October 29-November 1
Gaylord National Harbor • National Harbor, MD

AMCP

NEXUS2019

The Intersection of Value and Care

1

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

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

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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.

3

Financial Relationship Disclosures

Disclosure Information	Advisory Board	Consultant	Grants/ Research	Salary/ Contractual	Supported Promotional Education	Stock/ Shareholder	Other Financial Support
Lynn Nishida, RPh, FAMCP Speaker	Regeneron	None	None	None	None	None	None

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

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Faculty

Lynn Nishida, RPh, FAMCP

Vice President – Clinical Product & Contracting

WithMe Health

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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!

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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

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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)

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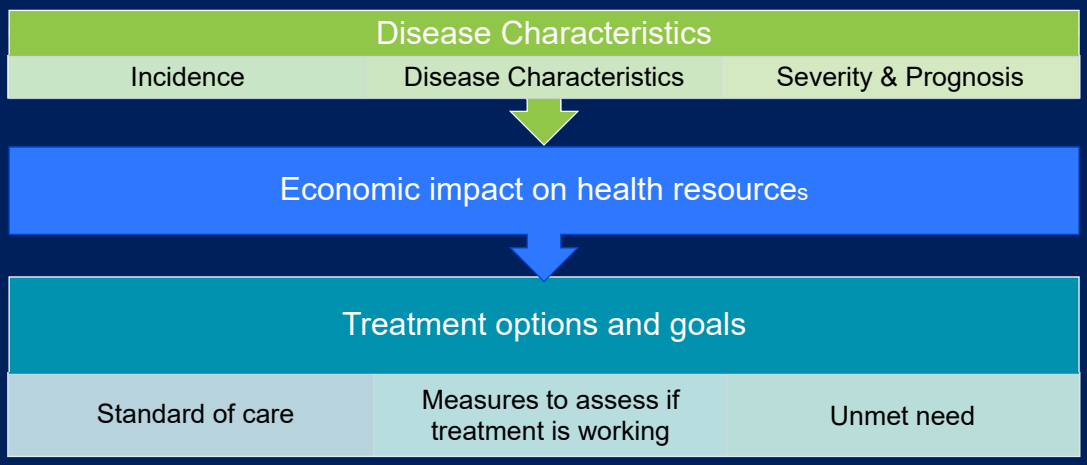
Background Information



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Applying PICOT [2]

- **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.

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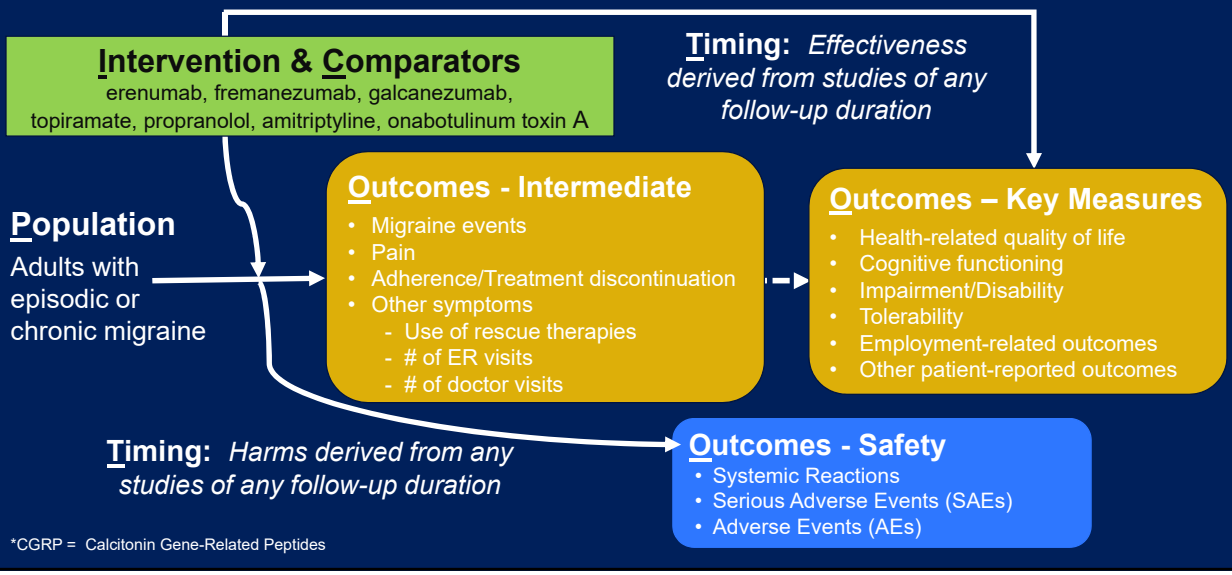
PICOT - Example
CGRP* Inhibitors for Migraines



