Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention Systematic Review

Washington P&T Committee Meeting
October 18, 2023
Presented by Sara Kennedy, MPH
Background: Migraine Headache

• Diagnostic criteria for migraine headaches
  ▪ Headache attacks from 4 to 72 hours with or without aura
  ▪ Chronic migraine (15 or more headaches per month for at least 3 months)
  ▪ Episodic migraine (fewer than 15 headaches per month)

• Preventive treatments: antidepressants, anticonvulsants, beta blockers, and botulinum toxin

• Acute treatments: triptans, dihydroergotamine, nonsteroidal anti-inflammatories, and anti-nausea drugs

• Calcitonin gene-related peptide (CGRP) is a neuropeptide involved in migraine headache pathophysiology
Background: Cluster Headache

• Multiple headaches occurring within a period of days to weeks to months (cluster periods); severe, unilateral pain, often located around the eye, with tearing, runny nose, and sweating
  - Episodic: at least 2 cluster periods (lasting from 7 days to 1 year) separated by a pain-free remission of 3 months or longer
  - Chronic: lack of a sustained remission between clusters

• Acute treatments: oxygen, triptans, lidocaine, and ergots

• Preventive treatments: verapamil, steroids, ergots, topiramate, lithium, and nerve blocks

• Etiology is complex; CGRP also appears to be involved in pathophysiology
Background: CGRP Inhibitors

### Monoclonal antibody targeting CGRP Receptor
- **Erenumab SC**
- **Fremanezumab SC**
- **Galcanezumab SC**

### Monoclonal antibodies targeting CGRP ligand
- **Eptinezumab IV**
- **Atogepant PO**
- **Rimegepant PO**

### Small molecule inhibitors
- **Ubrogepant PO**
- **Zavegepant PO**

**Abbreviations.** CGRP: calcitonin gene-related peptide; FDA: US Food and Drug Administration; IV: intravenous; PDUFA: Prescription Drug User Fee Act; PO: oral; SC: subcutaneous.

**Notes.** a Added to scope since most recent report. b New indication since most recent report.
Expanded Report Scope

• 2018 report included:
  - 4 drugs (eptinezumab, erenumab, fremanezumab, and galcanezumab)
  - 1 indication (migraine prevention)

• 2020 report included:
  - 2 additional drugs (rimegepant and ubrogepant)
  - 2 additional indications (acute migraine treatment and cluster headache prevention)

• 2023 report includes:
  - 2 additional drugs (atogepant and zavegepant)
PICOS

• Populations:
  - Adults
  - Episodic or chronic migraine
  - Chronic cluster headache
  - Acute migraine headache

• Interventions: CGRP inhibitors

• Comparators:
  - Placebo/sham
  - Other CGRP inhibitors or pharmacological treatment
PICOS

• Outcomes:
  - Migraine events and pain relief
  - Quality of life (QoL), functional ability, and disability
  - Use of rescue therapies
  - Number of emergency room or primary care visits
  - Adverse events (AEs), serious adverse events (SAEs), and discontinuation due to AEs.

• Study Designs: Randomized controlled trials (RCTs)
Key Questions

1. Effectiveness and harms of CGRP inhibitors for preventing migraine and cluster headache

2. Effectiveness and harms of CGRP inhibitors for the acute treatment of migraine and cluster headaches

3. Characteristics of ongoing studies of CGRP inhibitors
Methods
Methods

MEDLINE via PubMed, Cochrane Library
Through August 18, 2022, and October 27, 2022, respectively (active surveillance through November 8, 2022)

Individual study risk-of-bias assessment

OpenEpi for risk ratio (RR) and confidence interval (CI) calculations

Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach for overall certainty of evidence
DERP Risk of Bias Assessment

- **Low**
  Clear reporting of methods and mitigation of potential biases and conflicts of interest

- **Moderate**
  Incomplete information about methods that might mask important limitations or a meaningful conflict of interest

- **High**
  Clear flaws that might introduce serious bias
**GRADE Certainty of Evidence**

