Decoding Complexities
Strategies in Diagnosis and Treatment of Migraine
2018
Migraine Diagnosis and Treatment

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**Disclosure: Merle L. Diamond, MD**

| Consultant            | • Alder BioPharmaceuticals  
|                       | • Allergan  
|                       | • Amgen  
|                       | • Depomed  
|                       | • Lilly  
|                       | • Supernus Pharmaceuticals  
| Advisory Boards       | • Avanir Pharmaceuticals  
|                       | • Lilly  
|                       | • Pernix Therapeutics  
| Speaker Bureau        | • Avanir Pharmaceuticals  
|                       | • Depomed  
|                       | • Pernix Therapeutics  
|                       | • Teva Pharmaceutical Industries  |
Background

Treatment guidelines recommend preventive treatments for people with frequent and disabling headaches.

Only one-third of people with migraine who meet guidelines for preventive treatments receive them.

Of those who start preventive treatment, 80% lapse over the course of 1 year.

- Why aren’t preventive treatments being more widely utilized?
- How can we optimize the appropriate use of preventive treatments?

Migraine Is a Global Problem

Affects >10% of population (959 million globally)¹

>44 million individuals affected in the United States²

30 to 39 years³ Prevalence peaks in middle life during prime years³

~20% to 35% of people with migraine have ≥4 days per month³

2 to 3x more common in women vs men⁵⁻⁷

Global prevalence⁴ 15-25% 6-8%
Lifetime prevalence⁴ 43% 18%

Migraine Frequency Exists on a Spectrum

- One-third of people with migraine have headache on ≥4 days per month, and 6% have headache on 15 or more days per month.\(^1\)

- Traditional criteria for preventive treatment are defined in part by headache days.

Migraine Frequency Is Dynamic

• Migraine frequency can increase over time and may transition from episodic to chronic, a process termed “chronification”\(^2\)

• Migraine can also transition from chronic to episodic\(^2\)

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**Migraine Frequency Is Dynamic**

<table>
<thead>
<tr>
<th>Frequency of Headache Days in Migraine ((N=8281)) (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache Days per Month</td>
</tr>
<tr>
<td>% of Patients</td>
</tr>
<tr>
<td>0-1             23.7</td>
</tr>
<tr>
<td>2-3             41.4</td>
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<tr>
<td>4-6             14.7</td>
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<tr>
<td>7-9             8.9</td>
</tr>
<tr>
<td>10-11           4.1</td>
</tr>
<tr>
<td>12-14           1.6</td>
</tr>
<tr>
<td>15-18           1.9</td>
</tr>
<tr>
<td>19-21           1.4</td>
</tr>
<tr>
<td>22-24           0.6</td>
</tr>
<tr>
<td>25-27           0.7</td>
</tr>
<tr>
<td>28-31           1.0</td>
</tr>
</tbody>
</table>

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Migraine Is Usually Associated With Severe Impairment or Need for Bed Rest

Migraine-related impairment was common in the American Migraine Prevalence and Prevention (AMPP) study of >18,000 individuals with migraine.\(^1\)

Respondents were asked how they are “usually affected by severe headaches” with the following response options:\(^2\)

- Able to work/function normally
- Working ability or activity impaired to some degree
- Working ability or activity severely impaired
- Bed rest required

Severe Impairment or Bed Rest Required

- 54%

Some Impairment

- 39%

Function Normally

- 7%

Disability Increases Progressively With Increasing Number of Headache Days

International Burden of Migraine Study (N=8281)

- <15 headache days/month (n=7812)
- ≥15 headache days/month (n=469)

Level of disability based on Migraine Disability Assessment (MIDAS) score:
- Little or no disability (score 0-5)
- Mild disability (score 6-10)
- Moderate disability (score 11-20)
- Severe disability (score 21-40)
- Very severe disability (score 41-270)

Little or no disability (score 0-5)
Mild disability (score 6-10)
Moderate disability (score 11-20)
Severe disability (score 21-40)
Very severe disability (score 41-270)

