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Drug Use Evaluation: Migraine Prophylaxis

Research Questions:

1. How many patients in the Oregon fee-for-service (FFS) Medicaid population are prescribed triptans chronically for abortive migraine treatment?
2. What percentage of patients on chronic triptans are co-prescribed a guideline recommended migraine prophylactic agent?
3. How does use of a prophylactic agent affect triptan utilization, hospitalization, and emergency department (ED) visit rates for migraines?
4. How many patients have been prescribed a Calcitonin Gene-Related Peptide (CGRP) antagonist for migraine prophylaxis?
5. What are the most common reasons a CGRP antagonist claim or prior authorization (PA) request for migraine prophylaxis was denied?

Conclusions:

- Very few patients in the Oregon FFS Medicaid population are utilizing triptans chronically (N=113,228 total enrolled patients from Oct 2018 – Sept 2019; N=1,178 used at least one triptan; N=169 used triptans chronically).
- Of the patients using chronic triptans, about half (N=92, 54%) were also prescribed a guideline recommended prophylaxis agent. Guidelines would suggest that all of these patients would qualify for prophylaxis use.
- If a prophylaxis agent was initiated, the majority of patients (N=78, 85%) received an adequate trial of those agents. This suggests the primary barrier to appropriate prophylaxis use is initiation of therapy rather than continuation of use.
- No major conclusions could be drawn about the impact of prophylaxis use on hospitalization rates or ED visit rates given the small sample size and low number of ED visits and hospitalizations overall.
- Since the PA criteria for CGRP antagonists was implemented in Nov 2018, 525 unique claims were submitted for a CGRP antagonist with an indication for migraine prophylaxis, of which 257 (49%) were paid.
- The most common reason a claim for the prophylaxis CGRP antagonists was denied (N=268) is because it required a PA (N = 253, 94%). However, only 180 unique PAs were requested. What portion of these denied claims, if any, that would have met PA criteria if they had requested one is unknown. However, the majority of PAs that were requested were approved (N = 127, 71%).

Recommendations:

- No policy changes for triptan therapy are recommended at this time
- Consider provider education (such as continuing education or a brief pamphlet/newsletter) to increase migraine prophylaxis use in patients taking chronic triptans
- No PA criteria changes for CGRP antagonists were made.

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Current Policy:

- Oregon FFS Medicaid currently has the following quantity limits for preferred triptans to prevent medication overuse headaches. See **Appendix A** for a list of all triptans (preferred and non-preferred) and their respective quantity limits.

Table 1: Preferred Triptans and their Quantity Limits for Oregon FFS Medicaid[1]

Generic Name	Brand Name	Quantity Limit per Month
Naratriptan	Amerge®	9 tabs
Sumatriptan tablets	Imitrex® & generics	9 tabs
Sumatriptan nasal spray	Imitrex® & generics	18 spray units
Sumatriptan injectable	Imitrex® & generics	6 vials
Zolmitriptan tablets	Zomig® Zomig® ZMT	6 tabs
Zolmitriptan nasal spray	Zomig® NS	3 packages (18 spray units)
Abbreviations: NS – nasal spray; ZMT – zolmitriptan orally disintegrating tablet		

- Oregon FFS Medicaid currently has at least one formulation of the following guideline recommended migraine prophylactic agents (see **Table 3**) with a "preferred" designation: topiramate, propranolol, metoprolol (both tartrate and succinate formulations), divalproex sodium, valproic acid, amitriptyline, venlafaxine, and atenolol.
- Timolol and nadolol are the only recommended migraine prophylaxis agents with a "non-preferred" designation on the Oregon FFS Medicaid PDL.[1]
- Oregon FFS Medicaid currently lists the CGRP antagonists Ajovy® (fremanezumab) and Emgality® (galcanezumab) as preferred agents for migraine prophylaxis with PA criteria (see **Appendix F**). This PA criteria was implemented on 11/1/2018 and last reviewed and edited by the Pharmacy and Therapeutics (P&T) committee in August 2020.[1]

Background:

Migraine headaches are a common ailment that affect approximately 16% of Americans.[2] These are divided into episodic migraines and chronic migraines. Episodic migraines are defined as experiencing zero to fourteen headache days per month; chronic migraines cause at least fifteen migraine days per month for more than three months consecutively.[2,3] Chronic migraines are much less common than episodic migraine and are estimated to affect 1-5% of Americans with migraines.[2] Migraine headaches appear to affect different patient populations at varying rates. Prevalence estimates by race from 2012 showed that migraines most affect Native Americans (17.7%), followed by Caucasians (14.3%), African Americans (14%), Hispanic Americans (12.9%), and least commonly Asian Americans (9.2%).[4] Migraines affect more women than men, with a sex prevalence ratio of 3:1.[2] By age, migraines affect mostly 18-44 year-old patients (17.9% prevalence), followed by 45-64 year-old patients (15.9%), and 65-74 year-old patients (7.3%).[5] Migraines affect more patients who earn less than $35,000 per year for family income (19.9% prevalence) than those earning greater than $35,000 per year (13.8%).[5] For patients younger than 65 years old, migraines affect 26% of Medicaid insured patients, which is much more than those covered by private insurance (15.1%).[5] Although estimates of migraine prevalence in Medicaid populations are known, estimates on abortive treatment utilization rates in this population are lacking in the medical literature and warrant investigation.