*Outcomes Rated: Efficacy outcomes, QoL, SAEs, and discontinuation due to AEs*

- **High** *(RCTs start here)*
  Very confident that the estimate of effect of intervention on outcome lies close to the true effect

- **Moderate**
  Moderately confident in estimate of effect of intervention on outcome; true effect is likely close to estimate, but possibly different

- **Low** *(Nonrandomized studies start here)*
  Little confidence in estimate of effect of intervention on outcome; true effect may be substantially different from estimate

- **Very Low**
  No confidence in estimate of effect of intervention on outcome; true effect is likely substantially different from estimate
Findings

Literature Yield and Study Characteristics
Study Flow Diagram

New titles/abstracts identified through database searching (n = 419)

Additional citations identified through other sources (n = 2)

Titles/abstracts screened (n = 421)

Titles/abstracts excluded (n = 365)

Full-text articles assessed for eligibility (n = 56)

Full-text articles excluded, with reasons (n = 26)
- 15 ineligible study design
- 6 ineligible outcomes
- 2 ineligible comparator
- 1 ineligible setting
- 1 study protocol
- 1 abstract superseded by paper publication

Previously included studies (n = 32 articles reporting on 27 RCTs)

Studies included in narrative synthesis (n = 62 articles reporting on 42 RCTs)

Chronic migraine prevention n = 7 RCTs

Episodic migraine prevention n = 18 RCTs

Chronic or episodic migraine prevention n = 6 RCTs

Acute migraine treatment n = 9 RCTs

Cluster headache prevention n = 2 RCTs

Cluster headache treatment n = 0 RCTs

Abbreviations. RCT: randomized controlled trial.
Findings: Study Characteristics

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<td>1 topiramate</td>
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Structure of Findings

• Migraine Prevention
  □ Clinical Improvement and Functioning Outcomes
    o Chronic Migraine Prevention
    o Episodic Migraine Prevention
    o Chronic or Episodic Migraine Prevention
  □ Harms
    o Chronic Migraine Prevention
    o Episodic Migraine Prevention
    o Chronic or Episodic Migraine Prevention

• Acute Migraine Treatment
  □ Clinical Improvement and Functioning Outcomes
  □ Harms

• Cluster Headache
  □ Clinical Improvement and Functioning Outcomes
  □ Harms

• Ongoing Studies
## Outcomes and Abbreviations Used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td><strong>HIT-6</strong></td>
<td>6-item Headache Impact Test (clinically meaningful difference: 1.5-points)</td>
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<td><strong>MIDAS</strong></td>
<td>Migraine Disability Assessment (clinically meaningful difference: 4.5-points)</td>
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<td><strong>MSQL</strong></td>
<td>Migraine-specific Quality of Life score (clinically meaningful difference: 5.0 to 10.6 range for domains)</td>
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<td><strong>PGI-C</strong></td>
<td>Patient Global Impression of Change (clinically meaningful difference varies)</td>
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<tr>
<td><strong>PGI-S</strong></td>
<td>Patient Global Impression Survey (clinically meaningful difference varies)</td>
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- AE: adverse event
- CI: confidence interval
- COE: certainty of evidence
- GRADE: Grading of Recommendations, Assessments, Development and Evaluation
- HR: hazard ratio
- OR: odds ratio
- QoL: quality of life
- SD: standard deviation
- SE: standard error
- RCT: randomized controlled trial
- RD: risk difference
- RoB: risk of bias
- RR: risk ratio
Findings

Clinical Improvement and Functioning Outcomes: Chronic Migraine Prevention
Findings: Chronic Migraine Prevention
Eptinezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 2 RCTs, N = 1,393
- Migraine days per month
  - Significantly larger reductions ranging from -2.0 to -2.7 days at 12 weeks for both 100-mg and 300-mg doses
- Percentage ≥ 50% reduction migraine days per month
  - Significantly larger improvements for both doses