What Can We Offer This Patient?
Abortive Medical Toolbox

Real case.
1899
(introduced in)

NSAIDs (nonsteroidal anti-inflammatory drugs)

- Block cyclooxygenase (COX) enzymes
- Reduce prostaglandins
Ergots

- 5-HT$_{1B/1D}$ agonist
- Prolonged interaction with 5-HT$_{1A}$, 5-HT$_{5}$, 5-HT$_{2}$, 5-HT$_{7}$, $\alpha$-adrenoceptors, and dopamine (DA) D2 receptors
Triptans

- 5-HT$_{1B/1D}$ agonist
- 5-HT$_{2A}$ receptors in peripheral arteries

1992 (FDA approval)
2008
(FDA approval)

Triptan/NSAID
• 5-HT_{1B/1D} agonist + NSAID
Recent
(FDA approval)

Neuromodulatory devices

- Transcranial magnetic stimulation (sTMS, eNeura)
- Supraorbital external trigeminal nerve stimulation (TENS, Cefaly)
- Noninvasive vagus nerve stimulator (nVNS, gammaCore)
Consider Prevention When...

**Significant Interference**
With routine activities—despite use of acute treatment

**Elevated Risk**
Medication overuse

**Attack Frequency**
> 1/week

**Acute Medications**
Ineffective
Contraindicated
Troublesome AEs
Overused

**Patient Preference**

**Uncommon Subtypes Present**
Hemiplegic
Brainstem
Prolonged aura
Migrainous infarction
Migraine Prevention Is Underused

The AMPP study surveyed 18,968 individuals with migraine and found that

- Approximately 39% were candidates for or should be considered for prophylactic treatment\(^1\)
- Approximately 29% had received prophylactic medication for migraine in the past but discontinued treatment\(^2\)
- Approximately 12% were current users of prophylactic medication for the treatment of migraine\(^1\)

Data from the AMPP study suggest that approximately two-thirds of individuals with migraine who qualify for prophylaxis do not receive it\(^2\)

Adherence to Current Migraine Preventives Is Poor

Retrospective Claims Database Analysis:
Insured Patients With Migraine and ≥15 Headache Days/Month (N=8688)*

83% of people with migraine discontinue preventive treatment over 1 year

*Oral prophylactic medications analyzed in this retrospective study were limited to specific antidepressants, β-blockers, and anticonvulsants. Adherence rates were reported as the proportion of patients with a proportion of days covered ≥80%.

Reasons Patients Discontinue Oral Prophylactic Medication

International Burden of Migraine Study-II Assessed Prophylactic Therapy Patterns in 1165 Patients With Migraine

Patient-Reported Reasons for Discontinuation of Prophylactic Medication

Lack of efficacy and medication side effects are the most common reasons for discontinuation of prophylactic medications.
Defining Success in Migraine Prevention

1. Standard definition of success is a 50% headache response rate (50% reduction in migraine days from baseline to weeks 9 to 12 or later).

2. This definition is predicated on the art of the possible or on what available treatments deliver.

3. Patients would prefer greater reductions in migraine days that would be achieved more quickly.

4. High discontinuation rates on current therapies may reflect unmet and inadequately managed patient expectations.
What Can We Offer This Patient?
Preventive Medical Toolbox

Real case.
Tricyclic antidepressants

- Increase levels of norepinephrine (NE) and 5-HT
- Block histaminic, cholinergic, and α1-adrenergic receptor sites

mid-1960s
(case reports showing benefit)
1979 (FDA approval)

Beta blockers
- Noradrenergic receptor antagonists
Antiepileptics

- Enhance gamma-aminobutyric acid (GABAergic) inhibitory neurotransmission
- Decrease glutamatergic excitatory neurotransmission

1996 (FDA approval)
OnabotulinumtoxinA

- Block acetylcholine release
- May act in part through blocking CGRP release

2010 (FDA approval)
Recent (FDA approval)