Migraines are treated acutely with abortive agents. Serotonin agonists (5-$HT_{1B, 1D}$), prescription only agents commonly referred to as "triptans", are the most commonly used abortive treatment.[3,6,7] However, there are many other abortive agents that can be obtained and utilized via prescription or over the counter, including acetaminophen and

nonsteroidal anti-inflammatory drugs (NSAIDs). For adult patients, the American Headache Society, the Canadian Headache Society, and the National Institute for Health and Care Excellence (NICE) guidelines recommend combination or monotherapy with the following medication classes for abortive treatment: triptans, NSAIDs, and acetaminophen containing products (e.g. Excedrin® [acetaminophen/aspirin/caffeine]).[3,6,7] Opioids (e.g. tramadol, codeine, and nasal butorphanol), ergot derivatives (e.g. dihydroergotamine), and butalbital containing products (e.g. Fioricet® [butalbital/acetaminophen/caffeine]) are generally *not* recommended by these guidelines for acute migraine treatment.[3,6,7] This is due to a lack of efficacy (for opioids and butalbital containing products) and increased safety risks (for opioids, ergot derivatives, and butalbital containing products).[3,6,7] For pediatric patients, the NICE guidelines give similar recommendations as they are intended for application in patients at least 12 years of age.[3] The American Academy of Neurology pediatric guidelines, which are endorsed by the American Academy of Pediatrics, recommend the use of ibuprofen, naproxen, or acetaminophen as first-line abortive agents.[8] If ineffective, triptans are reasonable second-line abortive therapy options.[8] Specifically, they recommend sumatriptan, zolmitriptan, rizatriptan, or almotriptan since these are the only triptans that have been Food and Drug Administration (FDA)-approved for use in pediatric patients.[8] Sumatriptan (when co-formulated with naproxen), zolmitriptan, and almotriptan are all FDA-approved for patients at least 12 years of age; rizatriptan is FDA-approved for patients 6 years and older.[9] Regardless of age, triptans are contraindicated for abortive treatment in patients with a past medical history of ischemic cardiovascular disease, cerebrovascular disease such as strokes, or uncontrolled hypertension as triptan use can increase the risk of potentiating these disease states.[9]

Since the publication of these guidelines, two CGRP antagonists (rimegepant and ubrogepant) have been FDA-approved for acute migraine treatment.[10,11] Some CGRP antagonists are approved exclusively for acute migraine treatment, while others are approved for prophylaxis (see **Table 2**). Lasmiditan, a serotonin (5-HT_{1F}) agonist, was also FDA-approved for acute migraine treatment in Oct 2019.[12]

Table 2: CGRP Antagonists and FDA Approved Uses[9]

Brand Name	Generic Name	FDA Approved Uses*
Nurtec®	Rimegepant	Migraine Treatment Migraine Prophylaxis†
Ubrelvy®	Ubrogepant	Migraine Treatment
Vyepti®	Eptinezumab	Migraine Prophylaxis
Aimovig®	Erenumab	Migraine Prophylaxis
Ajovy®	Fremanezumab	Migraine Prophylaxis
Emgality®	Galcanezumab	Migraine Prophylaxis Cluster Headache Prevention
*In adults only †Not included in data analysis for Table 12 and Table 13 as indication received 5/27/21.		

Medication overuse headaches (MOH) are a form of migraines or headaches that are caused by frequent utilization of abortive agents. Although the pathophysiology of MOH is not entirely clear, neuronal excitability in the cortical and trigeminal systems is known to increase after medication overuse and is strongly suspected to contribute to MOH.[13] All abortive agents have the potential for causing MOH, but to varying degrees.[6] Triptan use is generally limited to a maximum of 9 days per month to prevent the risk of MOH whereas acetaminophen and NSAIDs should be limited to a maximum of 14 days per month.[3,6] If patients are utilizing more than one medication class simultaneously, they should have at least 20 days per month free of abortive treatments in order to prevent MOH.[6]

Guidelines on when to initiate migraine prophylaxis vary slightly by professional society. For example, the American Family Physician guidelines recommend initiation of migraine prophylaxis in adult patients with at least 4 distinct migraines per month or at least 8 migraine days per month.[2] In contrast, the Canadian Headache Society guidelines recommend prophylaxis for adult patients with at least 3 moderate to severe migraines or at least 8 migraine days per month.[14] The NICE Guidelines recommend discussion of

the benefits and risks of prophylactic treatment for migraine with all patients 12 years old and over regardless of number of migraines per month by taking into account the patient's preferences, comorbidities, risk of adverse events and the impact of the headache on their quality of life.[3]

The American Academy of Neurology guidelines for pediatric migraine prevention, which is endorsed by the American Academy of Pediatrics, recommend discussion of the use of preventative therapies for patients with "frequent headaches or migraine-related disability or both."[15] Additionally, the pediatric guidelines also recommend emphasizing non-pharmacological interventions (such as trigger avoidance and encouraging good sleep hygiene) since the efficacy data for pharmacological interventions is less robust in pediatric patients.[15] In the majority of randomized controlled trials (RCTs) in pediatric patients, migraine prevention medications fail to demonstrate superiority to placebo. Broadly, placebo use alone led to a 50% or greater reduction in headache frequency in 30-61% of children.[15] Only three medications (topiramate, propranolol, and amitriptyline (when combined with cognitive behavioral therapy)) are recommended for migraine prevention in pediatric patients due to their slightly better evidence for efficacy as compared to placebo. For topiramate, a random effect model of 4 RCTs comparing topiramate to placebo led to a standardized mean difference (SMD) of 0.391 [95% confidence interval (CI) 0.127-0.655] in reducing the frequency of migraine days.[15] A SMD of 0.391 indicates that patient taking topiramate had on average 0.391 fewer days with migraines than patients taking placebo. A SMD of at least 0.2 is deemed clinically significant.[15] Propranolol use as compared to placebo in one RCT led to a risk ratio (RR) of 5.2 [95% CI 1.59-17] in leading to at least a 50% reduction in headache attacks.[15] Pediatric patients who receive amitriptyline plus cognitive behavioral therapy are more likely to have a reduction in headaches than those who receive amitriptyline alone (SMD 0.48 [95% CI 0.14-0.82]).[15]

