nerve Stimulation (nVNS)
- For Preventive Treatment of Migraine:
  - Transcutaneous Supraorbital Neurostimulation, External Trigeminal Nerve Stimulation (tSNS, eTNS)
  - Single-pulse Transcutaneous Magnetic Stimulation (sTMS)
  - Noninvasive Caloric Vestibular Stimulation (CVS) — not commercially available
- In Development for Acute Treatment of Migraine:
  - Remote Nonpainful Cutaneous Stimulation
  - Combined Supraorbital, Supratrochlear, and Greater Occipital Nerve Stimulation

Important Aspects of Noninvasive Neuromodulation for Headache Treatment

- All the approved devices and those in development have been accepted by the FDA as “non-significant risk” devices, meaning minimal, no, or trivial adverse events of no consequence
- The risk-benefit because of the absence of side effects shifts
- The FDA has set different standards for approval of noninvasive neuromodulation for headache treatment than for medications
- The devices do need to be safe and effective for approval
- The devices do not necessarily need to achieve the study primary end point if other end points are positive
- The devices do not necessarily need to have a sham-controlled trial to obtain an indication
tSNS

FDA Approved:

- **Transcutaneous Supraorbital Neurostimulation, External Trigeminal Nerve Stimulation (tSNS, eTNS)**
  - Single-pulse Transcranial Magnetic Stimulation (sTMS)
  - Noninvasive Vagal Nerve Stimulation (nVNS)
  - Noninvasive Caloric Vestibular Stimulation (CVS)

In Development:

- Remote Nonpainful Cutaneous Stimulation
- Combined Supraorbital, Supratrochlear, and Greater Occipital Nerve Stimulation (OS-TNS)

*FDA approved

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Transcutaneous Supraorbital Neurostimulation (tSNS)

**FDA-Approved Acute and Preventive**

- One 67-patient RCT for prevention; Turn it on and wear it **20 minutes/d**
- Migraine days/month in 3rd month: Not Significant
- ≥50% reduction in migraine days/month, 38.2% (P= .023)
- tSNS received FDA approval 2014 as non-significant risk device for migraine preventive treatment; in 2017 for migraine acute treatment; now Dual device

HA=headache; NS=not significant; RCT=randomized controlled trial.
**tSNS: Acute Treatment of Migraine Trial**

- Single-center, 30-patient, open-label trial of 1 hour stimulation with eTNS for acute migraine treatment: patients could have episodic migraine or chronic migraine (EM or CM)
- Primary end point was change in pain intensity after 1 hour of treatment
- Mean pain intensity was reduced by 57% after 1 hour of treatment
- 77% of patients reported >50% pain relief at 1 hour


**How and Where Does tSNS/eTNS Work?**

- Inhibitory neuromodulation travels in on the supraorbital and supratrochlear branches of V1
- These synapse in the trigeminocervical complex and ascend to thalamus and cortex
- With time, there is a down-regulation of the central pain matrix and normalization of cortical pain control centers

PET = positron emission tomography.
**sTMS**

**FDA Approved:**
- Transcutaneous Supraorbital Neurostimulation, External Trigeminal Nerve Stimulation (tSNS, eTNS)*
- **Single-pulse Transcranial Magnetic Stimulation (sTMS)**
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**Single-pulse Transcranial Magnetic Stimulation (sTMS)**

**FDA-Approved for Acute and Preventive Migraine Treatment**

N=164 (82 sham); 2 pulses 30 sec apart within 1 hour of aura onset

2 h pain-free (PF): 39% sTMS vs 22% sham (P=0.0179)

CSD=cortical spreading depression.

sTMS ESPOUSE Prevention Trial

- **Open-label** sTMS study, 4 pulses twice daily for prevention with as-needed extra pulses for acute treatment, N=132, compared with statistical sham
- EM or CM, 4 to 25 headache days/mo, mean 9 days/mo
- Primary end point at 3 months: ≈ ↓ 3 days/mo from baseline
- Positive for ≥50% responder rate (46%), decrease in acute migraine medication days, and ↓HIT6

