Treatment of migraine: a review of disease burden and an update on the therapeutic landscape for pharmacists

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Abstract

Given the key role of pharmacists as a healthcare resource for patients seeking treatment of headache associated with migraine, this review highlights the burden of migraine, recent advances in preventive migraine therapies, and key takeaways from the most recent migraine management consensus statement. For at least two decades, it has been understood that correct diagnosis of migraine is key to its effective management. Migraine attacks should be treated promptly with acute medications, with preventive treatment for patients with regular, frequent, and/or disabling migraine attacks. Nonetheless, most patients with migraine are still not correctly diagnosed, and do not receive appropriate therapy for acute or preventive treatment of their disease. In addition, patients may be refractory to or unable to tolerate traditional oral preventive treatments, leading to underutilization of preventive treatment and subsequent reliance on acute treatment. Overuse of acute medications is associated with increased risk of progression from episodic to chronic migraine and development of medication overuse headache; therefore, pharmacists should counsel patients receiving over-the-counter or prescription acute migraine medications on when to seek options for preventive treatment to help avoid medication overuse. Pharmacists are well-positioned to identify those patients who would benefit from physician referral for further assessment and treatment with preventive therapy. They also have an important role in educating patients on the benefits of preventive medications, and realistic expectations of treatment outcomes.

Background

The recent emergence of novel therapies has expanded the tools and options for clinicians to treat migraine [1]. Before the introduction of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway in 2018 [2], it had been > 25 years since sumatriptan, a therapy developed specifically for the acute treatment of migraine, was approved by the US Food and Drug Administration (FDA)

[3], and a decade since FDA approval of a preventive medication (onabotulinumtoxinA) for chronic migraine (CM) [4]. Further, prior to the development of monoclonal antibodies targeting the CGRP pathway, all medications used for preventive treatment of migraine had been initially approved for other indications [1].

The purpose of this review is to highlight the burden of migraine and unmet need in appropriate migraine management, describe recent advances in preventive migraine therapies, and highlight key takeaways from the most recent migraine management consensus statement [5] to provide pharmacists with an overview of the current expert opinion on the management of migraine. The information in this review is applicable to pharmacists in all pharmacy settings, such as community, ambulatory care, specialty, and clinical pharmacists. Nonetheless, the information may be more readily incorporated in the practices of community and ambulatory pharmacists because migraine is primarily addressed as an outpatient.

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Migraine: burden of disease

Worldwide migraine affects > 10% of the world's population (≈ 1.04 billion individuals) and is the second leading cause of years-lived-with-disability (YLD) [6]. In the USA, migraine is the fifth leading cause of YLD [6]. The American Migraine Prevalence and Prevention study (AMPP) found the prevalence of migraine was $\approx 12\%$, that migraine is 2–3 times more common in women than men, and that it peaks in mid-life (age 30–39 years) [7].

Migraine, a relapsing and remitting disease, presents with a variable frequency of attacks [8]. Patients diagnosed with migraine with ≥ 15 headache days per month (≥ 8 of which meet migraine diagnostic criteria, including lasting 4–72 h when untreated or unsuccessfully treated) for ≥ 3 months are classified as having CM; those with < 15 headache days per month are considered to have episodic migraine (EM) [9]. However, due to the high level of variability in monthly headache days for individual patients, classification is not straightforward and patients can move between EM and CM [8]. Between 2.5 and 14% of patients with EM transition to CM annually [10–12]; factors such as acute medication overuse, ineffective acute treatment, obesity, insomnia, snoring, and stressful life events are associated with an increased risk of transition [10, 12–14].

Despite the categorical distinction of EM and CM based on monthly headache days [9], the impact of migraine is not as distinct. To enable a broader understanding of the impact of migraine beyond number of headache days and an understanding of the disease from a patient's perspective, a range of patient-reported outcome (PRO) assessments have been developed, each with unique advantages and disadvantages (Table 1) [15–23]. Two of the most common PROs are the Headache Impact Test-6 (HIT-6TM) [16, 17] and Migraine Disability Assessment Scale (MIDAS) [18, 19]. The Migraine-Specific Quality-of-Life Questionnaire (MSQ) is another validated PRO assessment used specifically in migraine [20]. Newer instruments such as the Migraine Physical Function Impact Diary (MPFID) [21, 23] and the Migraine Functional Impact Questionnaire (MFIQ) [22, 23] have shorter recall times reflecting the FDA guidance [24]. These PRO instruments have painted a consistent picture of the substantial burden of migraine [25–30].

