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Population Trends in the Use of Migraine Preventative Treatments

Deanna Moretz, PharmD, BCPS Oregon State University Drug Use Research and Management Group

Introduction

Migraine is a disorder characterized by recurrent attacks of headaches of moderate to severe intensity, often accompanied by photophobia, phonophobia, nausea, and vomiting.[1] A migraine headache condition can be classified as chronic if occurring on 15 or more days per month with migraine features on 8 or more days.[2] Episodic migraine is a similar condition, but headaches occur less frequently, typically between 4 to 14 days per month.[2] The prevalence and burden of self-reported migraine and severe headache in the United States (US) adult population is high, affecting roughly 1 out of every 6 Americans and 1 in 5 women over a 3-month period.[3]

In 2015, the prevalence of self-reported migraine or severe headache was highest in American Indian or Alaska Natives (18%) compared with Blacks (16%), Whites (15%), and Hispanics (15%) with the lowest prevalence in Asians (11%).[3] There is a higher burden of migraine in those aged 18 to 44 (18%), unemployed people (21%), those with family income less than $35,000 per year (20%), and the elderly and disabled (16%).[3] The percentage of persons with migraine with Medicaid health insurance coverage (26%) and uninsured people (17%) was higher than those with private insurance (15%).[3] In reproductive aged women, headache is the third leading cause of emergency department (ED) visits.[3]

Patients affected by frequent migraines may need preventive treatment in order to reduce the frequency and severity of attacks. This newsletter will describe population trends in use of migraine preventative agents and discuss a drug use evaluation (DUE) that analyzed the use of guideline-recommended migraine preventative therapy in the Oregon Medicaid Fee-For-Service (FFS) population.[4]

Oral Migraine Preventative Agents

Preventative therapy is indicated for people who experience 4 or more migraine headaches per month or if headaches last longer than 12 hours.[5] The 2012 American Academy of Neurology (AAN) and American Headache Society guideline recommends divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol and timolol as first-line therapies for migraine prevention (**Table 1**).[5]

Table 1. Classification of Migraine Preventative Therapies[5]

Level A: Medications with Established Efficacy	Divalproex Sodium, Sodium Valproate, Topiramate, Metoprolol, Propranolol, Timolol
Level B: Medications which are Probably Effective	Amitriptyline, Venlafaxine, Atenolol, Nadolol
Level C: Medications which are Possibly Effective	Lisinopril, Candesartan, Clonidine, Guanfacine, Carbamazepine, Nebivolol, Pindolol

High-quality evidence shows these agents should be offered to patients with episodic or chronic migraine to reduce migraine attack frequency and severity, improve function, and reduce disability.[5] Dosing should be initiated at a low dose and gradually increased as tolerated. An adequate trial to determine efficacy requires at least 8 weeks at goal dose range.[6] The full effect of prophylactic therapy may take up to 6 months. Due to the risk of congenital birth defects, valproate and topiramate should not be prescribed to women of childbearing potential who are not using reliable methods of birth control.[5]

The recently FDA-approved small molecule, oral calcitonin gene-related peptide (CGRP) inhibitors for migraine prevention, rimegepant and atogepant, have not been included in high-quality guidelines as of 2022. Approval for rimegepant as preventative therapy in adults with episodic migraine was based on one phase 2/3 study.[7] The mean number of migraine days per month at baseline was 7.8 days.[7] In this 12-week trial, rimegepant 75 mg every other day reduced the mean migraine days per month by -0.8 more than placebo (-4.3 versus -3.5 days; 95% confidence interval [CI], -1.46 to -0.20; p=0.0099).[7] Adverse events occurring in at least 2% of rimegepant-treated participants were nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection.[7] Seven (2%) participants who received rimegepant and 4 (1%) who received placebo discontinued the study due to an adverse event.[7]

A phase 3 trial also showed atogepant was more effective than placebo in reducing the mean number of migraine days per month over 12 weeks.[8] The mean number of migraine days per month at baseline ranged from 7.5 to 7.9 in the four groups (10 mg, 30 mg, 60 mg and placebo).[8] The mean differences from placebo in the change from baseline were −1.2 days with 10 mg atogepant (95% Confidence Interval [CI], −1.8 to −0.6), −1.4 days with 30 mg atogepant (95% CI, −1.9 to −0.8), and −1.7 days with 60 mg atogepant (95% CI, −2.3 to −1.2) (P<0.001 for all comparisons with placebo).[8] The most common adverse events in patients taking atogepant were constipation, nausea, and upper respiratory tract infections.[9] Nine (4%) participants who received atogepant 10 mg, 4 (1.8%) people who received atogepant 30 mg, 6 (2.6%) people who received atogepant 60 mg, and 6 (2.7%) participants who received placebo discontinued the study due to an adverse event.[8] Dosing of atogepant ranges from 10 mg to 30 mg to 60 mg per day depending on renal function and possible drug interactions with concomitant medications.[9]

