The effectiveness and value of novel acute treatments for migraine

A summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council

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Migraine is a common episodic disorder, typically characterized by headache that is often associated with nausea and sensitivity to light and sound. An estimated 40 million adults (12%-15% of adults) in the United States report migraine or severe headaches.[1,2] The frequency and intensity of migraine attacks vary widely, but migraine can be a disabling, chronic condition affecting all aspects of life.[3] Patients with migraine have higher costs of care, decreased work productivity, and increased disability claims, accounting for $9-$11 billion in total costs per year between 2004-2013.[4-7]

Treatment strategies for migraine include acute therapies to abort episodic symptoms and preventive therapies to reduce the frequency of attacks.[8] The most commonly used prescription medications for acute treatment are "triptans" (5- hydroxytryptamine [5-HT] 1b/1d receptor agonists).[9] Although effective for many patients, triptans are not universally successful in aborting migraines, and because of their vasoconstrictive effects, triptans are labeled as contraindicated in patients with known cardiovascular disease.[10]

In recent years, 2 new novel classes of acute migraine medications have emerged: selective 5-HT 1F agonists (commonly referred to as "ditans") and CGRP antagonists (commonly referred to as "gepants"). The U.S. Food and Drug Administration has approved 3 of these novel agents: lasmiditan (Reyvow, Lilly, October 2019); ubrogepant (Ubrelvy, Allergan, December 2019); and rimegepant (Nurtec, Biohaven, February 2020).

The Institute for Clinical and Economic Review (ICER) conducted a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of these 3 novel acute treatments for migraine attacks. Complete details of ICER's systematic literature search and protocol, as well as the methodology and model structure for the economic evaluation, are available on ICER's website. Here, we present the summary of our findings and highlights of the policy discussion with key stakeholders held at a public meeting of the Midwest Comparative Effectiveness Public Advisory Council on January 23, 2020. The detailed report is available on the ICER website at https://icer-review.org/material/acute-migraine-final-evidence-report-and-meeting-summary/.

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Summary of Findings

CLINICAL EFFECTIVENESS

Comparators of interest for the 3 novel agents included (a) no additional migraine-specific acute treatment (i.e., placebo arms of clinical trials) and (b) triptans (eletriptan and sumatriptan). These specific triptans were chosen because, among all triptans, sumatriptan is one of the most widely used in clinical practice, whereas eletriptan was shown in a recent network meta-analysis to be one of the most efficacious and well tolerated.[11,12]

We identified 3 randomized controlled trials (RCTs) of lasmiditan (one phase 2 and two phase 3),[13-15] 3 RCTs of ubrogepant (one phase 2 and two phase 3),[16-18] 4 RCTs of rimegepant

TABLE 1 Results for Lasmiditan, Rimegepant, Ubrogepant, and Usual Care for Triptan-Ineligible Population

Treatment	Total Cost	QALY	Life-Years	evLYG	Hours of Pain	New Interventions Versus Usual Care	
						Cost per QALY	Cost per Hour of Pain Avoided
Lasmiditan	$12,000	1.8271	1.95	1.8271	1,650	$151,800	$4.32
Ubrogepant	$10,660	1.8295	1.95	1.8295	1,580	$40,000	$1.15
Rimegepant	$10,660	1.8295	1.95	1.8295	1,570	$39,800	$1.15
Usual care	$10,050	1.8142	1.95	1.8142	2,100	comparator	comparator

evLYG = equal value of life-years gained; QALY = quality-adjusted life-years.

(one phase 2 and three phase 3),[19-22] and 23 RCTs of the 2 triptans.[23-44] The RCTs were predominantly placebo-controlled, with only 4 head-to-head trials (1 of rimegepant vs. sumatriptan and 3 of eletriptan vs. sumatriptan). The primary efficacy endpoint in the trials of lasmiditan and CGRP antagonists was pain freedom assessed at 2 hours after dose. Outcome data from all RCTs were combined and analyzed using a Bayesian network meta-analysis (NMA).