Functioning, GRADE: Moderate

- 2 RCTs, N = 1,393
- HIT-6
  - Significant improvement in 300-mg dosage groups (-4.2 and -2.9) in both trials and 100-mg group in 1 RCT (-1.7) at 12 weeks
Findings: Chronic Migraine Prevention
Erenumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 1 RCTs, N = 656
- **Migraine days per month**
  - Change in mean monthly headache days per month at 12 weeks
    - Both 70-mg and 140-mg doses: -2.5 (95% CI, -3.5 to -1.4)
- **Percentage ≥ 50% reduction migraine days per month**
  - Significantly larger improvements at 12 weeks
    - 70-mg RR: 1.70 (1.29 to 2.23, \( P = .0002 \))
    - 140-mg RR: 1.75 (1.34 to 2.30, \( P < .0001 \))

Functioning, GRADE: Moderate

- 1 RCTs, N = 656
- **HIT-6**
  - Significant larger improvements for both dosage groups at 12 weeks
Findings: Chronic Migraine Prevention
Fremanezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- **Migraine days per month**
  - 3 RCTs, N = 1,948
  - Significantly larger reductions ranging from -1.3 to -2.1 days at 12 weeks
- **Percentage ≥ 50% reduction migraine days per month**
  - 2 RCTs, N = 1,687
  - Significantly larger improvements in fremanezumab dosage groups

Functioning, GRADE: Moderate

- 2 RCTs, N = 1,662
- **HIT-6**
  - Significantly larger improvements ranged from -1.5 to -2.9 points
Findings: Chronic Migraine Prevention
Galcanezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 1 RCT, N = 1,085
- Migraine days per month
  - Significantly larger reductions ranging from -1.9 to -2.1 days at weeks 4 to 12
  - Percentage ≥ 50% reduction migraine days per month
    - Mean difference from placebo was 28% ($P < .001$) in 120-mg and 28% ($P < .001$) in 240-mg dosage groups

Functioning, GRADE: Moderate

- 1 RCT, N = 1,085
- MSQL
  - Significant improvement ranged from -5.1 to -7.0 points
Findings

Clinical Improvement and Functioning Outcomes: Episodic Migraine Prevention
Findings: Episodic Migraine Prevention
Atogepant Versus Placebo

Clinical Improvement, GRADE: Moderate to Low

- 2 RCTs, N = 1,668
- **Migraine days per month, GRADE: Moderate**
  - Significantly larger reductions ranging from -0.7 to -1.7 days at 12 weeks
- **Percentage ≥ 50% reduction migraine days per month; GRADE: Low**
  - Improvements in all dosage groups compared with placebo but only significant in 1 of 2 trials

Functioning, GRADE: Low

- 1 RCT, N = 873
- **MSQL Role Function Restrictive**
  - Statistically significant improvements ranging from 9.9 to 10.8 points but wide confidence intervals
Findings: Episodic Migraine Prevention
Eptinezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 2 RCTs, N = 832
- Migraine days per month
  - Significantly larger reductions in larger of 2 studies; -0.7 days for 100-mg dose and -1.1 days for 300-mg dose
- Percentage ≥ 50% reduction migraine days per month
  - Significantly larger improvement in larger of 2 studies (50% 100-mg vs. 56% 300-mg vs. 37% placebo)

Functioning, GRADE: Low

- 2 RCTs, N = 825
- QoL/Function (HIT-6 or SF-36)
  - Improvements in all dosage groups but only statistically significant in the larger of the 2 studies
Findings: Episodic Migraine Prevention
Erenumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 6 RCTs, N = 3,301
- Migraine days per month
  - Significantly larger reductions ranging from -1.0 to -2.3 days for 70-mg and -1.6 to -1.9 days for 140-mg
- Percentage ≥ 50% reduction migraine days per month
  - Significantly larger improvements across doses and studies with ORs ranging from 1.5 to 5.6