All patients with chronic migraines (defined as at least fifteen migraine days per month for more than three months) qualify for preventative therapy regardless of which guidelines are referenced, and about 25-38% of patients with episodic migraines may also benefit from prophylaxis.[2,3,14,15] Of the patients who qualify for prophylaxis, the American Family Physician guidelines estimate that only about 3-13% of patients are prescribed a prophylactic agent.[2] This suggests that there is a gap in appropriate prophylactic agent use. Estimates of how many Medicaid patients with migraines are prescribed prophylactic agents are lacking and warrant investigation. **Table 3** lists the guideline recommended agents used to prevent migraines in adults who qualify for preventative therapy.

Table 3: Migraine Prophylaxis Agents Based on Highest Level of Evidence for Use in Adults[2,3,14-17]

Level of Evidence for Use	Medication Examples	
Level A Evidence – Established Efficacy (≥2 Class I studies)	Divalproex sodium Metoprolol tartrate Metoprolol succinate Propranolol	Sodium valproate (valproic acid) Timolol Topiramate
Level B Evidence – Probably Effective (1 Class I or 2 Class II studies)	Amitriptyline Atenolol	Nadolol Venlafaxine
Not Recommended – Established as possibly or probably ineffective	Clonazepam Feverfew Gabapentin Lamotrigine	Nabumetone Oxcarbazepine Telmisartan

Use of a migraine prophylactic agent reduces the utilization of abortive medications and other healthcare related costs (such as ED visits).[18] A retrospective study assessed healthcare resource utilization 6 months prior to and 12 months (broken into two 6-month time frames) after the initiation of a preventative agent. Patients with migraines used a mean of 7.1 units of sumatriptan per month prior to being prescribed a preventative agent. This decreased to 6.6 units per month in the first 6 months after preventative therapy initiation and decreased further to 5.6 units per month in the second 6 months (a decrease of 21.1%, P= 0.0004).[18] Comparing the 6 months prior to preventative therapy and the second 6 month segment after preventative agent initiation, office and other outpatient visits for migraines reduced by 51.1%. ED visits for migraines were

reduced by 81.8%.[18] Thus, appropriately using preventative therapies for migraines has the potential to significantly reduce healthcare costs associated with utilization of abortive therapies, outpatient visits, and ED visits.

The purpose of this drug use evaluation is to determine what percentage of the Oregon FFS Medicaid population is currently utilizing triptans chronically, how many of those patients are also utilizing a migraine preventative therapy, and if there is a gap in treatment for preventative therapy use. Additionally, an analysis of CGRP antagonist use since PA implementation was conducted to assess CGRP utilization and evaluate if current PA criteria is overly burdensome.

Methods:

This descriptive and retrospective analysis included all Oregon FFS Medicaid patients (all ages) who had been prescribed any FDA-approved triptan chronically (defined below). Other abortive agents, such as NSAIDs, were excluded since they can readily be obtained over the counter and the data would be less reliable. Additionally, claims data from 2020 was excluded due to the anticipated confounders as a result of the COVID-19 pandemic. High stress levels are a common trigger for migraines,[2] and thus patients may have utilized triptans more frequently during 2020. Additionally, changes in insurance status and ability to access healthcare services for conditions such as migraines were likely fundamentally altered from a "typical" year.

Chronic use of triptans was defined as any three FFS claims within a 120-day period to indicate fills of triptan for three consecutive months. A 4-month window was chosen to allow for gaps between refills. The index date was defined as the date of the first claim for the first triptan within the 120-day window. Patients with 3 claims for *any* triptan were included to allow for switching between different agents. Additionally, all patients with at least 1 triptan claim during this time frame were queried for a medical claim with a diagnosis of migraine (see **Appendix B** for a list of included ICD-10 codes) to better describe what the triptan and prophylaxis agent (if any) was being utilized for. Patients on chronic triptans were evaluated for prophylactic medication use. Any claim for one of the prophylactic agents with level A or B evidence from **Table 3** (HSN and GSN codes included in **Appendix C**) during the time frame of April 1, 2018 through Dec 31, 2019 (6 months prior to 3 months after the chronic triptan use time frame) was evaluated.