NMA results showed that all 3 of the novel agents have superior odds of achieving pain freedom at 2 hours versus placebo: lasmiditan (OR = 3.01; 95% credible interval [CrI] = 2.20-4.14); ubrogepant (OR = 2.12; 95% CrI = 1.58-2.88); and rimegepant (OR = 2.11; 95% CrI = 1.67-2.72). Similar trends were observed on other comparisons with placebo: pain relief, freedom from most bothersome symptom (MBS), and functional disability at 2 hours. In contrast, all 3 agents showed lower odds of achieving pain freedom or pain relief at 2 hours after dose compared with eletriptan or sumitriptan. For example, compared with eletriptan, ORs for pain freedom at 2 hours were 0.54 (95% CrI = 0.36-0.85), 0.38 (95% CrI = 0.26-0.59), and 0.38 (95% CrI = 0.27-0.57) for lasmiditan, ubrogepant, and rimegepant, respectively. We were unable to compare the novel agents to eletriptan or sumatriptan on freedom from MBS and ability to function because of inconsistent reporting on these outcomes in the triptan studies. Using the NMA to perform indirect comparisons of the 3 novel agents, results showed no statistically significant differences on any measure of patient benefit.

The majority of adverse events in these trials were mild to moderate, but lasmiditan had higher rates than other agents. In the open-label extension (OLE) study of lasmiditan, 12.8% of patients discontinued the trial because of adverse events, the most common of which was dizziness (2.7% of patients in the 100 mg group and 4.3% of patients in the 200 mg group).[45] Overall rates of discontinuation were considerably lower in the OLEs of ubrogepant (2.7%) and rimegepant (2.7%).[46,47]

LIMITATIONS OF THE CLINICAL EVIDENCE

First, because of the lack of head-to-head studies among the novel agents, we were required to use indirect analyses to compare lasmiditan, ubrogepant, and rimegepant to each other and to triptans. The results of indirect analyses are more uncertain than when the therapies are compared directly. Second, although the randomized trials of lasmiditan and CGRP antagonists were designed to assess the primary outcomes at 2 hours, published exploratory analyses and additional post hoc analyses of company data requested by ICER suggest there is some delayed benefit of these drugs versus placebo beyond 2 hours.[48] However, the magnitude and duration of the delayed benefit of these drugs remains uncertain. Third, most data for these drugs came from trials treating a single migraine attack. Therefore, efficacy and safety outcomes when used over time for repeated attacks are uncertain. Finally, while these new agents provide an option for patients with absolute or relative contraindications to triptans, we do not have enough clinical information on the safety of these new agents in these individuals.

LONG-TERM COST-EFFECTIVENESS

We evaluated the cost-effectiveness of the 3 new treatments for acute migraine over a 2-year time horizon from a U.S. health care sector perspective using a de novo semi-Markov model approach with 48-hour treatment cycles. The analysis for each drug was conducted in 2 different populations: (1) "triptan ineligible"—patients who had migraine attacks that did not respond to nonprescription medicines and for whom triptans had previously not been effective, were not tolerated, or were contraindicated; and (2) "triptan eligible"—patients who had migraine attacks that did not respond adequately to nonprescription medicines but who could use triptans as an option. For both populations, the

TABLE 2 Results for Lasmiditan, Rimegepant, Ubrogepant, and Sumatriptan and Eletriptan for Triptan-Eligible Population

Treatment	Total Cost	QALY	Hours of Pain	New Interventions Versus Sumatriptan		New Interventions Versus Eletriptan	
				Cost per QALY	Cost per Hour of Pain Avoided	Cost per QALY	Cost per Hour of Pain Avoided
Lasmiditan	$12,000	1.8271	1,650	Dominated	Dominated	Dominated	Dominated
Ubrogepant	$13,020	1.8221	1,876	Dominated	Dominated	Dominated	Dominated
Rimegepant	$13,010	1.8222	1,870	Dominated	Dominated	Dominated	Dominated
Sumatriptan	$6,630	1.8264	1,610	comparator	comparator	–	–
Eletriptan	$6,790	1.8293	1,480	–	–	comparator	comparator