Functioning, GRADE: Moderate

- 6 RCTs, N = 3,299
- HIT-6
  - Significantly larger improvements across dosages and studies ranging from -1.0 to -3.0 points
Findings: Episodic Migraine Prevention
Fremanezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 3 RCTs, N = 1,514
- Migraine days per month
  - Significantly larger reductions across dosages and studies ranging from -1.3 to -3.0 days
- Percentage ≥ 50% reduction migraine days per month
  - Significantly larger improvements across dosages and studies with RRs ranging from 1.6 to 4.1

Functioning, GRADE: Moderate

- 3 RCTs, N = 1,503
- MIDAS
  - Significantly larger improvements across dosages and studies ranging from -5.2 to -14.5 points
Findings: Episodic Migraine Prevention
Galcanezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 5 RCTs, N = 2,673
- **Migraine days per month**
  - Significantly larger reduction across dosages and studies ranging from -0.9 to -3.0 days
- **Percentage ≥ 50% reduction migraine days per month**
  - Significantly larger improvements across dosages and studies with RRs ranging from 1.2 to 2.4

Functioning, GRADE: Moderate

- 5 RCTs, N = 2,196
- **MIDAS/MSQL**
  - Significantly larger improvements across dosages and studies with mean differences from placebo ranging from -5.8 to -8.8 on the MSQL and -3.0 to -9.2 on the MIDAS
Findings

Clinical Improvement and Functioning Outcomes: Chronic or Episodic Migraine Prevention
Findings: Chronic/Episodic Migraine Prevention
Eptinezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

- 1 RCTs, N = 892
- **Migraine days per month**
  - Significantly larger reductions of -2.7 for 100-mg dose and -3.2 days for 300-mg groups over 12 weeks
- **Percentage ≥ 50% reduction migraine days per month**
  - Significantly larger improvements in the 100-mg dose (OR: 3.8) and 300-mg dose (OR: 5.3)

Functioning, GRADE: Moderate

- 1 RCT, N = 868
- **HIT-6**
  - Significantly larger improvements of -3.8 points in the 100-mg group and -5.4 points in the 300-mg group
Findings: Chronic/Episodic Migraine Prevention
Erenumab Versus Placebo

Clinical Improvement, GRADE: Moderate

• 1 RCTs, N = 261
• **Migraine days per month**
  • Significantly larger reductions of -1.6 at weeks 12 to 24
• **Percentage ≥ 50% reduction migraine days per month**
  • Significantly larger improvements in the erenumab group (OR: 2.3)

Functioning, GRADE: Moderate

• None reported
Findings: Chronic/Episodic Migraine Prevention
Eptinezumab Versus Topiramate

Clinical Improvement, GRADE: Moderate

- 1 RCT, N = 261
- **Migraine days per month**
  - Significantly larger reductions of -1.8 days in 70-mg and 140-mg groups
- **Percentage ≥ 50% reduction migraine days per month**
  - Achieved by more participants in 70-mg and 140-mg groups (RR: 1.8)

Functioning, GRADE: Moderate

- 1 RCT, N = 261
- **HIT-6**
  - Significant improvements of -3.2 points in 70-mg and 140-mg group
Findings: Chronic/Episodic Migraine Prevention
Fremanezumab Versus Placebo

Clinical Improvement, GRADE: Moderate

• 1 RCT, N = 838
• Migraine days per month
  • Significantly larger reductions of -3.1 days for 225-mg and -3.5 days for 675-mg
• Percentage ≥ 50% reduction migraine days per month
  • Achieved by more participants in 225-mg and 675-mg groups (OR: 5.8)

Functioning, GRADE: Moderate

• 1 RCT, N = 838
• HIT-6
  • Significantly larger improvements of -3.0 points for 225-mg and -3.8 points for 675-mg
Findings: Chronic/Episodic Migraine Prevention
Galcanezumab Versus Placebo

Clinical Improvement, GRADE: Moderate to Low

- 1 RCT, N = 463
- Migraine days per month, GRADE: Moderate
  - Significantly larger reductions of -3.1 days at 15 weeks
- Percentage ≥ 50% reduction migraine days per month; GRADE: Low
  - Achieved by significantly more participants in active treatment (OR: 3.9)

