[SP2] Identifying and Evaluating Information for Evidence-Based Drug Formularies

Lynn Nishida, RPh, FAMCP
VP – Clinical Product & Contracting
WithMe Health
Learning Objectives

1. Describe key sections of a drug monograph.
2. Define a clinical question that follows the PICOT framework.
3. Explain how to assess the quality of individual studies and an entire body of evidence.
4. Identify important considerations in determining the value proposition for a drug.

Financial Relationship Disclosures

<table>
<thead>
<tr>
<th>Disclosure Information</th>
<th>Advisory Board</th>
<th>Consultant</th>
<th>Grants/Research</th>
<th>Salary/Contractual</th>
<th>Supported Promotional Education</th>
<th>Stock/Shareholder</th>
<th>Other Financial Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynn Nishida, RPh, FAMCP Speaker</td>
<td>Regeneron</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

This slide deck has been peer reviewed by an Educational Affairs Committee member and AMCP staff members to mitigate the risk of promotional bias.
Time and Resources

- Best practice in writing a therapeutic drug monograph mirrors a systematic review.
- Experts in the field estimate:¹
  - Writing the initial protocol can take 2 - 6 months.
  - Completing the full review can take up to 24 months, depending on the complexity of topic and team resources.

WOW! This could take a long time!
Getting Started

“The secret to getting ahead is getting started.”

“The secret to getting started is breaking your complex, overwhelming tasks into small manageable tasks, and then starting on the first one.”

Mark Twain
American Author & Humorist
1835 – 1910

Therapeutic Drug Monograph
Areas of Emphasis

Key sections of a drug monograph:

- Executive Summary
- Recommendations
- Background Information
- Key Questions
- Literature Search Method
- Critical Appraisal/Evaluation
- Evidence Synthesis and Summary
- Clinical/Cost Effectiveness (Model)
Applying PICOT

- **P** stands for patient population
- **I** is the intervention or issue of concern
- **C** stands for the comparator that the intervention is to be compared
- **O** means the outcome of interest
- **T** refers to the applicable time duration or time horizon

Using "PICOT" helps scope your review, develop key questions, and focus on what to research.
**PICOT - Example**

**CGRP* Inhibitors for Migraines**

- **Population**: Adults with episodic or chronic migraine

- **Intervention & Comparators**: erenumab, fremanezumab, galcanezumab, topiramate, propranolol, amitriptyline, onabotulinum toxin A

- **Timing**: Effectiveness derived from studies of any follow-up duration

- **Outcomes - Intermediate**:
  - Migraine events
  - Pain
  - Adherence/Treatment discontinuation
  - Other symptoms
    - Use of rescue therapies
    - # of ER visits
    - # of doctor visits

- **Outcomes – Key Measures**:
  - Health-related quality of life
  - Cognitive functioning
  - Impairment/Disability
  - Tolerability
  - Employment-related outcomes
  - Other patient-reported outcomes

- **Outcomes - Safety**:
  - Systemic Reactions
  - Serious Adverse Events (SAEs)
  - Adverse Events (AEs)

- **Timing**: Harms derived from any studies of any follow-up duration

---

**Key Question - Examples**

- What is the clinical effectiveness, tolerability, and safety of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab) relative to no preventive treatment (placebo) or commonly-used preventive therapies in adults with chronic or episodic migraine?
  - For both episodic and chronic migraine populations, commonly-used preventive therapies include topiramate, propranolol, and amitriptyline.
  - For chronic migraine, onabotulinum toxin A is included.

- For subgroup analysis, what is the clinical effectiveness, tolerability, and safety of CGRP inhibitors (erenumab, fremanezumab, and galcanezumab) relative to no preventive treatment (placebo) or commonly-used preventive therapies in adults in whom at least one prior commonly-used preventive therapy was not effective?
**Search and Screen**

<table>
<thead>
<tr>
<th>Literature Search Inclusion &amp; Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date conducted</td>
</tr>
<tr>
<td>Databases (PubMed/Ovid, Embase, Cochrane)</td>
</tr>
<tr>
<td>Search Method (including manual hand searches)</td>
</tr>
<tr>
<td>Search terms &amp; Parameters</td>
</tr>
<tr>
<td>Exclusion Criteria / Limitations</td>
</tr>
<tr>
<td>Search Results</td>
</tr>
</tbody>
</table>
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analysis\(^3\)

- Focuses on 27 items in reporting methods applied (databases searched, search terms) in conducting a systematic literature search.