Neuromodulatory devices

- Supraorbital external trigeminal nerve stimulation (TENS, Cefaly)
- Transcranial magnetic stimulation (tTMS, eNeura)
- Caloric vestibular stimulation (CVS, Scion NeuroStim)
Anti-CGRP MAB therapy

- Targets the CGRP receptor or ligand
- 3 compounds have FDA-approval

2018 (FDA approval)
Addressing the Unmet Need in Preventive Treatment

Approximately 80% of patients discontinue oral preventive therapy after 1 year of treatment\(^1\)

More than 40% of patients receiving therapy still experience at least one migraine-related issue, including headache-related disability, treatment dissatisfaction, and/or excessive opioid use\(^2\)

Up to 13% of patients with migraine receiving acute or preventive therapy still have at least 1 emergency department visit a year\(^3\)

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All Approved Oral Drugs Share Similar Efficacy to Prevent Migraine

215 publications of RCTs provided mostly low-strength evidence because of the risk of bias and imprecision

<table>
<thead>
<tr>
<th>Approved Drugs</th>
<th>Off-Label Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate (9 RCTs)</td>
<td>Metoprolol (4 RCTs)</td>
</tr>
<tr>
<td>Divalproex (3 RCTs)</td>
<td>Atenolol (1 RCT)</td>
</tr>
<tr>
<td>Timolol (3 RCTs)</td>
<td>Nadolol (1 RCT)</td>
</tr>
<tr>
<td>Propranolol (4 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

- Topiramate and antidepressants result in more adverse events
- No significant differences in treatment discontinuation due to adverse events between labeled drugs
- Angiotensin-converting enzyme inhibitors and beta blockers most tolerable and effective
- Long-term evidence is lacking (>3-month duration)

RCTs=randomized, controlled trials.
Communication

Establish goals

Headache toolbox

Check in

Calendar/diary
Disclosures 2017-2018 Robert Kaniecki, MD

Consultant/Advisory Boards

Alder Biopharmaceuticals
New Horizons in Headache Treatment!
Overview

• New formulations of existing medications

• New medications and devices
  • New classes of acute medication in development
    • Gepants, serotonin (5-HT$_{1F}$) agonists [ditans]
  • New classes of preventive medication released or in development
    • Anti-calcitonin gene-related peptide (CGRP) or anti-CGRP receptor monoclonal antibodies (MABs)
  • Neuromodulation
    • Noninvasive, FDA approved: Transcutaneous supraorbital neurostimulation (tSNS), single pulse transcranial magnetic stimulation (sTMS), non-invasive vagal nerve stimulation (nVNS), and caloric vestibular stimulation (CVS)
    • Noninvasive in development: Remote nonpainful electrical upper arm skin stimulation and combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS)
    • Minimally invasive in development: Sphenopalatine ganglion stimulation (SPG)
Pathophysiology and Neurotransmitter Targets
Pathophysiology

Peripheral pain mechanisms:
CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP)

Meningeal blood vessel
Sensitized peripheral neuron (trigeminal ganglion)
Cutaneous allodynia
Throbbing pain

Activated central neuron (thalamus)
Pain processing:
Sensitized central neuron (trigeminal cervical complex)
Neck muscle tenderness

Central generator?

Tepper SJ. Adapted from C79, Comprehensive Migraine Education Program 1 presented at AAN 2017; Boston.
Serotonin (5-HT) Mechanisms in Migraine

- Anti-migraine targets: 
  5-HT$_{1B/1D}$ receptors
  5-HT$_{1F}$ receptors
CGRP Mechanisms in Migraine

- Neuropeptide belonging to calcitonin family
  - Calcitonin
  - Amylin
  - Adrenomedullin
  - Intermedin

- Present at all migraine pathogenesis sites
- Increases in migraine, decreases with treatment

CGRP = cyclic adenosine monophosphate. CLR = calcitonin receptor-like receptor. NS = nervous system. RAMP = receptor activity modifying protein. RCP = receptor component protein.