Epidemiologic studies suggest approximately 38% of adults with migraines need preventive therapy, but only 3% to 13% currently use it.[10] Studies have shown oral preventive therapies are associated with a high degree of non-adherence (approximately 35–50%) mainly due to bothersome side effects and relatively low and inconsistent efficacy.[11,12] A 2014 systematic review assessed oral prophylaxis medication adherence and persistence among patients with migraine.[13] Adherence refers to the extent to which a patient follows prescribed directions with respect to timing, dose, and frequency.[13] Persistence refers to the time during which a patient remains on a prescribed medication after initiating therapy.[13] This review demonstrated a downward trend in migraine

prophylaxis adherence and persistence over time.[13] Observational studies (n=14) showed migraine preventative adherence ranges of 41% to 95% at 2 months, 21% to 80% at 6 months, and 35% to 56% at 12 months.[13] Persistence ranges of 41% to 88% at 2 months, 19% to 79% at 6 months, and 7% to 55% at 12 months were also reported.[13] There was a substantially lower rate of discontinuation among trials evaluating propranolol compared with amitriptyline or topiramate.[13] Adverse events including cognitive effects, somnolence, and weight gain, were the most common reason for discontinuation (24% for topiramate, 17% for amitriptyline, and 8% for propranolol).[13]

Injectable Migraine Preventative Agents: OnabotulinumtoxinA and CGRP Antagonists

OnabotulinumtoxinA is indicated for the prophylaxis of headaches in adults with chronic migraine who have headaches that occur at least 15 days per month and last four hours a day or longer.[14] The recommended re-treatment schedule is every 12 weeks.[14] Safety and efficacy of botulinum toxin have not been established for prophylaxis of episodic migraine.[14,15] The 2016 AAN guideline on therapeutic uses of botulinum toxin recommends onabotulinumtoxinA as a safe and effective treatment for chronic migraine to reduce the number of headache days (Level A effective).[15] OnabotulinumtoxinA is probably effective and should be considered to improve health-related quality of life (Level B effective).[15]

A 2018 Cochrane review assessed the effects of botulinum toxin for the prevention or reduction in frequency of chronic migraine in adults.[16] The number of chronic migraine days at baseline ranged from 12 to 20 days.[16] Pooled data from 2 trials (n=1384) showed that compared to placebo, botulinum toxin may reduce the number of migraine days per month in patients with chronic migraine by 2 days at 12 weeks post-treatment (95% CI -2.8 to -1.1, moderate-quality evidence).[16] Analysis of adverse events showed an increase in the risk ratio with treatment with botulinum toxin over placebo 30% (RR 1.28, 95% CI 1.12 to 1.47, moderate-quality evidence).[16] For every 100 participants, 60 experienced an adverse event in the botulinum toxin group compared with 47 in the placebo group.[16]

Three trials compared botulinum toxin with 2 alternative oral prophylactic medications (topiramate 100 to 200 mg/day and sodium valproate 250 mg twice daily).[16] Meta-analyses were not possible for number of migraine days, number of headache days or number of migraine attacks due to insufficient data, but individual trials reported no differences between groups for a variety of efficacy measures in the population of both chronic and episodic migraine participants (low-quality evidence).[16] In the botulinum toxin group 73 in every 100 people experienced any adverse event, and in the alternative oral treatment group 86 in every 100 treated people experienced an adverse event.[16] The difference in risk between groups of any adverse event was not statistically significant (P=0.67, low-quality evidence).[16] There was a difference in favor of botulinum toxin in the relative risk of withdrawing due to adverse events of 0.28 compared with the alternative prophylactic agents (95% CI 0.10 to 0.79, low-quality evidence).[16] The proportion of patients discontinuing treatment with botulinum toxin compared to alternative prophylactic agents was low (7%).[16]

Medications targeting CGRP or its receptor approved for migraine prevention include atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab and rimegepant. Atogepant and rimegepant are available as oral tablets. Eptinezumab is administered via intravenous infusion. Erenumab, fremanezumab and galcanezumab can be self-administered via subcutaneous injection. There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab and galcanezumab reduce the number of chronic migraine days per month (decrease of 1.8 to 3.5 days a month) compared to placebo.[17] For episodic migraine prevention, the number of migraine days per month were reduced with eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, with a difference ranging from -0.7 to -2.8 days (moderate quality of evidence).[17] Evidence for CGRP inhibitors is limited to indirect treatment comparisons which prevents comparative efficacy assessment. These brand name medications are more costly compared to the generic availability of most of the oral prophylaxis agents.