- Provides number of records identified, included and excluded, and reasons for exclusions.

PRISMA represents best practice in showing transparency of your literature search

PRISMA Flow Chart\(^3\)

- **Identification**: "n" records identified through database search + any additional records identified through other sources

- **Screening**: "n" records screened

- **Eligibility**: "n" full-text articles assessed for eligibility

- **Included**: "n" publications included for appraisal and qualitative synthesis

Examples of excluded records or full-text articles:
- Duplicates
- Full text not available
- Study not relevant
- Studies already in included systematic reviews
- Publication date outside of period for inclusion
- Wrong outcomes
- Wrong study design
- Methodological limitations
PRISMA – Literature Search
CGRP’s and Other Comparators in Migraines

Pubmed Search 8/31/2019: 1024 total citation hits

Fremanezumab 64 hits

Topiramate 476 hits

Onabotulinum toxin A 38 hits

Propranolol 133 hits

Amitriptyline 166 hits

Galcanezumab 61 hits

Erenumab 86 hits

PRISMA Flow Chart - Example
Literature Selection Process

Identification

“1024” Records identified through Ovid, Embase, and Cochrane database search or other sources (hand-search)

Screening

“68” records

“956” records excluded*

Eligibility

“50” full-text articles

“18” full-text articles excluded*

Included

“50” full-text articles included in qualitative analysis
• 12 for CGRP inhibitors
• 38 for other comparators of interest

*Reasons for excluded records/articles.
- Duplicates
- Records/articles already covered within systematic reviews.
- Wrong population (PICOT)
- Wrong interventions (PICOT)
- Sample size
- Conference abstracts, lacking details
PRISMA Flow Chart
Final Results

50 publications to be included in qualitative synthesis for report

- Systematic Reviews or Meta-analyses (n = 4)
- Randomized Controlled Trials (n = 46):
  - 12 CGRP inhibitors
  - 34 Other Comparators of interest
- Other Study Types Not Applicable

Show transparency in your literature search for final number of publications to be included and appraised in your report

Appraising Individual Studies
**Individual Study Quality Assessment Tools**

<table>
<thead>
<tr>
<th>Grading of Individual Studies</th>
<th>NHLBI⁴</th>
<th>CER Collaborative⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading Assessment Nomenclature Used</td>
<td>Good, Fair, or Poor</td>
<td>Relevance &amp; Credibility: Sufficient vs Insufficient</td>
</tr>
</tbody>
</table>

**Appraisal Tools for Individual Studies**

<table>
<thead>
<tr>
<th>NHLBI⁴</th>
<th>CER Collaborative⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Randomized Controlled Trials</td>
<td>Yes</td>
</tr>
<tr>
<td>- Systematic Reviews</td>
<td>Yes</td>
</tr>
<tr>
<td>- Case/Case Series Studies</td>
<td>Yes</td>
</tr>
<tr>
<td>- Before/After (Pre/Post) Studies with No Control Group</td>
<td>Yes</td>
</tr>
<tr>
<td>- Observational Studies (Prospective &amp; Retrospective)</td>
<td>Yes</td>
</tr>
<tr>
<td>- Indirect Treatment Comparison Study</td>
<td>Yes</td>
</tr>
<tr>
<td>- Modeling studies</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*If Other, indicate “CD” = Cannot determine; “NA” = Not applicable; or NR=“Not Reported”

**Individual RCT - NHLBI Appraisal Tool⁴**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study described as randomized, a randomized trial, a randomized clinical trial, or an RCT</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2. Method of randomization adequate (use of randomly generated assignment)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3. Treatment allocation was concealed (so that assignment could not be predicted)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>4. Study participants and providers blinded to treatment group assignments</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5. Those assessing the outcomes were blinded to the participants treatment assignments</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6. Groups similar at baseline for pertinent characteristics/demographics that if different could affect outcomes</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7. Overall drop-out rate from study at endpoint was 20% or less of number(s) allocated to treatment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>8. Differential drop-out rate (between treatment groups) at endpoint was 15% or lower</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>9. High adherence to the intervention protocols for each treatment group (e.g., 80% or more)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10. Other interventions avoided or similar in groups (e.g., background treatments)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>11. Outcomes assessed using valid, reliable measures, implemented consistently across all study subjects</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>12. Reported sample size is large enough to detect difference in primary outcome between groups (80% power)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>13. Outcomes reported or subgroups analyzed were <em>a priori</em> (e.g., prespecified before analysis conducted)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>14. All randomized participants were analyzed in the group to which they were originally assigned (e.g., an intent-to-treat analysis is used)</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*If Other, indicate “CD” = Cannot determine; “NA” = Not applicable; or NR=“Not Reported”
Individual RCT Evidence Table