In addition to the personal and societal burden of migraine, migraine has a high burden on healthcare systems. It has been reported that there is an emergency room visit for headache or migraine every 10 s in the USA, representing ≈ 1.2 million visits annually for acute migraine attacks [31], and a substantive burden on the healthcare system [15, 32, 33].

Table 1 Overview of patient-reported outcome (PRO) assessment tools [15]

PRO	Key features	Advantages	Disadvantages
HIT-6 [16, 17]	Assesses impact of headache on social and role functioning, pain severity, fatigue and mood over previous 4 weeks	Accurate across all headache severity levels in clinical research and clinical practice; only contains 6 questions so easy to complete	Not migraine specific
MIDAS [18]	Assesses time lost due to migraine work/school, household work, family/leisure/social activities over previous 3 months	Reliable, accurate and easy to use in research and clinical practice; migraine specific	Only covers the moderate through to severe spectrum of migraine; some consider too heavily weighted toward headache frequency
MSQ [20]	Assesses the degree activities are prevented or restricted by migraine, and emotional functioning over previous 4 weeks	Reliable, with construct validity	May be too complex to use routinely in clinical practice
MPFID [21, 23]	Assesses the impact of migraine on everyday activities and physical impairment over previous 24 h	Patient input into the conceptualization of tool; designed to comply with FDA guidelines for PROs	Ability to offer a complete picture of migraine is unclear
MFIQ [22, 23]	Assesses the impact of migraine on physical, social and emotional function, and on everyday activities over 7 days	7-day recall may capture variability of impact, without the burden of daily assessments	Ongoing analysis of tool underway to develop responder definitions

HIT-6 6-item headache impact test; *MFIQ* Migraine Functional Impact questionnaire; *MIDAS* Migraine Disability Assessment questionnaire; *MSQ* Migraine-Specific Quality of Life Questionnaire

Unmet medical need in migraine

In addition to characterizing the population affected by severe migraine, the AMPP study illustrated the unmet medical need experienced by patients with migraine, with $\approx 44\%$ of people with migraine having never received a medical diagnosis [34]. Additionally, patients with a migraine diagnosis were shown to have extreme difficulty accessing both acute and preventive treatment [35, 36]. An exploratory analysis from the AMPP study found that only 26% of the original EM cohort successfully overcame all three barriers (consultation, diagnosis, and treatment) [35]. Data from patients with CM suggest even more challenges, with the Chronic Migraine Epidemiology and Outcomes Study (CaMEO) reporting $< 5\%$ of patients with CM successfully traversed the same three barriers, with difficulties particularly in seeking a consultation and receiving an accurate diagnosis of CM [36]. Furthermore, of those who consulted a healthcare professional and were accurately diagnosed, less than half received preventive and acute treatment [36]. More recent data confirm migraine remains underdiagnosed and undertreated [29].

Since most migraine patients do not receive a correct diagnosis and appropriate care, there is greater reliance on over-the-counter (OTC) medications and prescription analgesics to manage symptoms of migraine headache and pain. The AMPP study found 49% of patients exclusively used OTC medications for acute treatment of migraine; 29% sometimes used OTC medications and sometimes used prescription medications [34]. While some OTC acute medications may be useful for migraine, patients who use acute medications too frequently can develop medication overuse headache (MOH). MOH is a secondary headache occurring on ≥ 15 days per month in patients with underlying headache disorders, such as migraine, as a consequence of regular overuse of acute headache therapies (i.e., ≥ 10 days per month of ergotamine, triptans, opioids, combination analgesics, or ≥ 15 days per month of acetaminophen [paracetamol], NSAIDs, or acetylsalicylic acid) for > 3 months [9, 37]. In December 2017, the FDA issued a final decision requesting the inclusion of a new warning on all OTC migraine headache medications (e.g., Excedrin Migraine) to ensure patients were informed that “headaches may worsen” if the OTC headache medication “is used for 10 or more days per month” [38]. It is important that pharmacists inform patients of label warnings when recommending acute OTC headache therapies, advise on the importance of seeking medical guidance, and counsel against overuse of prescribed acute medications. This is especially important with opioids, as $\approx 20\%$ of patients with migraine currently use opioids or

are administered opioids in emergency room encounters for migraine [39, 40].