CGRP Signaling and Blockade

New Devices for Delivering Medications
Devices for Delivering Medications

**FDA-approved and available**¹
- Sumatriptan autoinjectors
- Sumatriptan breath-powered dry nasal powder

**In development**²
- **Phase 3 RCTs completed**
  - Zolmitriptan skin patch (ADAM)
  - DFN-02 sumatriptan nasal spray
- **In development**
  - Oxytocin nasal spray, T1-001
  - Sumatriptan skin patch, KC5010
  - Zolmitriptan oral inhalation, CVT-427
  - Sumatriptan oral spray, SUD-001
  - DHE HFA nasal spray, powder nasal spray, novel autoinjectors

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New Acute Migraine Treatments
Lasmiditan - 5-HT$_{1F}$ Agonist
Phase 3 Trials for Acute Treatment of Episodic Migraine

• 2-Hour Pain Freedom:
  100 mg- 28.2-31.4%
  200 mg- 32.4-38.8%
  Placebo- 15.3%-21.3%

• Both doses also eliminated the Most Bothersome Symptom (MBS), chosen by the patient from nausea, photophobia, or phonophobia at 2 hours

• Adverse events in the Phase 3 RCTs:
  Dizziness + vertigo =100 mg average 15.5%
  200 mg average 16.8%
  Somnolence + fatigue + lethargy =100 mg average 10.4%
  200 mg average 12%

• For comparison, rizatriptan 10 mg prescribing information:
  Dizziness 20% greater than lasmiditan
  Somnolence + fatigue 15% greater than lasmiditan

Conclusions for lasmiditan acute treatment:
- Efficacy and side effects similar to rizatriptan
- Central adverse events probably due to central 5-HT$_{1F}$ activity and likely no vasoconstrictive effects

Gepants - Small Molecule CGRP Receptor Antagonists

**Acute Treatment of Episodic Migraine**

- 6 gepants effective in acute migraine treatment: olcegepant, BI 44370 TA, telcagepant, MK-3207, rimegepant, and ubrogepant
- BI 44370 TA, telcagepant, and MK-3207 all reportedly liver toxic
- Efficacy: **Ubrogepant** Phase 3 acute treatment of episodic migraine:
  - 2-hour pain freedom: 50 mg 19.2%; 100 mg 21.2%; placebo 11.8%; Also relieved 2-hour MBS
- Efficacy: **Rimegepant** Phase 3 acute treatment of episodic migraine:
  - 2-hour pain freedom: 75 mg 19.2-19.6%; placebo 12%-14.2%; also relieved 2-hour MBS
- Adverse events
  1. Liver, **Ubrogepant**: 6 cases with ALT >3x ULN, one of which was 10X ULN; 1 case with placebo >3x ULN; **Rimegepant**: one case each from active and placebo with >3x ULN
  2. Tolerability, **Ubrogepant**: nausea, somnolence, dry mouth in <5% of patients; **Rimegepant**: nausea in <2% of patients

**Conclusions for gepants acute treatment:**

- Efficacy and side effects similar to naratriptan
- Tolerability is excellent
- Liver safety will still need to be explored
- Prevents vasoconstriction; no expectation of vasoconstriction

**Preventive Treatment of Episodic Migraine**

- Telcagepant had liver toxicity when given daily
- **Atogepant** vs placebo positive phase 2 for migraine prevention, no liver signal; **Rimegepant** to be tested

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New Preventive Migraine Treatments
MABs to CGRP or the CGRP Receptor

• Physiological differences from presently available options
  • MABs are big molecules that do not cross the blood brain barrier
    • Peripheral, not central, mechanism of action
  • MABs are eliminated by the reticuloendothelial system
    • No hepatic, renal toxicity
• Clinical differences from presently available options
  • Work to prevent episodic and chronic migraine, and medication-overuse headache
  • Have quick onset, separating from placebo within 1 week
    • Clinically meaningful response by 1 month
  • Have favorable responder rates for ≥50%, 75%, and 100%
  • Have safety and tolerability similar to placebo
### 4 Injectable MABs to CGRP or Its Receptor