<table>
<thead>
<tr>
<th>End Points per protocol</th>
<th>Baseline</th>
<th>Change, Mean at 3 months</th>
<th>P vs created placebo rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache Days</td>
<td>9.06</td>
<td>-2.98 to 7.04</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Acute Medication Days</td>
<td>10.30</td>
<td>-3.18 to 7.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HIT-6</td>
<td>64.04</td>
<td>-3.63 to 60.41</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

HIT6=Headache Impact Test.

sTMS FDA-Approved for Acute 2013; Approved for Prevention 2017

- Adverse events consistent with a non-significant risk device
- Likely works at least 2 ways: terminates cortical spreading depression/depolarization (CSD) and down-regulates central pathways
- Appears to inhibit thalamocortical pathways
- FDA approved for **both acute treatment and prevention of migraine** in July 2017
nVNS

FDA Approved:
- Transcutaneous Supraorbital Neurostimulation, External Trigeminal Nerve Stimulation (tSNS, eTNS)*
- Single-pulse Transcranial Magnetic Stimulation (sTMS)*
- **Noninvasive Vagal Nerve Stimulation (nVNS)***
  - Noninvasive Caloric Vestibular Stimulation (CVS)*

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**Noninvasive Vagal Nerve Stimulation (nVNS)**

- Hand-held, patient-controlled device
- Preferentially activates vagal afferent, not those vagal efferent pathways that cause bradycardia and bronchoconstriction
- Inhibits rat CSD, central trigeminovascular, and thalamocortical pathways
- **Approved in the United States for**
  - Acute treatment of episodic cluster headache (April 2017)
  - Acute treatment of migraine (January 2018)
  - Adjunctive use in prevention of cluster in (late 2018)
- No serious adverse events, non-significant risk device

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nVNS Randomized Controlled Trial (RCT) for Acute Treatment of Migraine

- Randomized controlled trial in Italy of 2-minute cycles in sequence bilaterally
- OK to repeat in 15 minutes and again in 2 hours

<table>
<thead>
<tr>
<th>End Point %</th>
<th>Placebo</th>
<th>nVNS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary End Point 2-hour Pain Free</td>
<td>19.7</td>
<td>30.4</td>
<td>.067</td>
</tr>
<tr>
<td>2-hour Headache Relief</td>
<td>27.6</td>
<td>40.8</td>
<td>.030</td>
</tr>
<tr>
<td>2-hour 50% Responder Rate for Pain Free</td>
<td>18.2</td>
<td>32.4</td>
<td>.020</td>
</tr>
<tr>
<td>2-hour 50% Responder Rate for Headache Relief</td>
<td>32.3</td>
<td>47.6</td>
<td>.026</td>
</tr>
</tbody>
</table>


The Future for nVNS

- nVNS has the most and highest quality RCTs of any non-invasive neuromodulation device studies in headache
- FDA approved for acute treatment of migraine:
  - 2 cycles of 2 minutes each and the option of 2 more 2-minute cycles 15 minutes later if pain not resolved
- FDA approved for acute treatment of episodic cluster headache attacks:
  - 3 cycles of 2 minutes at attack onset
- FDA approved as adjunctive treatment for prevention of cluster headache
- Need a longer RCT for prevention of chronic migraine
- An RCT under way for episodic migraine prevention
CVS

FDA Approved:
- Transcutaneous Supraorbital Neurostimulation, External Trigeminal Nerve Stimulation (tSNS, eTNS)*
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Caloric Vestibular Stimulation (CVS) RCT: FDA-Approved for Prevention
- 6-site, placebo-controlled, blinded, home-use protocol
- Active N = 28; Placebo N = 18
- 4 to 14 HA days/mo
- Worn 20 minutes twice/d
- Positive for:
  - 1° end point: ↓ migraine d, 3rd mo
  - 2°: RR, acute meds, mood, cognition, balance
  - ↓ 3.6 days per month per protocol

AEs = adverse events; RR = relative risk.
Hypothetical Mechanism of Action: VIII, V, Trigeminocervical Overlap in Brainstem

![Diagram of Trigeminocervical Complex]


The Future for CVS Prevention

- FDA approved 2018 for migraine prevention
- New design proved necessary
- To be tested in 20 minutes qd vs bid with new design in 2019
- Non-significant risk device, no adverse events greater than with placebo
- Not commercially available
- Not yet tested in vestibular migraine
Cost and Access for Approved Noninvasive Neuromodulation Devices