Preventive therapy for migraine

Non-migraine specific therapies

Prior to the approval of monoclonal antibodies targeting the CGRP pathway, onabotulinumtoxinA was the only drug approved by the FDA specifically for the preventive treatment of CM [4]. Other FDA-approved medications that are used for the prevention of migraine headache include topiramate, propranolol, divalproex sodium and timolol (Table 2) [41–56]. Some of these medications were not studied specifically in patients with CM, as studies were conducted before the definition of CM was fully established. Furthermore, none of the current oral preventive options were developed specifically for migraine; in addition, many treatments are used off-label for the prevention of migraine headaches [5]. For example, valproate sodium and metoprolol are rated by the American Headache Society (AHS) as having established efficacy for treatment of migraine despite lacking an FDA indication for this condition [5]. Preventive therapy is initiated based on frequency of migraine attacks as well as overall severity and disability of disease (Fig. 1) [5]. The AHS consensus statement “The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice” recommends that preventive treatment be *considered* for patients with 2 monthly headache days with moderate disability, 3 monthly headache days with some disability, and 4 or 5 monthly headache days without any disability. In contrast, preventive treatment should be *offered* to all patients with ≥ 3 monthly headache days with severe disability, ≥ 4 monthly headache days with some disability, and ≥ 6 monthly headache days with no disability [5]. Goals of preventive therapy include reducing frequency, duration, and severity of migraine attacks, enhancing responsiveness to migraine-specific headache therapy, avoiding escalation in use of and reliance on acute treatment, improving ability to function, reducing disability, improving health-related quality of life (HR-QoL), and reducing healthcare costs [5, 57].

Only 12% of patients in the AMPP population used preventive therapy; another 17% were coincidental users (i.e., used a known preventive medication, but not reportedly for prevention of migraine) [34]. Based on expert consensus at that time [7], which was the precursor to, and mirrors, current guidelines [5], preventive therapy could have been at least considered for $\approx 40\%$ of these patients with migraine

Table 2 Summary of preventive treatments available for migraine (level A or B evidence) [5]

Treatments	Key counselling notes	Recommended dosage ^a	Duration of adequate trial ^b
FDA approved			
Antiepileptic drugs			
Divalproex sodium [41]	Risk of hepatotoxicity, ensure liver testing throughout treatment and advise pts that symptoms such as nausea, vomiting, abdominal pain requires medical assessment; avoid in women of childbearing age, not using reliable birth control; advise pts and family to report signs of depression or changes in mood to their healthcare provider	For the extended release product: Wk 1: 500 mg daily Wk 2 onwards: 1000 mg daily	At least 8 wks after TT reached
Topiramate [42]	Avoid in women of childbearing age, not using reliable birth control; avoid alcohol within 6 h of dose; advise pts and family to report signs of depression or changes in mood to their healthcare provider; seek immediate medical attention for visual disturbances or periorbital pain	Dose titration as follows: Wk 1: 25 mg daily Wk 2: 50 mg daily Wk 3: 75 mg daily Wk 4: 100 mg daily	At least 8 wks after TT reached
β-blockers			
Propranolol [43]	Use with caution in pts with renal or hepatic impairment, or with CHF; advise on potential risk of hypersensitivity; reduce dose gradually over at least 3 wks if discontinuing therapy	Initial dose: 80 mg daily in divided doses Usual effective dose: 160–240 mg daily	At least 8 wks after TT reached
Timolol [44]	Use with caution in pts with cardiovascular disease; avoid during pregnancy if possible; advise on the potential risk of hypersensitivity	10–20 mg daily	At least 8 wks after TT reached
Inhibitors of the CGRP pathway			
Erenumab [45]	Provide advice on use of the SC autoinjector; advise on potential risk of constipation, injection site pain, and hypertension or worsening of pre-existing hypertension; safety in pregnancy not yet known	70 mg SC q1mo (some pts may benefit from 140 mg q1mo)	At least 3 mo after initial dose
Galcanezumab [46]	Provide advice on use of the SC prefilled pen and syringe; advise on potential risk of hypersensitivity reactions and injection site reactions; safety in pregnancy not yet known	Loading dose of 240 mg SC, then 120 mg SC q1mo	At least 3 mo after initial dose
Fremanezumab [47]	Provide advice on use of the SC prefilled syringe and autoinjector; advise on potential risk of hypersensitivity reactions and injection site reactions; safety in pregnancy not yet known	Either: 225 mg SC q1mo, or 675 mg SC q3mo When switching dosage, administer new dose on next scheduled day	At least 3 or 6 mo after initial dose for q1mo and q3mo administration, respectively
Eptinezumab [48]	Advise on potential risk of hypersensitivity reactions and stuffy nose and scratchy throat; safety in pregnancy not yet known	100 mg as IV infusion q3mo (may ↑ to 300 mg)	At least 6 mo after initial dose
Others			
OnabotulinumtoxinA (approved for CM only) [49]	Advise to seek medical advice if swallowing, speaking or breathing difficulties develop	155 U IM across 7 specific head/neck muscle areas	At least 6 mo after initial dose
Medications with established efficacy [5], not FDA-approved for migraine prevention			
Valproate sodium [50]	Hepatotoxicity within first 6 mo, monitor liver tests and advise on symptoms such as malaise, lethargy, anorexia and vomiting; risk of pancreatitis with similar symptoms; women of childbearing potential should use effective contraception	500–2000 mg daily	At least 8 wks after TT reached
Metoprolol [51]	Contraindicated in pts with sinus bradycardia or cardiac failure; use with caution in pts with impaired hepatic function; hypersensitivity may occur	100–200 mg daily	At least 8 wks after TT reached