<table>
<thead>
<tr>
<th>Study Design</th>
<th>Drug Regimens</th>
<th>N</th>
<th>Time Horizon</th>
<th>Study Population</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-center, double-blind randomized placebo-controlled</td>
<td>SQ every 4 weeks: 1. Placebo 2. erenumab 70mg 3. erenumab 140 mg</td>
<td>319</td>
<td>24 wks</td>
<td>Episodic migraine, Includes patients on preventive migraine medication if on stable dose.</td>
<td>↓ in monthly migraine days</td>
</tr>
</tbody>
</table>

**Endpoints**
- ↓ in monthly migraine days
- % achieving ≥ 50% ↓ in mean monthly migraine days at 4 to 6 months vs baseline.
- ↓ days of acute migraine-specific medication use from baseline.

**Study Quality:** Good

**Study Weaknesses**
- Not an ITT analysis and excludes 9 of 955 (0.9%) randomized patients.
- Dropouts: 955 randomized, 858 (89.8%) completed the 24-week trial. Drop-out = 10.1%
- Power described/reported.

**Safety**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Placebo (n = 316)</th>
<th>Erenumab 70mg (n = 312)</th>
<th>Erenumab 140mg (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ in monthly migraine days from baseline (Primary Endpoint)</td>
<td>-1.8 days</td>
<td>-3.2 days (p &lt; 0.001)</td>
<td>-3.7 days (p &lt; 0.001)</td>
</tr>
<tr>
<td>% achieving ≥ 50% ↓ in mean monthly migraine days from baseline during 4 to 6 months</td>
<td>26.6%</td>
<td>43.3%, NNT = 6, p &lt; 0.001</td>
<td>50.0%, NNT = 4</td>
</tr>
<tr>
<td>↓ days of acute migraine medication use per month</td>
<td>-0.2</td>
<td>-1.1</td>
<td>-1.6</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>-0.9 (-1.2 to -0.6)</td>
<td>-1.4 (-1.7 to -1.1)</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Events**

<table>
<thead>
<tr>
<th># (%) with Adverse Events (AE)</th>
<th>Placebo (n = 319)</th>
<th>Erenumab 70mg (n = 314)</th>
<th>Erenumab 140mg (n = 319)</th>
</tr>
</thead>
<tbody>
<tr>
<td># (%) with Serious AEs</td>
<td>7 (2.2%)</td>
<td>8 (2.5%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td># (%) Drop-outs due to AEs</td>
<td>8 (2.5%)</td>
<td>7 (2.2%)</td>
<td>7 (2.2%)</td>
</tr>
</tbody>
</table>

*Based on all randomized patients that received at least 1 dose of erenumab or placebo.

**Quality Assessment:** Weaknesses identified are minimal and unlikely to significantly impact validity of results.
Systematic Review
NHLBI Appraisal Tool

**Citation:** Lattanzi S et al. Erenumab for preventive treatment of migraine: A systematic review and meta-analysis of efficacy and safety. Drugs 2019; 79(4): 417-431.13

<table>
<thead>
<tr>
<th>Appraisal Elements</th>
<th>Description</th>
<th>Concerns that Impact Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type:</strong></td>
<td>Systematic Review with meta-analysis</td>
<td></td>
</tr>
<tr>
<td><strong>Appraisal:</strong></td>
<td>This review concludes that erenumab is efficacious and well tolerated as preventive treatment in adults with episodic &amp; chronic migraine.</td>
<td></td>
</tr>
<tr>
<td><strong>Funding Source</strong></td>
<td>• None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Interventions / Conditions</strong></td>
<td>• Efficacy and safety of erenumab as preventive treatment in patients with chronic or episodic migraine.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Number of Studies</strong></td>
<td>• 5 studies (2,393 patients)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Literature Search</strong></td>
<td>Documented systematic and comprehensive search using PRISMA. Period covered through October 31, 2018</td>
<td>None</td>
</tr>
<tr>
<td><strong>Quality of Studies Included</strong></td>
<td>• Study Selection: Explicit, documented and appropriate selection criteria chosen in advance for included studies. • Study Design: Randomized controlled trials comparing erenumab vs placebo were included in patients with migraine. • Critical Appraisal: The quality of each study was assessed by evaluating randomization, allocation, blinding, attrition, and ITT analysis; meta-analysis was performed with tests for heterogeneity (Chi² and F).</td>
<td>None</td>
</tr>
</tbody>
</table>