- As of August 2018, there is almost no insurance coverage for these FDA-approved devices, a serious and unjustified obstacle to use
- **tSNS (eTNS):** Cost: $550 to buy; can return for money back 60 days; $25 every 2 to 3 months for replacement electrodes
  - Must be ordered online by the patient with a provider prescription
  - Covered by the VA, but no other insurance
- **sTMS:** Current cost – rent, can not buy: $150/mo for the first 3 months with 90 day money back guarantee; $230/mo for the first year thereafter
- **nVNS:** Cost: ≈$575/month. The device is re-loaded at this rate; covered by some Pharmacy Benefit Managers
- **CVS:** Not commercially available

Remote Nonpainful Cutaneous Stimulation

**FDA Approved:**

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In Development:

- **Remote Nonpainful Cutaneous Stimulation**
  - Combined Supraorbital, Supratrochlear, and Greater Occipital Nerve Stimulation (OS-TNS)
Remote Nonpainful Electrical Upper Arm Skin Stimulation for Acute Migraine Treatment

- Prospective, double-blinded, randomized, crossover, sham-controlled trial
- Migraineurs applied electrical patch to upper arm soon after attack onset for **20 minutes**, at various pulse widths, for up to 20 attacks
- 50% pain reduction for 64% of participants based on best of 3 pulse width stimuli per individual vs 26% sham, N=71 patients, 299 treatments
- Second study completed in the United States; positive results for both primary and secondary endpoints presented in November 2018


Remote Nonpainful Skin Stimulation

- Possible mechanism of action:
  - The device likely activates descending inhibition pathways via *conditioned pain modulation (CPM)* effect
- Premise: Pain inhibits pain
- Once there is a noxious stimulus at any body location (migraine), it may be inhibited by a second stimulus at a different location (device) with high intensity, not perceived as painful

Combined Stimulation

FDA Approved:
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In Development:
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Combined Supraorbital, Supratrochlear, and Greater Occipital Nerve Stimulation (OS-TNS)

- Randomized, sham-controlled trial for acute treatment of episodic migraine attacks, N=30, treatment duration 45 minutes
- Primary End Point:
  - Decreased pain VAS score in the treatment group vs increased pain VAS score in the control group (-79.2% vs +14.9%, P=.0002)
- 2-hour Pain-free: active OS-TNS vs sham (P=.0031)

*FDA approved

VAS=visual analog scale.
Hering-Hamel R. Cephalalgia 2017;37(suppl 1):73. (Abstract PO-01-035)
How Might the Combined Device Work?

- This device may inhibit nociceptive traffic either by direct inhibition or indirectly by activating descending neuromodulation.
- Occipital nerve blocks work by inhibiting the trigeminocervical complex.
- A large US RCT will be starting in 2018 for regulatory approval for acute treatment.

In General, How Do Neuromodulation Devices Work?

- Some work by specific mechanisms, such as suppression of cortical spreading depression/depolarization by sTMS and nVNS.
- The noninvasive devices access afferent input and inhibit or modulate central pain pathways:
  - Both sTMS and nVNS inhibit thalamocortical pathways.
  - It is likely CVS inhibits the trigeminocervical system as the vestibular afferents come in at the same level as V, and there is cross talk.
  - Supraorbital and greater occipital nerve blocks can terminate acute attacks, and sTNS and OS-TNS both may access central pathways via these afferents.
- Similarities for the devices in terms of MOA may be more than differences.
- As with oral prophylaxis, remember, neuromodulation takes time to work.
- Neuromodulation is not neuro-termination!
Summary of Devices

FDA Approved:
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The Future Is Now!

- We can try noninvasive neuromodulation first in some patients, add them second, or adjunctively
  - tSNS and sTMS work for both migraine acute and preventive treatment
  - nVNS is approved for migraine acute treatment and is being studied for prevention
- Since monoclonal antibodies work in migraine, should minimally invasive neuromodulation come before biologics or after?
- Further noninvasive devices are in development for both migraine prevention (CVS and nVNS) and migraine acute treatment (remote nonpainful skin stimulation and OS-TNS)
- Patients want these treatments, and the risk-benefit ratio strongly suggests their use
- Providers should lobby payers to get the FDA-approved devices covered