*CGRP = Calcitonin Gene-Related Peptides

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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?

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Search and Screen

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Literature Search Inclusion & Exclusion Criteria

- Date conducted
- Databases (PubMed/Ovid, Embase, Cochrane)
- Search Method (including manual hand searches)
- Search terms & Parameters
- Exclusion Criteria / Limitations
- Search Results

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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

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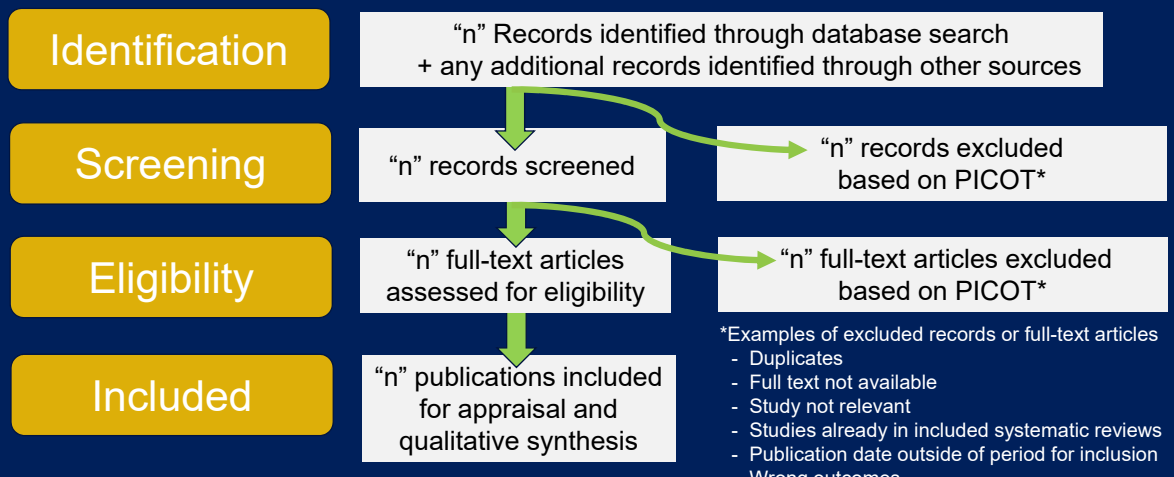
PRISMA Flow Chart[3]



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PRISMA – Literature Search CGRP's and Other Comparators in Migraines

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

Fremanezumab 64 hits
(("fremanezumab"[Supplementary Concept] OR "fremanezumab"[All Fields])

Galcanezumab 61 hits
("galcanezumab"[Supplementary Concept] OR "galcanezumab"[All Fields]) AND ("migraine disorders"[MeSH Terms]

Erenumab 86 hits
(("erenumab"[Supplementary Concept] OR "erenumab"[All Fields]) AND ("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields])) AND ("2010/01/01"[PDAT] : "2019/08/31"[PDAT])

Topiramate 476 hits
(("topiramate"[MeSH Terms] OR

Onabotulinum toxin A 38 hits
(("onabotulinum toxin A" [Supplementary

Propranolol 133 hits
(("propranolol"[MeSH Terms] OR

Amitriptyline 166 hits
(("amitriptyline"[MeSH Terms] OR "amitriptyline"[All Fields]) AND ("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields])) AND ("2010/01/01"[PDAT] : "2019/08/31"[PDAT])

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PRISMA Flow Chart - Example Literature Selection Process

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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

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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

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Appraising Individual Studies

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Individual Study Quality Assessment Tools