Medicaid FFS Prior Authorization Requirements for CGRP antagonists:
Patient must have an adequate trial (at least 6 weeks) without response or have contraindications to 1 medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants.

Oregon FFS Medicaid Drug Use Evaluation Results

The purpose of a 2021 DUE was to determine what percentage of the Oregon FFS Medicaid population chronically utilized triptans and evaluate use of preventative migraine therapy for these patients.[4] 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.[4] In addition, the number of emergency department (ED) visits, and hospitalizations was assessed.[4] From October 2018 through September 2019, only a small percentage (1%) of Oregon FFS Medicaid patients had at least one triptan claim (n=1,178 patients).[4] Even fewer were chronic triptan users (n=169).[4] With an estimated 26% prevalence of Medicaid patients with migraines,[3] this finding may suggest: 1) the Oregon FFS Medicaid population has a lower prevalence of patients with migraines; 2) Medicaid patients are utilizing non-triptan therapies (such as acetaminophen or NSAIDs) more often;3) patients are not staying enrolled in FFS long enough to accurately identify patients with migraines based on claims data alone; or 4) FFS patients often have other insurance which may result in gaps in pharmacy claims data.[4] 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 self-reported data.[3]

Based on guideline recommendations, all patients meeting the definition of chronic triptan use would qualify for preventative migraine treatment.[4] However, only about half (54%) of chronic triptan users were prescribed an oral guideline-recommended prophylaxis agent.[4] When 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.[4] Anticonvulsants (47%) and beta-blockers (46%) were used more frequently than antidepressants (36%).[4] This is consistent with guidelines that 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.[4] Regardless of the specific medication being utilized, the majority of patients were prescribed medications with Level A evidence (**Table 1**).[4]

Because there were so few chronic triptan users (n=169) and even fewer who were also prescribed a preventative agent (n=92), the impact of prophylaxis therapy on triptan utilization, ED visits, and hospitalizations is unclear.[4] However, prophylaxis users did appear to use slightly less triptans (6.8 claims per year versus 7.1 claims per year for non-prophylaxis users).[4] Decreased triptan utilization implies fewer migraine days per month (a marker of prophylaxis agent efficacy).[4] Very few patients (4 to 5%) sought ED care for migraines.[4]

Oregon FFS Medicaid Drug Use Evaluation Limitations

The main limitation of this analysis is that there was no guaranteed way to ensure that the oral agents assessed for migraine prophylaxis were prescribed for migraine prophylaxis since all of these agents have other indications, including pain management for other chronic conditions.[4] Another limitation of this analysis is that it did not assess non-triptan abortive therapy use (such as non-steroidal anti-inflammatory drugs or acetaminophen) since these agents can be obtained over the counter and their use would have been difficult to identify.[4] Because this analysis only included patients with triptan claims, this population may under-represent the number of patients treated for migraine in the Oregon FFS Medicaid population.[4] For patients prescribed triptans, there may have been a gap in true representation of triptan utilization if patients paid cash for the triptan (rather than using their Oregon FFS Medicaid benefits).[4] The primary reason a patient might pay cash rather than using insurance is to by-pass the quantity limits imposed by the preferred drug list.[4] Additionally, using claims data alone to identify chronic triptan users may inherently exclude patients due to the nature of Medicaid patients entering and exiting Oregon FFS Medicaid over time by joining and leaving coordinated care organizations.[4]

Conclusion

In summary, the use of preventative therapy to reduce the frequency and severity of migraine attacks is supported by clinical guidelines.[5] A recent DUE using pharmacy claims in the Oregon Medicaid FFS population revealed that 54% of chronic triptan users were prescribed a guideline-recommended oral preventative medication.[4] Although this percentage appears higher than national statistics, there is an opportunity to improve utilization of migraine preventative therapies to reduce the frequency of severe migraine headaches in the Medicaid population. Injectable options for migraine prophylaxis include onabotulinumtoxinA and 4 of the recently approved CGRP antagonists. Prior authorization criteria have been implemented to ensure appropriate utilization of the injectable agents.

Peer Reviewed By: Kelsey Blom, PharmD, BCACP, Clinical Pharmacy Specialist – Neurology, Kaiser Permanente and Steve Wahls, MD, FAAFP, Assistant Professor of Family Medicine, Oregon Health and Science University

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