Patients identified as having a claim for a prophylaxis agent ("prophylaxis users") were assessed for the presence of an adequate prophylaxis trial. Guidelines recommend that all prophylactic agents be tried for at least 2 consecutive months to determine their efficacy at reducing migraine severity and/or frequency. An adequate trial was defined as having at least two claims of the same prophylactic medication in consecutive months. A 14-day gap in therapy between fills was allowed to account for imperfect refill timing. The average number of claims for triptans per month was compared between chronic triptan users who did and did not have a co-prescribed prophylactic agent. Additionally, the number of unique patients with ED visits and hospitalizations for migraines (utilizing the same ICD-10 codes listed in **Appendix B**) was compared between chronic triptan users who did and did not have a co-prescribed prophylaxis agent. However, prophylaxis users may interact with the healthcare system more in general than non-prophylaxis users, potentially introducing a confounding variable. In order to assess baseline rates of ED visits and hospitalizations for prophylaxis and non-prophylaxis users, unique patient ED visits and hospitalizations for *any* diagnosis was also gathered. We also compared patients who did and did not have an adequate trial of a prophylactic medication.

To describe overall utilization of the CGRP antagonists over time, we included the number of unique prior authorizations (both approved and denied) for all FDA-approved CGRP antagonists (see **Table 2**) from Nov 1, 2018 through Dec 31, 2020. We identified unique PAs via unique PA numbers. All unique prescriptions for a CGRP antagonist medication from Nov 1, 2018 through Dec 31, 2020 with error codes listed in **Appendix D** and without error codes listed in **Appendix E** were included in the analysis. Error codes in **Appendix E** would indicate these claims were denied for procedural reasons. The identified claims were then assessed for the most common reasons for denial using a descriptive analysis.

Results:

From Oct 1, 2018 through Sept 30, 2019, an average of 113,228 patients were enrolled in Oregon Medicaid FFS for the entire year (9,436 enrolled patients per month). Of those patients, 1,178 (1% of the entire Oregon FFS Medicaid population) had at least one triptan claim during the same time frame. Of the 1,178 triptan users, only 169 patients (14% of all triptan users) met the definition of a "chronic triptan user" (3 FFS claims for triptans in a continuous 120-day period). Demographics for patients with at least one triptan claim and chronic triptan users is listed in **Table 4**. There are no obvious differences between all triptan users and chronic triptan users. However, chronic triptan users included slightly more female patients (88% vs. 83%). Of note, only 66% of all triptan users and 62% of chronic triptan users had a migraine diagnosis. The majority of chronic triptan users were 18-44 years old (63%); however, 6% of chronic triptan users were 0-17 years old.

Table 4: Demographic Data for All Triptan Users and Chronic Triptan Users in the Oregon Medicaid FFS Population:

Demographic Parameter	All Triptan User (N = 1178) Number of patients (% of *all* triptan users)	Chronic Triptan User (N=169) Number of patients (% of *chronic* triptan users)
Average Age (years)	35 (range 5-64)	38 (range 10-63)
0-17 years	149 (13%)	10 (6%)
18-44 years	733 (62%)	107 (63%)
45-64 years	296 (25%)	52 (31%)
65+ years	0 (0%)	0 (0%)
Sex		
Female	978 (83%)	149 (88%)
Race		
White	511 (43%)	89 (53%)
Black	17 (1%)	0 (0%)
Other	172 (15%)	30 (18%)
Unknown	478 (41%)	50 (30%)
Patients with Migraine Diagnosis	772 (66%)	105 (62%)
Number of months/year triptan filled		
10-12	6 (1%)	6 (4%)
7-9	24 (2%)	24 (14%)
4-6	70 (6%)	63 (37%)
1-3	1078 (92%)	76 (45%)

Of the 169 chronic triptan users, 92 (54%) also had a claim for one or more guideline recommended prophylactic agents (see **Table 5**). Of the 92 patients with prescriptions for prophylaxis medications, 78 (85%) had an adequate trial of an agent (see **Table 6**). All three medication classes were utilized roughly equally with 47% of patients prescribed an anticonvulsant, 46% a beta-blocker, and 36% an antidepressant. The most commonly prescribed prophylaxis medications are topiramate (40%), propranolol (30%), and amitriptyline (23%). The majority of the prescribed prophylaxis agents have Level A evidence for their use (60%).

Table 5: Type of Prophylaxis Agent (N=92)

	Number of patients (percent of those prescribed ***any*** prophylaxis agent use)*
Breakdown by specific generic medication:	
Anticonvulsants	43 (47%)
• Topiramate	37 (40%)
• Divalproex	5 (5%)
• Valproate or Valproic Acid	1 (1%)
Beta-blockers	42 (46%)
• Propranolol	28 (30%)
• Metoprolol (tartrate or succinate)	10 (11%) 4 (4%)
• Atenolol	0 (0%)
• Timolol	0 (0%)
• Nadolol	
Antidepressants	33 (36%)
• Amitriptyline	21 (23%)
• Venlafaxine	14 (15%)
Breakdown by level of evidence**	
Prescribed a Level A agent only	55 (60%)
Prescribed a Level B agent only	20 (22%)
Prescribed both a Level A and Level B agent†	17 (18%)
*Medications and classes are not mutually exclusive as patients may have been prescribed more than one prophylaxis agent **see **Table 3** for a list of medications by evidence for use level †this includes concurrent or consecutive use	

Table 6: Patients with the same prophylactic agent for at least 2 consecutive months (N=78)

	Number of patients (percent of those on ***prophylaxis agent for at least 2 months***)*
Breakdown by specific generic medication:	
Anticonvulsants	32 (41%)
• Topiramate	29 (37%)
• Divalproex	3 (4%)
• Valproate or Valproic Acid	0 (0%)
Beta-blockers	36 (46%)
• Propranolol	23 (29%)