**Terms:** n=neurologic; umab=fully human; zumab=humanized, 90-95% human

<table>
<thead>
<tr>
<th></th>
<th>Erenumab-aooe (fully human)</th>
<th>Galcanezumab-gnlm (90% humanized)</th>
<th>Fremanezumab-vgrm (95% humanized)</th>
<th>Eptinezumab (90% humanized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studied for</td>
<td>EM, CM</td>
<td>EM, CM, eCH, cCH</td>
<td>EM, CM, eCH, cCH</td>
<td>EM, CM</td>
</tr>
<tr>
<td>Dosing</td>
<td>Monthly SC</td>
<td>Monthly SC</td>
<td>Monthly or quarterly SC; IV load for CH</td>
<td>Quarterly IV</td>
</tr>
<tr>
<td>Target</td>
<td>CGRP receptor</td>
<td>CGRP ligand</td>
<td>CGRP ligand</td>
<td>CGRP ligand</td>
</tr>
<tr>
<td>Regulatory status</td>
<td>FDA approved May 17, 2018; EM &amp; CM registration</td>
<td>FDA approved September 28, 2018; EM &amp; CM registration</td>
<td>FDA approved September 14, 2018; EM &amp; CM registration</td>
<td>Presented (+) phase 3 EM &amp; CM RCTs</td>
</tr>
</tbody>
</table>

Clinical Utility of the 4 MABs

- All data announced to date for EM and CM have shown a reduction in mean monthly migraine days (MMDs) with a magnitude of 1-3 days drop over placebo
  - Using MMDs is necessary from a regulatory standpoint, but not clinically useful endpoint
  - More useful are certain secondary endpoints, such as responder rates

- Erenumab in CM prevention showed a 6.7-day **reduction in MMDs** in the pivotal trial, which would represent 79 fewer migraine days/year\(^1\); for eptinezumab, an **8-day reduction** from baseline would be 96 fewer migraine days per year

- The **≥50% responder rates** (secondary endpoints) in the galcanezumab EM registration studies were ≥50%, in the eptinezumab CM study 61%, and the **≥75% responder rates** for both were about 1/3 of patients\(^2,3\)

- Erenumab 140 mg worked in patients who had failed 2-4 preventive medications in a prospective randomized placebo-controlled trial\(^4\)

Practical dosing

- Erenumab – 70 mg or 140 mg SQ monthly
- Fremanezumab – 225 mg SQ monthly or 775 mg SQ quarterly
- Galcanezumab – 240 mg SQ month 1, then 120 mg SQ monthly
- Eptinezumab – Dosing TBA, IV infusion every 3 months
## Neuromodulation

<table>
<thead>
<tr>
<th>FDA-approved</th>
<th>In development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td><strong>5</strong></td>
</tr>
<tr>
<td>Transcutaneous supraorbital neurostimulation</td>
<td>Remote, nonpainful stimulation for acute treatment of migraine (Nerivio Migra)</td>
</tr>
<tr>
<td>(tSNS, e-TNS, Cefaly)</td>
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<tr>
<td><strong>2</strong></td>
<td><strong>6</strong></td>
</tr>
<tr>
<td>Single Pulse Transcranial Magnetic Stimulator</td>
<td>Combined occipital and supraorbital transcutaneous nerve stimulation</td>
</tr>
<tr>
<td>(sTMS, SpringTMS)</td>
<td>(OS-TNS, Relievion)</td>
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<tr>
<td><strong>3</strong></td>
<td><strong>7</strong></td>
</tr>
<tr>
<td>Noninvasive vagal nerve stimulator</td>
<td>Sphenopalatine ganglion stimulation</td>
</tr>
<tr>
<td>(nVNS, gammaCore)</td>
<td>(SPGs, Pulsante)</td>
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<tr>
<td><strong>4</strong></td>
<td></td>
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<tr>
<td>Noninvasive caloric vestibular stimulation</td>
<td></td>
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<tr>
<td>(CVS, Scion NeuroStim)</td>
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</table>
Transcutaneous Supraorbital Neurostimulation (tSNS, e-TNS, Cefaly)