Table 2 (continued)

Treatments	Key counselling notes	Recommended dosage ^a	Duration of adequate trial ^b
Medications with probable efficacy [5], not FDA-approved for migraine prevention			
Amitriptyline [52]	Advise pts and family to report signs of depression or changes in mood to their healthcare provider; consider the possibility of drug interactions via the cytochrome P450 pathway	10–200 mg daily	At least 8 wks after TT reached
Venlafaxine [53]	Advise pts and family to report signs of depression or changes in mood to their healthcare provider; dosage adjustment in renal and hepatic impairment; avoid alcohol	75–225 mg daily	At least 8 wks after TT reached
Atenolol [54]	Use with caution in pts with renal or hepatic impairment, or with CHF; advise on potential risk of hypersensitivity; reduce dose gradually if discontinuing therapy	50–200 mg daily	At least 8 wks after TT reached
Nadolol [55]	Use with caution in pts with renal impairment, or with CHF; reduce dose gradually over 1–2 wks if discontinuing therapy	20–160 mg daily	At least 8 wks after TT reached

CGRP calcitonin gene-related peptide, CHF congestive heart failure, CM chronic migraine, IM intramuscular, IV intravenous, mo month, pt patient, qxmo every x mo, SC subcutaneous, TT therapeutic target, wk week

^aFor drugs which are not specifically approved for the prevention of migraine, daily dose is from Schwedt [56]

^bA 50% reduction in monthly headache days is considered to represent a response to treatment; however, other factors such as pain severity, level of disability and functional capacity should be taken in to account; pts demonstrating a partial response at the time of assessment may warrant continuation of the preventive treatment and further assessment

(i.e., considered for 13% of patients and offered to 26% of patients) [7].

Discontinuation rates are high for patients who initiate oral preventive therapy. The Second International Burden of Migraine Study (IBMS-II) assessed preventive therapy (i.e., antidepressants, anti-epileptics, β -blockers, and calcium channel blockers) patterns in 1165 patients with either EM ($n = 672$) or CM ($n = 493$) from six countries [58]. Discontinuation of ≥ 1 preventive medication was reported by 24% and 41% of EM and CM respondents, respectively. Patient-reported reasons for discontinuation were lack of efficacy ($> 40\%$) and adverse events ($> 35\%$) [58], highlighting an unmet need for improved preventive therapies and possibly unrealistic patient expectations for preventive therapy. Fewer than 15% of patients discontinued therapy because their symptoms had resolved sufficiently to warrant cessation [58]. Similarly, a recent analysis of persistence with preventive migraine medications over 2–5 years using data from the IBM MarketScan[®] database (IBM, Armonk, New York) and Medicare databases found that only 10% of 147,832 migraine patients maintained preventive therapy (mean time of persistence 3.6 years); of the 90% of patients who were nonpersistent, mean time to nonpersistence was 186.4 days [59]. Furthermore, 95% of patients received acute migraine medications during the study follow-up period. The most frequently used acute migraine medication class was opioids (strong and weak opioids, including NSAID and opioid combination drugs, 77%), with a mean of 13.6 prescription