*If Other, indicate "Cannot determine"; Not applicable; or Not Reported

---

**Evidence Table - Systematic Review**

**Appraisal:** This review concludes that erenumab is efficacious and well tolerated as preventive treatment in adults with episodic & chronic migraine.
### Evidence Table - Systematic Review


<table>
<thead>
<tr>
<th>Appraisal Elements</th>
<th>Description</th>
<th>Concerns that Impact Quality</th>
</tr>
</thead>
</table>
| **Endpoints Evaluated** | **Primary endpoints:**  
Monthly Migraine Days (MMD)  
Acute Migraine-Specific Medication Days (MSMD) | None |
| **Efficacy Results** | Across five included trials, erenumab subcutaneous injection at a monthly dosage of 70 mg and 140 mg was associated with a significantly greater reduction in baseline MMD and MSMD vs Placebo:  
**MMD**  
70 mg: Mean Difference: −1.3 days, 95% CI −1.7 to −1.0, p < 0.001;  
140 mg: Mean Difference: −1.9 days, 95% CI −2.3 to −1.4, p < 0.001  
**MSMD**  
70 mg: MD −1.0 days, 95% CI −1.6 to −0.4, p < 0.001;  
140 mg: MD −1.8 days, 95% CI −2.5 to −1.1, p < 0.001 | None |
| **Safety Results** | There were no differences in the occurrence of AEs, SAEs, and drug withdrawal due to AEs between the erenumab and placebo groups. | None |

---

### Economic Models – Appraisal

*Good Models Checklist* 6

**Structure**
- Disease-progression model with appropriate time horizon?
- Treatment pathways relevant to the decision?
- Model represents usual clinical practice?
- Mathematics of the model are accurate and available for inspection?

**Data**
- Sources of evidence valid?
- Data is interpreted and incorporated accurately?
- Uncertainties in the data addressed?
- Linkages between intermediate and long-term outcomes are:  
  - Valid?  
  - Based on appropriate (trial or retrospective) evidence?

**Analysis/Summary**
- Outcomes are relevant to payer decision-making?
- Incremental analyses performed on both health effects and costs?
- Outcomes are verifiable, and traceable back to inputs and model structure?
- Uncertainty in data tested in a reasonable fashion?
- Sensitivity analysis displayed via tornado diagram?
- Are results creditable?
Safety Considerations/Limitations

- Rarely have gold standard
  - Double blind randomized controlled trial?
  - Specific harms defined in advance?
  - Was trial powered to detect harms?
  - P-values reported between drug and placebo?
- How many subjects were studied?
- How long were the trials?
Evidence Synthesis

Hypothetical Snapshot

- Collate and summarize all appraised studies into a table.
- # of studies appraised = # of studies identified for inclusion from literature search.

<table>
<thead>
<tr>
<th>Ref #</th>
<th>Author</th>
<th>Study Type &amp; Duration</th>
<th>Population</th>
<th>Intervention</th>
<th>Key Results</th>
<th>Study Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Goadsby, et al 2017</td>
<td>DB, PC, MC, RCT</td>
<td>Episodic Migraine</td>
<td>Q month erenumab 70mg erenumab 140mg Placebo</td>
<td>Erenumab better than placebo in ↓ing monthly migraine days &amp; ≥ 50% ↓ in migraines (NNT = 4–6)</td>
<td>Good</td>
</tr>
<tr>
<td>9</td>
<td>Reuter U, et al 2018</td>
<td>DB, PC, RCT</td>
<td>Episodic Migraine (after failing prior preventive tx)</td>
<td>Q month erenumab 140mg Placebo</td>
<td>Erenumab better than placebo in ↓ing monthly migraine days &amp; ≥ 50% ↓ in migraines (NNT = 6)</td>
<td>Fair</td>
</tr>
<tr>
<td>10</td>
<td>Sun H, et al 2016</td>
<td>DB, PC, RCT X months</td>
<td>Episodic Migraine</td>
<td>&lt;insert&gt;</td>
<td>&lt;insert&gt;</td>
<td>&lt;insert&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Dodick DW et al 2018</td>
<td>DB, PC, RCT</td>
<td>Episodic Migraine</td>
<td>&lt;insert&gt;</td>
<td>&lt;insert&gt;</td>
<td>&lt;insert&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Tepper S, et al 2017</td>
<td>DB, PC, RCT</td>
<td>Chronic Migraine</td>
<td>&lt;insert&gt;</td>
<td>&lt;insert&gt;</td>
<td>&lt;insert&gt;</td>
</tr>
</tbody>
</table>

Abbreviations used in this table: DB = double blind, PC = placebo control, MC = multicenter, RCT = randomized controlled trial, NNT = Number needed to treat.
Evidence Synthesis – ICER Matrix

What does the totality of the evidence tell us about a net health benefit?