- FDA approved in 2017 for preventive and acute treatment of migraine as nonsignificant risk device
- **Preventive RCT**: Turn it on and wear it 20 minutes/day; N=67
  - ≥50% reduction in migraine days/month
- **Acute RCT**: turn on in different setting for acute attack for 1 hour; N=57
  - Mean change in visual analog (VAS) 1-hour pain score reported as statistically significant in active vs placebo
  - Cost: $550 (initial)
  - Cost: $25 (3 electrodes every 3 months)

HA=headache. NS=non-significant

Single Pulse Transcranial Magnetic Stimulation (sTMS, SpringTMS)

- Magnetic pulses disrupt cortical spreading depression (CSD), the basis for aura, and down-regulate thalamocortical pain pathways
- 1 RCT for acute treatment of migraine with aura, N=167
  - 2 hours pain-free: 39% sTMS vs 22% sham (P=0.0179)
- 2 studies for prevention of migraine with prn extra pulses, N=249
  - 4-25 headache days for inclusion; 4 pulses BID with extra prn up to 17 pulses per day
- FDA-approved in 2017 as nonsignificant risk device for preventive and acute treatment of migraine
- Rental cost $225/month

Noninvasive Vagal Nerve Stimulator (nVNS, gammaCore)

- Handheld, patient-controlled device, which preferentially activates afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction\(^1\)
  - Inhibits CSD\(^2\) and central trigeminovascular and thalamocortical pathways\(^3,4\)
- 2 RCTs showed effectiveness in terminating attacks of episodic cluster headache, but not chronic cluster headache\(^5,6\)
- 2 RCTs failed primary endpoints in prevention and acute treatment of migraine, but showed suggestive secondary endpoints\(^7,8\)
- FDA-approved as nonsignificant risk device for acute treatment of episodic cluster headache attacks and acute treatment of migraine
- $575/month for loaded stimulation package

Caloric Vestibular Stimulation (CVS, Scion NeuroStim)

- 6-site, placebo-controlled, blinded
- 4-14 HA days/month
- 1° endpoint: ↓ migraine days, 3rd month
- Active: -3.6 HA days vs baseline ($P < 0.0001$), -2.7 HA days vs sham ($P=0.012$)
  - 2° endpoints also positive
- Approved by FDA in March 2018 for prevention of EM ages 12 and above; not commercially available yet

AEs >1 patient: nausea, dizziness, ear sx, tinnitus.

Placebo dizziness =
Active dizziness (4 in each).
Remote Nonpainful Electrical Upper Arm Stimulation (Nerivio Migra)

- Prospective, double-blinded, randomized, crossover, sham-controlled trial in acute migraine
- Participants with migraine 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 underway in US

Combined Occipital and Supraorbital Transcutaneous Nerve Stimulation (OS-TNS, Relievion)

- Randomized, sham-controlled trial for acute treatment of migraine attack, N=30, treatment duration 45 minutes
- Decreased pain VAS score in the treatment group vs increased pain VAS score in the control group (-79.2% vs + 14.9%, \( P=0.0002 \))
- 2-hour pain-free: active OS-TNS vs sham (\( P=0.0031 \))
Sphenopalatine Ganglion Stimulation (SPGs, Pulsante)

- Wireless device with programmable remote control
- Inserted via a minimally invasive oral procedure
- 1 RCT showed efficacy for acute and preventive treatment of chronic cluster headache
- Around 2/3 of cluster patients have relief after stimulation within 15 minutes and/or at least a 50% reduction in cluster attack frequency
- The US randomized controlled trial for acute treatment of chronic cluster headache was announced as positive in 6/18
Summary Of Migraine Management Advances

• New devices delivering existing medications
• New acute and preventive migraine medications
• New neuromodulatory devices for migraine
Q & A Session

For valuable resources related to this activity, please visit

forefrontcollabactivities.com
/Diamond2018