Grading of Individual Studies	NHLBI[4]	CER Collaborative[5]
Grading Assessment Nomenclature Used	Good, Fair, or Poor	Relevance & Credibility: Sufficient vs Insufficient
Appraisal Tools for Individual Studies	**NHLBI[4]**	**CER Collaborative[5]**
- Randomized Controlled Trials	Yes	
- Systematic Reviews	Yes	
- Case/Case Series Studies	Yes	
- Before/After (Pre/Post) Studies with No Control Group	Yes	
- Observational Studies (Prospective & Retrospective)	Yes	Yes
- Indirect Treatment Comparison Study		Yes
- Modeling studies		Yes

NHLBI = National Heart, Lung, and Blood Institute
CER Collaborative = Comparative Effectiveness Research Collaborative, formed by AMCP, ISPOR, and NPC to provide greater uniformity and transparency in the evaluation and use of coverage and health care decision-making for improved outcomes.

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Individual RCT - NHLBI Appraisal Tool[4]

Citation: Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med.* 2017;377(22):2123-2132.[8]	Quality: Good		
	YES	NO	OTHER
1. Study described as randomized, a randomized trial, a randomized clinical trial, or an RCT	X		
2. Method of randomization adequate (use of randomly generated assignment)	X		
3. Treatment allocation was concealed (so that assignment could not be predicted)	X		
4. Study participants and providers blinded to treatment group assignments	X		
5. Those assessing the outcomes were blinded to the participants treatment assignments	X		
6. Groups similar at baseline for pertinent characteristics/demographics that if different could affect outcomes	X		
7. Overall drop-out rate from study at endpoint was 20% or less of number(s) allocated to treatment	X		
8. Differential drop-out rate (between treatment groups) at endpoint was 15% or lower	X		
9. High adherence to the intervention protocols for each treatment group (e.g., 80% or more)	X		
10 Other interventions avoided or similar in groups (e.g., background treatments)	X		
11. Outcomes assessed using valid, reliable measures, implemented consistently across all study subjects	X		
12. Reported sample size is large enough to detect difference in primary outcome between groups (80% power)	X		
13. Outcomes reported or subgroups analyzed were *a priori* (e.g., prespecified before analysis conducted)	X		
14. All randomized participants were analyzed in the group to which they were originally assigned (e.g., an intent-to-treat analysis is used)		X	

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

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Individual RCT Evidence Table

Citation: Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017;377(22):2123-2132.[8]

Study Design	Drug Regimens	N	Time Horizon	Study Population	Endpoints	
					Primary	Secondary
Multi-center, double-blind randomized placebo-controlled	SQ every 4 weeks: 1. Placebo 2. erenumab 70mg 3. erenumab 140 mg	 319 317 319	24 wks	• Episodic migraine, • Includes patients on preventive migraine medication if on stable dose. Patients allowed to use acute migraine medications (triptans, ergots, and NSAIDs)	↓ 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.

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Individual RCT Evidence Table

Citation: Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017;377(22):2123-2132.[8]

Efficacy/Effectiveness

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

Safety*

Adverse Events	Placebo (n = 319)	Erenumab 70mg (n = 314)	Erenumab 140mg (n = 319)
# (%) with Adverse Events (AE)	201 (63.0%)	180 (57.3%)	177 (55.5%)
# (%) with Serious AEs	7 (2.2%)	8 (2.5%)	6 (1.9%)
# (%) Drop-outs due to AEs	8 (2.5%)	7 (2.2%)	7 (2.2%

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

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.

Quality Assessment:

Weaknesses identified are minimal and unlikely to significantly impact validity of results.