• Metoprolol (tartrate or succinate) • Atenolol • Timolol • Nadolol	9 (12%) 4 (5%) 0 (0%) 0 (0%)
Antidepressants • Amitriptyline • Venlafaxine	24 (31%) 16 (21%) 9 (12%)
Breakdown by level of evidence**	
Prescribed a Level A agent only	49 (63%)
Prescribed a Level B agent only	18 (23%)
Prescribed both a Level A and Level B agent†	10 (13%)
* Medications and classes are not mutually exclusive as patients may have been prescribed more than one prophylaxis agent **see **Table 3** for a list of medications by evidence for use level †this includes concurrent or consecutive use	

When comparing chronic triptan users who had any prophylaxis use versus no prophylaxis use, the average number of triptans dispensed/year is slightly lower (6.8 claims per year versus 7.1 claims per year, respectively). Patients with any prophylaxis use had more ED visits for any diagnosis (39 unique patients with ED visits for any diagnosis) as compared to non-prophylaxis user (25 patients) (see **Table 7**). Prophylaxis users and non-prophylaxis users had similar numbers of unique patients who had ED visits specifically for migraines. There was also no difference between adequate prophylaxis trial users and general prophylaxis use (see **Table 7**). However, numbers of hospitalizations and ED visits is low overall.

Table 7: Clinical Outcomes Associated with No Prophylaxis Use, Any Prophylaxis Use, and Adequate Trial Prophylaxis Use:

	Number of patients (% of ***chronic triptan users***)	Average number of triptan claims per year	Number of unique patients with ED visits for ***any*** diagnosis	Number of unique patients with ED visits for ***migraines***	Number of unique patients with hospitalizations for ***any*** diagnosis	Number of unique patients with hospitalizations for ***migraines***
No prophylaxis use	77 (46%)	7.1	25 (33% of NON-prophylaxis users)	3 (4% of NON-prophylaxis users)	4 (5% of NON-prophylaxis users)	0 (0%)
Any prophylaxis use	92 (54%)	6.8	39 (42% of prophylaxis users)	5 (5% of prophylaxis users)	7 (8% of prophylaxis users)	0 (0%)
Adequate trial use*	78 (46%)	6.7	32 (41% of adequate trial users)	4 (5% of adequate trial users)	4 (5% of adequate trial users)	0 (0%)
*Adequate trial defined as the same prophylactic agent dispensed for at least 2 consecutive months						

Since the PA criteria for CGRP antagonists was implemented, 579 unique paid and denied prescriptions for all CGRP antagonists were identified, regardless of indication. Of those 579 prescriptions, 525 (91%) are for agents specifically FDA-approved for migraine prophylaxis. For the migraine prophylaxis agents, 51% (N= 268) of the prescriptions

were denied. Since these data reflect a two-year time period and CGRP antagonists are indicated for chronic use, these values may reflect multiple prescription (Rx) numbers per patient. See **Tables 8 and 9** for a full analysis of paid and denied prescriptions for all CGRP antagonists and only those indicated for prophylaxis respectively.

During the same time frame of two years, 205 unique PAs were submitted for review for all CGRP antagonists. Of those 205 PAs, 180 (88%) were for prophylaxis agents. Of the 180 unique PAs submitted for prophylaxis agents, 71% were approved. This data was not delineated by initial PA approval versus renewal requests. Because the initial PA approval is valid for up to 3 months and the renewal approval is valid for up to 6 months, the data on unique PAs may represent multiple PA requests for individual patients. See **Tables 10 and 11** for a full analysis for approved and denied PAs for all CGRP antagonists and only those indicated for prophylaxis.

Table 8: Total Prescriptions for all CGRP Antagonists

Number of Unique Prescriptions for ***all*** CGRP Antagonists	Number of Rxs (% of total)
Total	579
Paid	274 (47%)
Denied	305 (53%)

Table 9: Total Prescriptions for Prophylaxis CGRP Antagonists

Number of Unique Prescriptions for ***prophylaxis-only*** CGRP Antagonists	Number of Rxs (% of total)
Total	525
Paid	257 (49%)
Denied	268 (51%)

Table 10: Total PAs for All CGRP Antagonists

Unique PAs for ***all*** CGRP Antagonists	Number of PAs (% of total)
Total	205
Approved PAs	141 (69%)
Denied PAs	64 (31%)

Table 11: Total PAs for Prophylaxis CGRP Antagonists

Unique PAs for ***prophylaxis-only*** CGRP Antagonists	Number of PAs (% of total)
Total	180
Approved PAs	127 (71%)
Denied PAs	53 (29%)

For CGRP antagonists indicated for migraine prophylaxis, the most common reason a claim was denied was for prior authorization (N = 253, 94%) (see **Table 12**). However, only a total of 180 PAs were requested (see **Table 11**). What portion of these denied claims, if any, that would have met PA criteria if they had requested one is unknown. However, the majority of PAs that were requested were approved (N = 127, 71%) (see **Table 11**).

For PA denials of CGRP antagonists indicated for migraine prophylaxis, the most common reason a PA was denied is that the request was determined not to be medically appropriate (did not meet PA approval criteria as outlined in **Appendix F**) with 94% of PAs being denied for this reason (see **Table 13**).

Table 12: Reasons for Prescription Denial for Prophylaxis-only* CGRP Antagonists

Reason for ***prescription*** denial for prophylaxis-only CGRP Antagonists	Number of Rxs (% of *denied* Rxs)
Total denied claims	268
NDC Requires PA	253 (94%)
Claim failed a ProDUR Alert	19 (7%)
Claim denied for ProDUR Reasons	9 (3%)
Day supply limit exceeded for covered NDC	5 (2%)
Prescribing physicians ID not on file	3 (1%)
Units exceed Authorized units on PA master file	2 (1%)
* Rimegepant not included as indication was received after data analysis.	