Functioning, GRADE: Low

- 1 RCT, N = 463
- MIDAS
  - Significant improvements of -17.8 points at 4 to 16 weeks
Findings: Chronic/Episodic Migraine Prevention
Rimegepant Versus Placebo

Clinical Improvement, GRADE: Moderate to Low

- 1 RCT, N = 463
- Migraine days per month, GRADE: Moderate
  - Significantly larger reductions of -0.8 days at 12 weeks
- Percentage ≥ 50% reduction migraine days per month; GRADE: Low
  - Achieved by more participants in active treatment (difference from placebo: 8%; 95% CI, 0% to 15%; \( P = .044 \)) at 12 weeks

Functioning, GRADE: Very Low

- 1 RCT, N = 463
- MIDAS
  - No significant difference at 12 weeks
Findings

Harms: Migraine Prevention
Findings: Chronic Migraine Prevention

Evidence (7 RCTs, N = 5,082)

• 2 RCTs comparing eptinezumab with placebo
• 1 RCT comparing erenumab with placebo
• 3 RCTs comparing fremanezumab with placebo
• 1 RCT comparing galcanezumab with placebo

Findings

• SAEs, GRADE: Very Low
  • Rare events, relationship cannot be determined
• Discontinuation due to AEs, GRADE: Very Low
  • Rare events, relationship cannot be determined
Findings: Episodic Migraine Prevention

Evidence (18 RCTs, N = 2,673)

- 2 RCTs comparing atogepant with placebo
- 2 RCTs comparing eptinezumab with placebo
- 6 RCTs comparing erenumab with placebo
- 3 RCTs comparing fremanezumab with placebo
- 5 RCT comparing galcanezumab with placebo

Findings

- SAEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
- Discontinuation due to AEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
Findings: Chronic/Episodic Migraine Prevention

Evidence (6 RCTs, N = 3,201)

- 1 RCT comparing eptinezumab with placebo
- 1 RCT comparing erenumab with placebo
- 1 RCT comparing fremanezumab with placebo
- 1 RCT comparing galcanezumab with placebo
- 1 RCT comparing rimegepant with placebo

Findings

- SAEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
- Discontinuation due to AEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
Findings: Chronic/Episodic Migraine Prevention

Evidence (1 RCT, N = 777)

- 1 RCT comparing erenumab with topiramate

Findings

- SAEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
- Discontinuation due to AEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
CGRP Inhibitors for Chronic or Episodic Migraine Prevention

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<tr>
<th>Chronic Migraine Prevention</th>
<th>Migraine days per month</th>
<th>≥ 50% reduction in migraine days per month</th>
<th>Functioning/Quality of Life</th>
<th>SAE</th>
<th>Discontinuation due to AEs</th>
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Notes. a No new studies included. b Results only statistically significant in larger of 2 trials. Color key: Favors CGRP; Favors Placebo; No significant differences; Unable to determine relationship. Bolded comparisons represent new studies or data for this update. GRADE certainty of evidence: No evidence (blank); Very Low ●◌◌◌◌; Low ●●◌◌; Moderate ●●●◌; High ●●●●. Abbreviations. AE: adverse event; CGRP: calcitonin gene-related peptide; GRADE: Grading of Recommendations, Assessments, Development and Evaluation; RCT: randomized controlled trial; SAE: serious adverse event.
Findings

Clinical Improvement and Functioning Outcomes: Acute Migraine Treatment
Findings: Acute Migraine Treatment
Eptinezumab Versus Placebo

Clinical Improvement, GRADE: Low

- 1 RCT, N = 480
- **Freedom from pain at 2 hours post-dose**
  - Achieved by significantly larger proportion; RD, 11.6%
- **Freedom from most bothersome symptoms at 2 hours post-dose**
  - Achieved by significantly larger proportion; RD, 19.6%