claims per patient [59]. Thus, current evidence demonstrates that patients are being treated acutely with non-preferred acute migraine medications (i.e., opioids) and are being undertreated with preventive therapies.

Calcitonin gene-related peptide inhibitors

The recent approval of monoclonal antibodies targeting the CGRP pathway for prevention of migraine in adults has expanded and improved available options for migraine treatment. CGRP, a vasodilatory neuropeptide with multiple sites of action, has been identified as a key player in migraine pathophysiology through its involvement in nociception and sensitization of peripheral and central neurons in the trigeminovascular system [60]. CGRP is also associated with neurogenic inflammation and pronociceptive activity [61]. CGRP levels in the jugular venous blood are elevated in patients with migraine, increase during migraine attacks, and can induce migraine-like headaches in people susceptible to migraine [60, 62, 63]. Sumatriptan has been shown to normalize plasma CGRP levels, reinforcing the role of CGRP in migraine [64].

Following recognition of the role of CGRP in the pathogenesis of migraine, small-molecule antagonists of the CGRP receptor (known as gepants) were developed and found to be effective for the acute and preventive treatment of migraine [65]. The early development of these small-molecule inhibitors for preventive treatment was stopped

Fig. 1 Pharmacist role, unless otherwise indicated, in identifying and supporting patients likely to benefit from preventive treatment. ^aRecommendations from the American Headache Society Consensus Statement [5]. ^bDisability as assessed by the Migraine Disability Assessment (MIDAS) tool. *OTC* over-the-counter.

largely due to hepatic toxicity [65]; however, ubrogepant and rimegepant have recently been approved for acute treatment of migraine [66, 67]. In the interim, monoclonal antibodies against the CGRP receptor (erenumab) or CGRP ligand (galcanezumab, fremanezumab, and eptinezumab) were approved for preventive treatment of migraine [48, 68]. The long half-life of these preventive medications enables monthly subcutaneous administration for erenumab, galcanezumab and fremanezumab (with an every-3-month administration option for fremanezumab) [68] and every-3-month intravenous administration for eptinezumab [48].

Key clinical trial results for the monoclonal antibodies targeting the CGRP pathway currently approved or under clinical development are provided in Table 3 [47, 69–75]. In summary, CGRP-inhibitors, whether they directly interact with the receptor or the ligand, significantly reduced monthly migraine days, significantly increased the proportion of patients achieving a $\geq 50\%$ reduction in monthly migraine days, and significantly reduced monthly acute migraine-specific medication use days compared with placebo in patients with CM and EM. In addition to those monoclonal antibodies that are currently approved, oral

small-molecule CGRP receptor antagonists are also being evaluated for the prevention of migraine [68].

Migraine treatment guidelines from the AHS and AAN

The leading organizations in the US for headache treatment and management are the American Academy of Neurology (AAN) and AHS. In 2000, these two organizations were joined by five other national organizations to form the US Headache Consortium, which developed the first consensus guidelines for acute treatment and prevention of migraine [57]. Key to the management of migraine is accurate diagnosis and the subsequent education of patients about their condition and treatment, including establishing realistic treatment expectations, and encouraging patients to identify and avoid migraine triggers [57]. For acute treatment, these early guidelines recommended treating attacks promptly with an effective acute migraine-specific treatment, selecting a non-oral medication with patients presenting with migraine associated with severe nausea and vomiting, identifying a self-administered “rescue”

medication for use if the initial acute medication was ineffective. To prevent MOH, the use of acute therapy for > 2 headache days per week was cautioned against [57]. For preventive treatment, it was recommended to use medications with the best evidence while taking comorbidities into account, initiate therapy at the lowest effective dose, give each drug an adequate (2–3 month) trial, monitor treatment response through a headache diary, and to consider the role of concurrent non-pharmacologic treatment [57]. These overarching treatment principles remain valid today and underpin current guidelines.