Table 13: Reasons for PA Denial for Prophylaxis-Only* CGRP Antagonists

Reason for ***PA*** denial for prophylaxis-only CGRP Antagonists	Number of Rxs (% of *denied* PAs)
Total denied PAs	53
Request was determined not medically appropriate	50 (94%)
Treatment of condition is not a covered service on OHP	2 (4%)
Drug requested is not covered by benefit package	1 (2%)
* Rimegepant not included as indication was received after data analysis.	

Discussion:

From Oct 1, 2018 through Sept 20, 2019, only a small percentage (1%) of Oregon FFS Medicaid patients had at least one triptan claim (1,178 patients). Even fewer were chronic triptan users (N = 169). This is much lower than the estimated 26% prevalence of Medicaid patients with migraines,[5] which may suggest that the Oregon FFS Medicaid population has a lower prevalence of patients with migraines, that patients are utilizing non-triptan therapies (such as acetaminophen or NSAIDs) more often, or that patients are not staying enrolled in FFS long enough to accurately identify patients with migraines based on claims data alone (because they switch to a coordinated care organization (CCO)). The majority of chronic triptan users were female and between the ages of 18 and 44 years old, which matches the expected demographics of patients with migraines based on epidemiological data.[5] However, there were also patients less than 18 years old who used triptans (n=149), and a small number of pediatric patients were on chronic therapy (n=10).

Based on guideline recommendations, all patients who meet the definition of chronic triptan use would qualify for prophylaxis treatment. However, only about half of chronic triptan users were prescribed a guideline recommended prophylaxis agent. This is still higher than rates reported in the literature. For patients with *episodic* migraines, prophylaxis use is estimated at 3-13% of patients (when approximately 38% would likely benefit).[2] A separate survey study looking at all migraines (both *episodic* and *chronic*) found that only 13% of patients were using a prophylaxis agent.[19] In that same study, 43% of patients had never used a prophylaxis agent before, but 32% of that 43% would qualify for prophylaxis use.[19] If a prophylaxis agent was initiated, the majority of patients had at least 2 consecutive months of claims for that agent, which follows guideline recommendations of at least 8 weeks of prophylactic therapy to determine efficacy. This appears to indicate that initiation of treatment (not continuation of therapy) is the primary barrier to appropriate prophylaxis use. However, 2 consecutive months of claims may not necessarily indicated 2 months of medication adherence. If patients were initiated on prophylaxis therapy, there does not appear to be one class of medications favored over others. All three major medication classes were utilized roughly equivalently. This is consistent with guidelines which do not recommend one specific prophylaxis agent over another, and instead recommend that patient specific factors and comorbidities should be taken into account when choosing an appropriate agent. Regardless of the specific medication being utilized, the majority of patients were prescribed medications with Level A evidence.

Because there are so few chronic triptan users (N = 169) and even fewer who were also prescribed a prophylaxis agent (N = 92), determining the impact prophylaxis therapy has on triptan utilization, ED visits, and hospitalizations is difficult. However, prophylaxis users do appear to use slightly less triptans (6.8 claims per year versus 7.1 claims per year for non-prophylaxis users). Decreased triptan utilization implies less migraine days per month (a marker of prophylaxis agent efficacy). Prophylaxis agents may also decrease migraine severity, which unfortunately cannot be assessed by claims data, but would certainly improve quality of life even if the number of migraine days per month remains the

same for patients. Very few patients (prophylaxis users and non-users alike) sought ED care for migraines. However, more prophylaxis users sought ED care for ALL diagnoses as compared to non-prophylaxis users. This may imply that non-prophylaxis users are generally less engaged with the healthcare system as a whole and may not have sought ED care for their migraines even if their migraine warranted ED levels of care. This less healthcare engagement in general may potentially be masking the true impact prophylaxis use has on ED utilization. Prophylaxis users having more ED visits may also suggest that those on prophylactic medications have more severe disease. There were no hospitalizations for migraine related diagnoses identified, which is expected as migraines do not typically require inpatient level of care.

Since Oregon FFS Medicaid implemented its PA criteria for CGRP antagonists on Nov 1, 2018 to Dec 31, 2020, about half of prescriptions were denied. If a PA was requested for the prophylaxis CGRPs, the majority of them were approved (71%). For many patients, a PA was not requested and it is unclear what portion of these patients may have met PA criteria. For the denied PAs, the most common reason for denial is that the request is not medically appropriate (i.e. does not meet PA criteria). Interestingly, 2 PAs were denied for the reason of "treatment of condition is not a covered service on OHP," suggesting that these specific PAs were requesting to use prophylaxis-only CGRP antagonists off-label but for what indication is unclear. Alternatively, these 2 PAs could indicate that those patients didn't have a drug benefit altogether (and may have only had emergency service coverage through FFS Medicaid, not medication coverage).

Overall, relatively few CGRP antagonists indicated for migraine prophylaxis were prescribed with a total prescription count over a two year period of 525; even fewer were successfully paid (N=257). Since a high proportion of requested PAs were approved, this indicates that the PA criteria is consistent with prescriber practice. This may also suggest that providers are only requesting the PA if they have determined their patient meets criteria (as most clinicians may not request PA approval if they know that their patient does not meet criteria). However, there is no way to determine if the un-requested PAs would or would not have met criteria.