Functioning, GRADE: Low

- 1 RCT, N = 480
- **HIT-6**
  - Significantly greater improvements, mean difference in change from baseline was -4.7 points

New study
Findings: Acute Migraine Treatment
Rimegepant Versus Placebo

Clinical Improvement, GRADE: Moderate

- Freedom from pain at 2 hours post-dose
  - 3 RCTs, N = 2,698
  - Significantly favored rimegepant; RDs range from 7.6% to 16.2%

- Freedom from most bothersome symptoms at 2 hours post-dose
  - 2 RCTs, N = 2,378
  - Achieved by significantly more participants in rimegepant group; RDs range from 8.3% to 12.4%

Functioning, GRADE: Moderate

- 2 RCTs, N = 2,378
- Ability to function normally within 2 hours post-dose
  - Achieved by significantly more participants in rimegepant group; RDs range from 9.2% to 12.3%
Findings: Acute Migraine Treatment
Rimegepant Versus Sumatriptan

Clinical Improvement, GRADE: Moderate

- 1 RCT, N = 338
- Freedom from pain at 2 hours post-dose
  - No significant difference (RD: -3.6%)
- Freedom from most bothersome symptoms at 2 hours post-dose
  - No significant difference: 27.9% (rimegepant) versus 26.0% (sumatriptan)

Functioning, GRADE: Not Applicable

- None reported
Findings: Acute Migraine Treatment
Ubrogepant Versus Placebo

Clinical Improvement, GRADE: Moderate

- **Freedom from pain at 2 hours post-dose**
  - 3 RCTs, N = 2,568
  - Significantly favored ubrogepant; ARDs range from 7.4% to 16.6%

- **Freedom from most bothersome symptoms at 2 hours post-dose**
  - 2 RCTs, N = 2,247
  - Significantly favored ubrogepant; RDs were 10.8% and 11.4%

Functioning, GRADE: Moderate

- 2 RCTs, N = 2,247
- **Ability to function normally within 2 hours post-dose**
  - Significantly favored ubrogepant; ORs ranged from 1.7 and to 1.9
Findings: Acute Migraine Treatment
Zavegepant Versus Placebo

Clinical Improvement, GRADE: Low

- 1 RCT, N = 1,581
- **Freedom from pain at 2 hours post-dose**
  - Significantly favored zavegepant for 2 of 3 dosage groups, RDs:
    - 5-mg: 4.2% (-1.1 to 9.5; \( P = .1214 \))
    - 10-mg: 7.0% (1.6 to 12.5; \( P = .0113 \))
    - 20-mg: 7.7% (2.2 to 13.1; \( P = .0055 \))
- **Freedom from most bothersome symptoms at 2 hours post-dose**
  - Significantly favored zavegepant for 2 of 3 dosage groups, RDs:
    - 5-mg: 5.4% (1.4 to 12.1; \( P = .1162 \))
    - 10-mg: 8.3% (1.5 to 15.0; \( P = 0.0155 \))
    - 20-mg: 8.9% (2.2 to 15.6; \( P = 0.0094 \))
Findings

Harms: Acute Migraine Treatment
Findings: Acute Migraine Treatment

Evidence (9 RCTs, N = 7,670)

- 1 RCT comparing eptinezumab with placebo
- 3 RCTs comparing rimegepant with placebo
- 3 RCTs comparing ubrogepant with placebo
- 1 RCT comparing zavegepant with placebo

Findings

- SAEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
- Discontinuations due to AEs, GRADE: Not Applicable
  - Not reported in above trials

2 new studies
Findings: Acute Migraine Treatment

Evidence (1 RCT, N = 885)

- 1 RCT comparing rimegepant with sumatriptan

Findings

- SAEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
- Discontinuation due to AEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
## CGRP Inhibitors for Acute Migraine Treatment