The AAN and AHS have worked together to update guidelines for preventive treatment of EM to include data on the safety and efficacy of newer preventive therapies [76], while the AHS has used the AAN protocols to update acute treatment guidelines [77]. In December 2018, AHS, building on earlier work of the US Headache Consortium, provided a position statement to update previous recommendations, providing greater specificity regarding criteria for preventive treatment (Table 2) and outlining the emerging role of inhibitors of the CGRP pathway in preventive treatment (Fig. 2) [5]. The AHS also reviewed and updated current guidelines

for acute treatment, confirming acute treatment goals and considerations and updating advice on the effectiveness of available acute treatments (Table 4) [5]; since that time ubrogepant [66], lasmiditan [78] and rimegepant [67] have been approved for acute treatment of migraine. The AHS guidelines provide increased clarity on the importance of preventive treatment in patients with severe, disabling or frequent migraine attacks and in those who are intolerant of or nonresponsive to acute treatment [5].

Role of pharmacists in management of patients with migraine

Pharmacists are well-placed to support patients with migraine, because they are extremely accessible healthcare professionals, with patients commonly seeking their advice [79]. Indeed, one survey found that 97% of community pharmacists made ≥ 1 OTC recommendation each day for the treatment of headache [80], with the most recent *Pharmacy Times* OTC survey estimating that pharmacists in the USA

Table 3 Pivotal studies of monoclonal antibodies targeting the CGRP pathway^a

CGRP pathway inhibitor	Trial ID (trial name)	Change in MMDs from BL	50% responder rate (%)	Change in monthly AMSM days from BL
Episodic migraine				
Erenumab 70 mg q1mo [69]	NCT02456740 (STRIVE)	− 3.2 (0.2)**	43.3**	− 1.1 (0.1)**
Erenumab 140 mg q1mo [69]	NCT02456740 (STRIVE)	− 3.7 (0.2)**	50.0**	− 1.6 (0.1)**
Galcanezumab 120 mg q1mo [70] ^b	NCT02614183 (EVOLVE-1)	− 4.7**	62.3**	− 4.0**
Galcanezumab 240 mg q1mo [70]	NCT02614183 (EVOLVE-1)	− 4.6**	60.9**	− 3.8**
Fremanezumab 225 mg q1mo [47]	NCT02629861	− 3.7**	47.7**	− 3.0**
Fremanezumab 675 mg q3mo [47]	NCT02629861	− 3.4**	44.4**	− 2.9**
Eptinezumab 100 mg q3mo [71]	NCT02559895 (PROMISE 1)	− 3.9*	49.8*	NR
Eptinezumab 300 mg q3mo [71]	NCT02559895 (PROMISE 1)	− 4.3**	56.3**	NR
Chronic migraine				
Erenumab 70 mg q1mo [72]	NCT02066415	− 6.6 (0.4)***	40**	− 3.5 (0.3)***
Erenumab 140 mg q1mo [72]	NCT02066415	− 6.6 (0.4)***	41***	− 4.1 (0.3)***
Galcanezumab 120 mg q1mo [73]	NCT02614261 (REGAIN)	− 4.8 (0.4)**	27.6**	− 4.7 (0.4)**
Galcanezumab 240 mg q1mo [73]	NCT02614261 (REGAIN)	− 4.6 (0.4)**	27.5**	− 4.3 (0.4)**
Fremanezumab 225 mg q1mo [74]	NCT02621931	− 5.0 (0.4)**	41**	− 4.2 (0.3)**
Fremanezumab 675 mg q3mo [74]	NCT02621931	− 4.9 (0.4)**	38**	− 3.7 (0.3)**
Eptinezumab 100 mg q3mo [75]	NCT02974153 (PROMISE 2)	− 7.7***	57.6***	− 3.3***
Eptinezumab 300 mg q3mo [75]	NCT02974153 (PROMISE 2)	− 8.2***	61.4***	− 3.5***

AMSM acute migraine-specific medication, BL baseline, CGRP calcitonin gene-related peptide, ID identification from the ClinicalTrials.gov website, MMD monthly migraine day, NR not reported, qxmo every x months

* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ vs placebo

^aData may have been assessed differently in each trial and may not be directly comparable head-to-head

^bGalcanezumab 300 mg q1mo is also indicated for the treatment of episodic cluster headache

make ≈ 1.9 million OTC recommendations for headache per month, with $\approx 800,000$ specifically for migraine [81, 82].