QALY = quality-adjusted life-years.

model used a hypothetical cohort of patients who entered 1 of 2 Markov states, either having a migraine or not having a migraine, based on the average daily rate of migraines. Among patients in the migraine health state, patients were classified as having moderate or severe migraine pain. In the triptan-ineligible population, the interventions were compared with each other and with usual care, represented by the placebo arm from clinical trials. In triptan-eligible patients, the interventions were compared with each other and with triptans (sumatriptan and eletriptan).

The model was informed by the ICER NMA of key clinical trials, previous relevant economic models, systematic literature reviews, and input from stakeholders. The outcomes of interest included the incremental cost per quality-adjusted life-year (QALY) gained, life-years gained, equal value of life-years gained, and cost per hour of migraine pain avoided. Full details on ICER's cost-effectiveness analysis and model are available on ICER's website at https://icer-review.org/material/acute-migraine-final-evidence-report-and-meeting-summary/.

As shown in Table 1, when compared with usual care for triptan-ineligible patients, the incremental cost-effectiveness ratio was highest for lasmiditan ($151,800 per QALY) and lower and nearly identical for ubrogepant and rimegepant ($39,800 and $40,000 per QALY, respectively). When all 3 novel agents were compared with each other, ubrogepant and rimgepant were more effective and less costly than lasmiditan. In the analysis of triptan-eligible patients, sumatriptan and eletriptan produced higher QALYs at a lower total cost and, therefore, dominated all 3 novel agents (Table 2).

LIMITATIONS OF THE COST-EFFECTIVENESS MODEL

The clinical trials of the new agents and the older triptans did not report response to treatment at later time points for patients who did not have freedom from pain or pain relief at 2 hours. As previously noted, post hoc analyses from the phase 3 trials of lasmiditan and ubrogepant, along with supporting evidence on rimegepant submitted to ICER, showed additional benefit of these drugs versus placebo for up to 4 hours after dose. These data were used to estimate a delayed effect for the new interventions in the analysis of the triptan-ineligible patient population. However, because of trial designs and the potential for attrition bias, the magnitude and duration of any delayed benefit of these drugs remains uncertain. Furthermore, the effectiveness of sumatriptan and eletriptan compared with usual care (placebo) beyond 2 hours could not be estimated. As a result, the model evaluating the new interventions compared with triptans for triptan-eligible patients did not include delayed benefits after 2 hours.

Policy Discussion

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC; https://icer-review.org/programs/midwest-cepac/) is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical effectiveness and cost-effectiveness of health care interventions. The Midwest CEPAC is composed of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberation includes input from clinical experts and patient representatives specific to the condition under review, as well as formal comment from manufacturers and the public. A policy roundtable concludes each meeting during which representatives from insurers and manufacturers join clinical experts and patient representatives to discuss how best to apply the findings of

TABLE 3 Votes on "Other Benefits" that Are Not Adequately Captured in the Base-Case Cost-Effectiveness Model

Is it likely that gepants offers 1 or more of the following "other benefits" compared with over-the-counter therapies? (select all that apply)	
This intervention will significantly reduce caregiver or broader family burden.	11/12
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	12/12
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity	11/12
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention (e.g., reduction of opioid misuse)	12/12
Is it likely that lasmiditan offers 1 or more of the following "other benefits" compared with over-the-counter therapies? (select all that apply)	
This intervention will significantly reduce caregiver or broader family burden.	10/12
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	11/12
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity	9/12
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention (e.g., reduction of opioid misuse)	12/12
Is it likely that gepants offers 1 or more of the following "other benefits" compared with lasmiditan? (select all that apply	
This intervention offers reduced complexity that will significantly improve patient outcomes.	9/12
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention (e.g., reduction of opioid misuse)	12/12

the evidence to clinical practice, insurance coverage, and pricing negotiations.