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Systematic Review NHLBI Appraisal Tool[4]

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]	Grade: Good Quality		
	Yes	No	Other*
1. Review based on focused key question(s), adequately formulated/described?	X		
2. Eligibility criteria for included/excluded studies predefined and specified?	X		
3. Literature search strategy uses a comprehensive, systematic approach?	X		
4. Peer reviewed by a second reviewer for inclusion/exclusion to minimize bias?	X		
5. Quality of each included study rated independently by two or more reviewers using standard method to appraise its internal validity	X		
6. Included studies listed with important characteristics/results of each study	X		
7. Publication bias assessed	X		
8. Heterogeneity assessed (Applies only to meta-analyses)	X		

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

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Evidence Table - Systematic Review

Lattanzi S et al. A systematic review and meta-analysis of efficacy and safety. Drugs 2019; 79(4): 417-431.[13]		
Type: Systematic Review with meta-analysis	**Appraisal:** This review concludes that erenumab is efficacious and well tolerated as preventive treatment in adults with episodic & chronic migraine.	**Appraisal: High Quality**
Appraisal Elements	**Description**	**Concerns that Impact Quality**
Funding Source	• None	None
Interventions / Conditions	• Efficacy and safety of erenumab as preventive treatment in patients with chronic or episodic migraine.	None
Number of Studies	• 5 studies (2,393 patients)	None
Literature Search	Documented systematic and comprehensive search using PRISMA. Period covered through October 31, 2018	None
Quality of Studies Included	• 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 (Chi^2 and I^2).	None

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Evidence Table - Systematic Review

Lattanzi S et al. A systematic review and meta-analysis of efficacy and safety. Drugs 2019; 79(4): 417-431.[13]		
Appraisal Elements	**Description**	**Concerns that Impact Quality**
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

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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?

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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?

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Synthesizing the Evidence

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Evidence Synthesis

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- Systematic Reviews
- Meta-analyses
- Individual Studies
- Economic Models

What does the collective body of evidence tell you in terms of a low, moderate or high certainty of a net benefit ?

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Evidence Synthesis Hypothetical Snapshot

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

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

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

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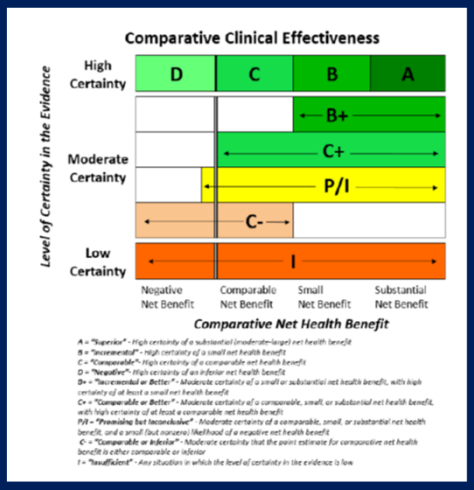
Evidence Synthesis – ICER Matrix[7]

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

What is your level of certainty?

Figure 1: ICER Evidence Rating Matrix*



*ICER Matrix used with permission from Institute of Clinical and Economic Review (ICER)[7]

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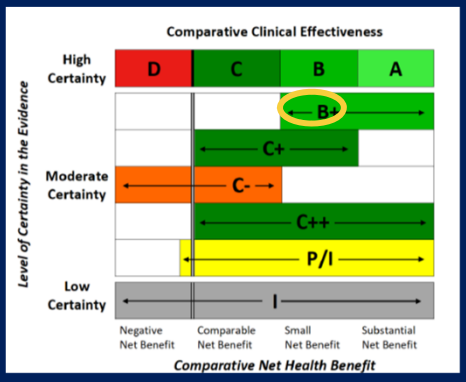
Pulling It All Together
Articulating Response to Key Questions

Key Question 1:

CGRP inhibitors vs <u>No Preventive Therapy</u>

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.



*ICER Matrix used with permission from Institute of Clinical and Economic Review (ICER)[7]

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Pulling It All Together
Articulating Responses to Your Key Questions

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

	Erenumab	Fremanezumab	Galacanezumab
Chronic Migraines			
Monthly Migraine Days*	↓ ~ 2 less days	↓ ~ 2 less days	↓ ~ 2 less days
Days Using Acute Medications	↓ ~ 2 less days	↓ ~ 2 less days	↓ ~ 2 less days
Episodic Migraine			
Monthly Migraine Days*	↓ ~ 2 less days	↓ of ~ 2 less days	↓ of ~ 2 less days
Days Using Acute Medications	↓ of ~ 2 less days	↓ of ~ 1 less day	↓ of ~ 2 less days
50% Responders**	Increase	Increase	Increase