What is your level of certainty?

Key Question 1:
CGRP inhibitors vs No Preventive Therapy
Grade: B+  (Moderate Certainty of a small net health benefit)

- CGRP inhibitors provide a small net health benefit of ~ two less monthly migraine days in patients with episodic or chronic migraine after 4 to 6 months of treatment.
- About 4 to 6 patients need to be treated for one to achieve at least a 50% decrease in monthly migraine headache days.
Pulling It All Together
Articulating Responses to Your Key Questions

Example Conclusion: Preventive treatment with CGRP inhibitors provides some clinical benefit in patients with chronic or episodic migraine compared with no treatment.

<table>
<thead>
<tr>
<th>Chronic Migraines</th>
<th>Erenumab</th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly Migraine Days*</td>
<td>↓ ~ 2 less days</td>
<td>↓ ~ 2 less days</td>
<td>↓ ~ 2 less days</td>
</tr>
<tr>
<td>Days Using Acute Medications</td>
<td>↓ ~ 2 less days</td>
<td>↓ ~ 2 less days</td>
<td>↓ ~ 2 less days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Episodic Migraine</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly Migraine Days*</td>
<td>↓ ~ 2 less days</td>
<td>↓ of ~ 2 less days</td>
<td>↓ of ~ 2 less days</td>
</tr>
<tr>
<td>Days Using Acute Medications</td>
<td>↓ of ~ 2 less days</td>
<td>↓ of ~ 1 less day</td>
<td>↓ of ~ 2 less days</td>
</tr>
<tr>
<td>50% Responders**</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
</tr>
</tbody>
</table>

*Average reductions in migraine days accounts for placebo effect.
**Patients experiencing at least a 50% decrease in monthly migraine days.

Key Question 2:
CGRP Inhibitors (erenumab, fremanezumab, and galcanezumab) vs commonly used therapies (amitriptyline, carbamazepine, botulinum toxin A, and propranolol).

Grade: <insert grade>

- <Describe/quantify the net health benefit over conventional options>
- <Place the where the net health benefit for CGRP inhibitors fall on the ICER matrix*>

*ICER Matrix used with permission from Institute of Clinical and Economic Review (ICER)
Pulling It All Together
Articulating Responses to Your Key Questions

Key Question 3: Subgroup analysis
CGRP Inhibitors (erenumab, fremanezumab, and galcanezumab) in adults whom at least one preventive therapy was not effective.
Grade: <insert grade>

- <Describe/quantify the net health benefit in this subgroup population>
- <Place the where the net health benefit for CGRP inhibitors fall on the ICER matrix*>

*ICER Matrix used with permission from Institute of Clinical and Economic Review (ICER)*

Pulling It All Together - Articulating Harms
Example language - CGRP inhibitors

Well tolerated, with drop-out rates of < 2.5% due to adverse events
Little is known about long-term effects
Harms observed in clinical trials were generally nonserious and uncommon

Most common adverse events were:
- Injection-site reactions in up to 30% of patients
- Cold symptoms and upper respiratory tract infection in < 12% of patients
- In the trials with other preventive therapies, most commonly reported adverse events were fatigue, difficulty with memory/concentration, prickling sensation, changes in taste, and weight change. These events were not frequently observed in the CGRP inhibitor trials.
Sources of Uncertainty

- Trial duration
- Rare harms
- Length of treatment
- Patient outcomes
- Generalizability

Financials and Economic Analysis Summary

- Long-term cost effectiveness
- Short-term budget impact
- Access
- Affordability
Final Recommendations

Formulary

Prior Auth

Treatment Limits

Contracting (Value-Based)

Final Check & Peer Review

- Tone/objectivity
- Conciseness
- Transparency and reproducibility
- Quality of evidence and grading (consistency)
- Practical considerations
- Supportable recommendations
- References – do citations add up?
P and T Committee Prep & Etiquette

- Anticipate questions and know who will take the lead for Q & A
- Work as a team
- Understand pro’s and con’s of “huddling” during a presentation
- Don’t guess

References

References (Continued)


Additional Resources