<table>
<thead>
<tr>
<th></th>
<th>Freedom from pain at 2 hours post-dose</th>
<th>Freedom from most bothersome symptom at 2 hours post-dose</th>
<th>Normal function within 2 hours post-dose</th>
<th>SAE</th>
<th>Discontinuation due to AEs</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute Migraine Treatment</strong></td>
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<td>Eptinezumab vs. Placebo (1 RCT)</td>
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<td>Rimegepant vs. Placebo (3 RCTs)</td>
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<td>Rimegepant vs. Sumatriptan (1 RCT)</td>
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<td>Ubrogepant vs. Placebo (3 RCTs)</td>
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<td>Zavegpant vs. Placebo (1 RCT)</td>
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</tbody>
</table>

**Notes.**

- "●" This outcome only reported for 2 of 3 RCTs.
- "●" This outcome only reported for 1 of 3 studies

**Color key:**
- Favors CGRP
- Favors Placebo
- No significant differences
- Unable to determine relationship

**Bolded comparisons represent new studies or data for this update.**

**GRADE certainty of evidence:**
- No evidence (blank)
- Very Low ●●●●
- Low ●●●●
- Moderate ●●●●
- High ●●●●

**Abbreviations.**

- AE: adverse event
- CGRP: calcitonin gene-related peptide
- GRADE: Grading of Recommendations, Assessments, Development and Evaluation
- RCT: randomized controlled trial
- SAE: serious adverse event

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Findings

Clinical Improvement and Functioning Outcomes: Cluster Headache Prevention
Findings: Cluster Headache Prevention
Galcanezumab Versus Placebo

Clinical Improvement, GRADE: Low

- 2 RCTs, N = 343
- Change in cluster headache attacks per week
  - Significantly larger improvements at weeks 1 to 3; No difference at weeks 8 to 12
  - Percentage with at least 50% reduction in number of cluster headache attacks per week
    - No significant difference at weeks 8 to 12

Functioning, GRADE: Low

- 1 RCT, N = 205
- Patient Global Impression of Improvement Scale
  - No significant difference

New study
Findings

Harms: Cluster Headache Prevention
Findings: Cluster Headache Prevention

Evidence (2 RCTs, N = 343)

- 2 RCTs comparing galcanezumab with placebo

Findings

- SAEs, GRADE: Very Low
  - Rare events, relationship cannot be determined
- Discontinuation due to AEs, GRADE: Very Low
  - Rare events, relationship cannot be determined

1 new study
CGRP Inhibitors for Cluster Headache

<table>
<thead>
<tr>
<th></th>
<th>Change in cluster headache attacks</th>
<th>≥ 50% reduction in cluster headache attacks per week</th>
<th>Functioning/quality of life</th>
<th>SAE</th>
<th>Discontinuation due to AEs</th>
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<tr>
<td>Cluster Headache Prevention</td>
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<td>Galcanezumab vs. Placebo (2 RCTs)</td>
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Notes. Color key: **Favors CGRP; Favors Placebo; No significant differences; Unable to determine relationship. Bolded comparisons represent new studies or data for this update. GRADE certainty of evidence: No evidence (blank); Very Low ●●●●; Low ●●●●●; Moderate ●●●●●; High ●●●●●. Abbreviations. AE: adverse event; CGRP: calcitonin gene-related peptide; GRADE: Grading of Recommendations, Assessments, Development and Evaluation; RCT: randomized controlled trial; SAE: serious adverse event.
Findings

Ongoing Studies
Findings: Ongoing Studies

• 17 ongoing studies
  □ 1 study was open-label RCT comparing erenumab with oral preventive medication
  □ 16 placebo-controlled RCTs
  □ All studies had a primary efficacy endpoint
Findings: Ongoing Studies

• 0 RCTs of atogepant

• 4 RCTs of eptinezumab
  - 1 for chronic migraine prevention
  - 1 for episodic migraine prevention
  - 1 for chronic/episodic migraine prevention
  - 1 for cluster headache prevention

• 3 RCTs of erenumab
  - 1 for chronic migraine prevention
  - 2 for episodic migraine prevention
Findings: Ongoing Studies