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

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Pulling It All Together
Articulating Responses to Your Key Questions

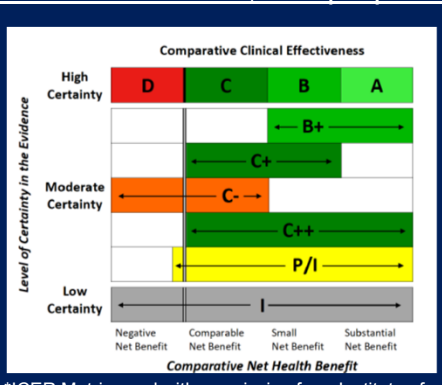
AMCP

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)[7]

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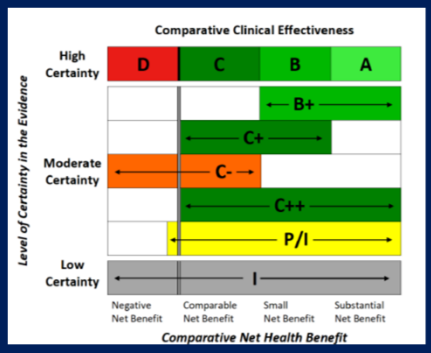
Pulling It All Together
Articulating Responses to Your Key Questions

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)[7]

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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.

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Sources of Uncertainty

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

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Financials and Economic Analysis Summary

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LONG-TERM COST EFFECTIVENESS

SHORT TERM BUDGET IMPACT

ACCESS

AFFORDABILITY

40

Final Recommendations

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Formulary

Prior Auth

Treatment Limits

Contracting (Value-Based)

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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?

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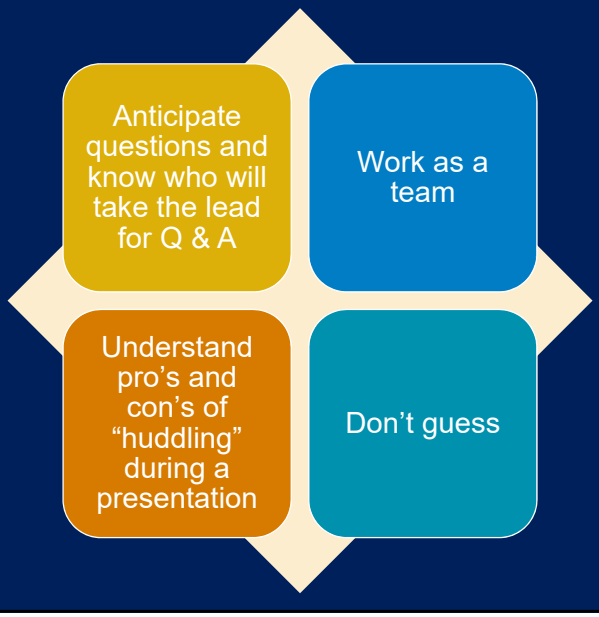
P and T Committee Prep & Etiquette



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11. Dodick DWA, M.; Brandes, J.L.; Kudrow, D.; Lanteri-Minet, M.; Osipova, V.; Palmer, K.; Picard H.; Mikol, D.D.; Lenz, R.A. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia.* 2018;38(6): 1026-37.
12. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* 2017;16(6):425-434.
13. Lattanzi S, Brigo F, Trinka E, et al. Erenumab for preventive treatment of migraine: A systematic review and meta-analysis of efficacy and safety. Drugs 2019; 79:417-31.

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Additional Resources

- National Centers for Biotechnology. Finding what works in health care: Standards for systematic reviews. National Academy of Sciences 2011. Found at https://www.ncbi.nlm.nih.gov/books/NBK209522/. Accessed October 10, 2019.
- Evidence Synthesis Academy. Brown School of Public Health and the Agency for Healthcare Research and Quality (AHRQ). Found at: https://evsynthacademy.org/index.php/citations/. Accessed October 10, 2019.
- The Centre for Evidence-Based Medicine (CEBM) Critical Appraisal Tools. University of Oxford. Found at https://www.cebm.net/2014/06/critical-appraisal/. Accessed October 10, 2019.

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