The ICER report on acute treatments for migraine was the subject of a Midwest CEPAC meeting on January 23, 2020. Following the discussion, the CEPAC panel members deliberated on key questions raised by ICER's report. The results of their votes on the clinical evidence are as follows: (a) the panel voted 12-0 that the clinical evidence was adequate to demonstrate greater net health benefit of each of the new agents compared with no treatment; (b) the panel voted 12-0 that there was inadequate evidence to distinguish between the net health benefit of rimegepant and ubrogepant; (c) the panel voted 11-1 that there was inadequate evidence to distinguish between the net health benefit of the gepants and lasmiditan; and (d) the panel voted 12-0 that the evidence was inadequate to demonstrate a superior net health benefit of any of the new agents compared with triptans.

The CEPAC panel also voted on "other potential benefits" and "contextual considerations" as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. The results of these votes are shown in Table 3 and Table 4. They highlight several factors that the CEPAC panel felt were particularly important for judgments of value, including the novel mechanism of action of the novel agents and the lifetime burden of illness suffered by patients with migraine. In addition, the panel highlighted as an important other benefit of these therapies, a potential for reduction of opioid (mis)use, since patients will now have alternative options.

The culminating vote of the CEPAC panel, intended to reflect its integration of the relevant elements of the value assessment framework, was on the "long-term value for money." The panelists did not vote on lasmiditan and rimegepant because prices were not available for these drugs at the time of the public meeting. For ubrogepant, a majority (8/12) of panel members voted that its long-term value for money is "intermediate" compared with no treatment. However, this vote was taken before the post hoc data were submitted to ICER showing a delayed benefit for the gepants. Assuming this delayed benefit, the incremental cost-effectiveness ratio for both gepants falls well below traditional cost-effectiveness thresholds and would therefore be considered "high" long-term value for money at current pricing.

The policy roundtable discussion explored how best to translate the evidence and additional considerations into clinical practice and into pricing and insurance coverage policies. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website (https://icer-review.org/material/acute-migraine-final-evidence-report-and-meeting-summary/). Several key

TABLE 4 Votes on "Contextual Considerations" Important in Assessing Long-Term Value for Money

Are any of the following contextual considerations important in assessing gepants' long-term value for money? (select all that apply)	
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	9/12
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	11/12
This intervention is the first to offer any improvement for patients with this condition.	12/12
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	4/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention	8/12
Are any of the following contextual considerations important in assessing lasmiditan's long-term value for money? (select all that apply)	
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	10/12
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	11/12
This intervention is the first to offer any improvement for patients with this condition.	12/12
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	6/12
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	6/12

policy recommendations are as follows:

- Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Considerations for prior authorization include the following:
  - *Patient eligibility (severity)*: There is no evidence-based reason to try to limit coverage for any of the 3 agents based on a metric of severity such as number of migraines per month.
  - *Patient eligibility (previous treatment course)*: Given that the evidence of response to these newer agents does not suggest they are superior to triptans, requiring patients to try triptans first before receiving coverage for these newer agents is reasonable if patients are clinically eligible. Many patients can find adequate relief with 1 triptan even after finding that other triptans are inadequate. However, the likelihood of finding a triptan that works diminishes after each trial, so a requirement of trying 1 to 2 triptans is viewed as reasonable, whereas requiring more is viewed as less reasonable.
  - *Provider criteria:* Given the benign safety profiles of these agents, it seems reasonable to allow primary care prescribing at their launch, although some payers may require specialist consultation to ensure accurate diagnosis of migraine and trials of appropriately dosed triptans have been attempted.
- For ubrogepant and rimegepant, given their similar mechanisms of action and available evidence suggesting no major differences in safety or effectiveness, payers may negotiate lower prices by offering preferential formulary status to one or the other drug, including the possibility of exclusion of one of the drugs.

DISCLOSURES

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