Limitations:

The main limitation of this analysis is that there is no guaranteed way to ensure that the agents assessed for migraine prophylaxis in research question 2 are indeed being used for migraine prophylaxis since all of these agents have other indications as well. For example, the anticonvulsants may be used for epilepsy and not necessarily migraine prophylaxis. The beta-blockers may be used for heart failure or post-myocardial infarction care rather than migraine prophylaxis. The antidepressants may be used for anxiety or depression rather than migraine prophylaxis. However, this limitation was mitigated as much as possible by only including first and second-line guideline recommended prophylaxis agents with the most efficacy data, and thus would theoretically be prescribed most often. Additionally, this limitation was mitigated by only assessing patients for prophylaxis use in chronic triptan users. Furthermore, guidelines recommend that patient factors (such as co-morbidities) be taken into account when selecting a prophylaxis agent anyway and would recommend that a patient with depression should be started on an antidepressant in order to treat both the depression and the migraines with one medication for example. Thus, it is likely safe to assume that the majority (if not all) of the data reported for research question 2 is likely to reflect agents prescribed for migraine prophylaxis, though they may treat another indication simultaneously.

Another limitation of this analysis is that it did not assess non-triptan abortive therapy use (such as NSAIDs or acetaminophen) since these agents can be obtained over the counter and their use would have been difficult to identify. This may lead to an under-representation of migraine sufferers in the Oregon FFS Medicaid population who may or may not be utilizing triptans for their abortive treatment.

For patients prescribed triptans, there may also be a gap in true representation of triptan utilization if patients paid cash for the triptan (rather than using their Oregon FFS Medicaid benefits). The primary reason a patient may pay cash rather than using insurance is to by-pass the quantity limits imposed by the PDL. If patients are doing this, the analysis would not be able to capture these prescriptions since claims information was used to gather data. Additionally, using claims data alone to identify chronic triptan users may inherently leave out patients due to the nature of Medicaid patients entering and exiting Oregon FFS Medicaid over time by joining and leaving coordinated care organizations (CCOs). Theoretically, there may be more chronic triptan users in the whole Oregon Medicaid population but because those patients were using CCO benefits (and not FFS) we would not have been able to capture these patients with this data analysis.

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Appendix A: Oregon FFS Medicaid Quantity Limits for Preferred and Non-preferred Triptans

Oregon FFS Medicaid Status	Generic Name	Formulation	Brand Name	Quantity Limit per Month
Preferred (Y)	Naratriptan	Tablets	Amerge	9 tabs
Preferred (Y)	Sumatriptan	Tablets	Imitrex & generics	9 tabs
Preferred (Y)	Sumatriptan	Nasal Spray	Imitrex & generics	18 spray units
Preferred (Y)	Sumatriptan	Injectable	Imitrex & generics	6 vials
Preferred (Y)	Zolmitriptan	Tablets	Zomig Zomig ZMT	6 tabs
Preferred (Y)	Zolmitriptan	Nasal spray	Zomig NS	3 packages (18 spray units)
Non-preferred (N)	Almotriptan	Tablets	Axert	12 tabs
Non-preferred (N)	Eletriptan	Tablets	Relpax	6 tabs
Non-preferred (N)	Frovatriptan	Tablets	Frova	9 tabs
Non-preferred (N)	Rizatriptan	Tablets	Maxalt Maxalt MLT	12 tabs
Non-preferred (N)	Sumatriptan	Nasal powder	Onzetra Xsail	6 nosepieces
Non-preferred (N)	Sumatriptan	Injectable	Sumavel	6 jet injectors
Non-preferred (N)	Sumatriptan	Injectable	Zembrace Symtouch	12 auto-injectors
Non-preferred (N)	Sumatriptan/naproxen	Tablets	Treximet	9 tabs

Appendix B: ICD-10 Codes of Interest for Migraine Diagnoses

ICD-10 Code	Meaning of ICD-10 Code
G43.001	Migraine without aura, not intractable, with and without status migrainosus
G43.009	
G43.011	Migraine without aura, intractable, with and without status migrainosus
G43.019	
G43.101	Migraine with aura, not intractable, with and without status migrainosus
G43.109	
G43.111	Migraine with aura, intractable, with and without status migrainosus
G43.119	
G43.401	Hemiplegic migraine, not intractable, with and without status migrainosus
G43.409	
G43.411	Hemiplegic migraine, intractable, with and without status migrainosus
G43.419	
G43.501	

G43.509	Persistent migraine aura without cerebral infarction, not intractable, with and without status migrainosus
G43.511	Persistent migraine aura without cerebral infarction, intractable, with and without status migrainosus
G43.519	
G43.601	Persistent migraine aura with cerebral infarction, not intractable, with and without status migrainosus
G43.609	
G43.611	Persistent migraine aura with cerebral infarction, intractable, with and without status migrainosus
G43.619	
G43.701	Chronic migraine without aura, not intractable, with and without status migrainosus
G43.709	
G43.711	Chronic migraine without aura, intractable, with and without status migrainosus
G43.719	
G43.A0	Cyclical vomiting in migraine not intractable and intractable
G43.A1	
G43.B0	Ophthalmoplegic migraine not intractable and intractable
G43.B1	
G43.C0	Periodic headache syndromes in child or adult not intractable and intractable
G43.C1	
G43.D0	Abdominal migraine not intractable and intractable
G43.D1	
G43.801	Other migraine, not intractable, with and without status migrainosus
G43.809	
G43.811	Other migraine, intractable, with and without status migrainosus
G43.819	
G43.821	Menstrual migraine, not intractable, with and without status migrainosus
G43.829	
G43.831	Menstrual migraine, intractable, with and without status migrainosus
G43.839	
G43.901	Migraine, unspecified, not intractable, with and without status migrainosus
G43.909	
G43.911	Migraine, unspecified, intractable, with and without status migrainosus
G43.919	