• 1 RCT of fremanezumab
  - 1 of chronic/episodic migraine prevention

• 2 RCTs of galcanezumab
  - 1 of cluster headache prevention
  - 1 of vestibular migraine prevention

• 5 RCTs of rimegepant
  - 2 of acute migraine treatment
  - 2 of chronic/episodic migraine prevention
  - 1 of episodic migraine prevention

• 2 RCTS of zavegepant
  - 2 of acute migraine treatment
Discussion
Discussion

• No head-to-head studies of CGRP inhibitors
• 1 study comparing rimegepant to sumatriptan for acute migraine treatment
• 1 study comparing erenumab to topiramate for migraine prevention in population with episodic or chronic migraine
• Studies of 2 new agents
  - 2 studies of atogepant for episodic migraine prevention
  - 1 study of zavegepant for acute migraine treatment
• No studies of CGRP inhibitors for acute cluster headache treatment
Discussion: Migraine Prevention

• Eptinezumab, erenumab, fremanezumab, and galcanezumab were more effective than placebo for chronic and episodic migraine prevention (moderate Certainty of Evidence [CoE])

• Atogepant was also more effective than placebo for episodic migraine (outcomes varied from moderate to low CoE).

• SAEs and discontinuations due to AEs occurred rarely in active drug and placebo groups, so a relationship cannot be determined (very low CoE).

• In head-to-head comparisons, erenumab was more effective than topiramate (moderate CoE), with similar SAEs (very low CoE) but fewer discontinuations due to AEs (moderate CoE).
Discussion: Migraine Prevention

• The magnitude of the treatment effect of CGRP inhibitors for migraine prevention was modest (-0.4 to -3.7 days)
  □ Similar to other available migraine preventive agents

• The clinical significance may vary based on severity and ability to tolerate other preventive medications

• On the HIT-6, a between-group difference of 1.5 points is considered clinically relevant
  □ 15 of the 17 identified studies that reported this had differences of 1.9 points or greater
  □ Suggests a clinically important improvement on this measure
Discussion: Acute Migraine Treatment

• Rimegepant, ubrogepant, and zavegepant were more effective than placebo for acute migraine treatment (moderate to low CoE)
  - Proportion of participants achieving freedom from pain at 2 hours post dose ranged from 4.2 to 16.6 percentage points higher

• SAEs were rare; thus, no relationship can be determined (very low CoE)

• In head-to-head comparison, no difference in efficacy between rimegepant and sumatriptan was observed (very low CoE), and discontinuations due to AEs were rare (very low CoE)
Discussion: Cluster headache

• Galcanezumab resulted in significantly fewer cluster headache attacks per week during weeks 1 through 3 of follow-up (ranged from 2.2 to 3.5 fewer attacks per week) compared with placebo but there was no difference at weeks 8 to 12 (Low CoE)
  □ May reflect lack of efficacy or the spontaneous remission of attacks, which is typical of cluster headaches
  □ Natural course of disease makes conducting and interpreting studies challenging

• No RCTs for acute cluster headache treatment
Discussion

• Limitations of the evidence
  - All studies were industry-sponsored
    - Some authors were employed by the manufacturer and nonemployee authors disclosed financial interest
  - Many trials limited to 12 weeks of follow up
    - Limits information on treatment durability and long-term safety
  - Limits to generalizability
    - Nearly all studies required compliance with an electronic headache diary during a run-in phase
    - Most studies excluded pregnant people and participants with clinically significant psychiatric or medical conditions
Discussion

• Limitations of this review
  ▣ Changes in chronic and episodic migraine populations
    o Early studies enrolled patients distinctly characterized as having either episodic or chronic migraine
    o Recent studies enrolled mixed chronic and episodic populations
    o This may be because no meaningful differences in effectiveness exist or to increase recruitment feasibility
    o It may be appropriate for future synthesis to combine these groups
  ▣ Only included studies published in English
  ▣ Did not include data from press releases, conference abstracts, or trial registries
Questions?
References: Included Studies


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