Appendix C: Guideline Recommended Migraine Prophylaxis Agents with Highest Level of Evidence for Use and their associated HSN and GSN codes:

Level of Evidence for Use	Medication Examples	HSN	GSN
Level A Evidence – Established Efficacy (≥2 Class I studies)	Topiramate	011060	064519 (exclude this GSN)
	Propranolol	002101	043103, 015995 (exclude these GSNs)
	Metoprolol (tartrate and succinate)	002102, 006323	005129, 019808, 025856, 023600 (exclude these GSNs)
	Timolol	002105	005140, 005141, 005142 (include *only* these GSNs)
	Divalproex sodium	001884	All
	Sodium valproate (valproic acid)	001882, 001883	051616, 031533 (exclude these GSNs)
Level B Evidence – Probably Effective (1 Class I or 2 Class II studies)	Amitriptyline	001643	023199 (exclude this GSN)
	Venlafaxine	008847	All
	Atenolol	002104	023195 (exclude this GSN)
	Nadolol	002103	023603 (exclude this GSN)

Appendix D: Error Codes INCLUDED in the Analysis of Denied CGRP Antagonist Claims and PAs:

Error Code	Error Code Description
3002	NDC Requires PA
7002	Claim denied for Pro-DUR reasons
7000	Claim failed a Pro-DUR alert
1026	Prescribing physician ID Not on file
4026	Day supply limit exceeded for covered NDC
3000	Units exceed authorized units on PA master file

Appendix E: Error Codes EXCLUDED in the Analysis of Denied CGRP Antagonist Claims and PAs:

Error Code	Error Code Description
2017	Recipient services covered by HMO Plan
2508	Recipient covered by private insurance
576	Claim has third-party payment
4999	This drug is covered by Medicare Part D
4002	Non-covered drug
2002	Recipient not eligible for header date of service
4890	Non covered drug class
4891	Not covered drug class
643	Invalid other coverage code
4007	Non-covered NDC due to CMS termination
628	Other coverage reject code required for OCC 3
2507	Recipient has more than one insurance carrier

Appendix F: PA Criteria for CGRP Antagonists for Oregon FFS Medicaid

Calcitonin Gene-Related Peptide (CGRP) antagonists

Goal(s):

- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling for migraine prevention, acute migraine treatment and cluster headache prevention (Table 1).

Length of Authorization:

- Initial: Up to 3 months
- Renewal: Up to 6 months

Requires PA:

- All calcitonin gene-related peptide (CGRP) antagonists (eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant) pharmacy and physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved Indications for CGRP antagonists

Drug	FDA Approved Indication
Eptinezumab	Preventative migraine treatment
Erenumab	Preventative migraine treatment
Fremanezumab	Preventative migraine treatment
Galcanezumab	Preventative migraine treatment and cluster headache prevention
Rimegepant sulfate	Acute migraine treatment
Ubrogepant	Acute migraine treatment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication (Table 1)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 7
7. Is the request for acute migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #12	**No:** Go to #8
8. Is the request for the prevention of cluster headache AND the patient is an adult (18 years or older)?	**Yes:** Go to #15	**No:** Go to #9
9. Is there documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult (18 years or older)?	**Yes:** Document migraine days per month _____ Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness

Specific to Rimegepant (Nurtec) and Ubrogepant (Ubrelvy), which are indicated for acute treatment

Specific to Galcanezumab (Emgality), which is indicated for both migraine and cluster headache prevention

10. Has the patient failed an adequate trial (≥6 weeks with a documented adherence of ≥80%) of an FDA-approved migraine prophylaxis medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis classes?	**Yes:** Document agents used and dates _____ _____ Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 3 months
12. Has the patient failed adequate trials (3 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.
13. Does the patient have chronic migraines?	**Yes**: Go to #14	**No**: Approve for 3 months
14. Does the patient have a history of at least 4 migraines a month AND is on preventative migraine therapy (excluding other CGRP inhibitors)?	**Yes:** Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

15. Does the patient have at least 4 headache attacks per week AND have a history of cluster headaches beyond one month?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Has the patient failed at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, frovatriptan, prednisone, subocciptal steroid injection, topiramate, and valproate)?	**Yes**: Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2
2. Is the renewal request for acute migraine treatment?	**Yes:** Go to #5	**No:** Go to #3
3. Is the renewal request for migraine prevention?	**Yes:** Go to #4	**No:** Go to # 6
4. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes:** Document response Approve for up to 6 months (e.g. minimum 2 doses for treatment given every 3 months)	**No:** Pass to RPh. Deny; medical Appropriateness
5. Has the patient demonstrated a response to therapy as indicated by a reduction in headache frequency and/or intensity?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
6. Is the renewal request for cluster headache prevention?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical Appropriateness

7. Does the patient have documentation of a reduction of at least 8 cluster headaches per month?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 11/1/2018