Pharmacists have the knowledge base to support patients with migraine, with the majority of the headache curricula in PharmD programs in the USA teaching information consistent with migraine treatment guidelines [83]. Residency programs also provide important information on drug selection and patient education [83]. The specific role of a pharmacist in the management of patients with migraine will, however, vary depending on their practice setting and patient relationships.

First and foremost, the community-based pharmacist is the only healthcare professional that some patients with migraine visit [84, 85]. Up to one-third of those with

migraine do not consider migraine a disease and, therefore, do not consult a primary-care physician [85]. Screening tools have been developed to assist pharmacists to identify patients with possible migraine based on a simple 4-question algorithm querying the percentage of headaches prohibiting normal activities and/or accompanied by vomiting, headache-free days per month, symptoms that accompany headaches, and the OTC products that have been tried [86]. In particular, the pharmacist can identify those who, based on headache frequency and disability level, would benefit most from physician referral and possible preventive treatment (Fig. 1) [87, 88].

In patients managed on OTC medication alone, the pharmacist has an opportunity to assess treatment outcome and

Fig. 2 Overview of role of inhibitors of the CGRP pathway for prevention of migraine as suggested by the American Headache Society [5]. ^aPatients with adverse events or an inadequate response to a 6-week trial of topiramate, divalproex sodium/valproate sodium, β -blocker, tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor or any other Level A or Level B treatments, per the Ameri-

can Academy of Neurology-American Headache Society guidelines. ^bPatients with adverse events or an inadequate response to a minimum of two quarterly injections (6 months of therapy). *CGRP* calcitonin gene-related peptide, *ICHD-3* International Classification of Headache Disorders, 3rd Edition.

discuss possible use of preventive treatment with those who do not achieve acceptable headache relief [88]. Importantly, patients need to understand the risks of overusing acute medication [86, 88–90]. With a unique view of both OTC and prescribed medicines, the community pharmacist is well-placed to detect medication overuse [85]. Pharmacists can also counsel patients to avoid lifestyle factors that may contribute to disease progression.

For all patients, pharmacists have a role in educating patients regarding realistic treatment expectations and providing drug-specific counseling to optimize adherence [88]. For patients on prescription medications, in particular, some suggest pharmacists could do more to provide medication-specific education and advice [87]. The pharmacist may also have a role in providing information on non-pharmacologic

treatment options including the identification and avoidance of triggers [91], an important area where pharmacists could have greater input [87].

In patients under the active management of a physician, pharmacists may serve as the medication use specialist, supporting the prescriber in selection of the most appropriate acute or preventive therapy based on patient-specific factors including comorbidities, identifying adverse events and managing drug-related problems, such as potential drug-drug interactions [79]. When working in collaboration with the physician, the pharmacist may also have a role in medication management [79], which in relation to migraine could involve managing the tapering or discontinuation of acute medicines, particularly in patients presenting with MOH or whose migraines are being managed with opioids or barbiturates [90].

It has been demonstrated that pharmacists can improve the HR-QoL of patients with migraine by providing structured evaluation and counseling in liaison with other health-care professionals [92]. Given the limited number of board-certified headache specialists in the USA (i.e., >39,000 patients for every specialist) [31] and the recognized shortage of primary care physicians, community-based pharmacists have an increasingly important role in the management of patients with migraine [79].

Conclusions

More than 39 million Americans have migraine [31], the treatment of which is healthcare resource intensive [32]. Given that pharmacists make > 1 million migraine-specific treatment recommendations per month, they are uniquely positioned and trained to identify patients with headache and potentially undiagnosed migraine, help patients manage acute migraine symptoms, and recommend referral to primary care physicians or specialists to ensure access to the most appropriate migraine treatment based on the patient's individual needs. Pharmacists are also well-placed to assist patients to understand what outcomes to expect from preventive medication and the importance of maintaining a headache diary. By providing an overview of the burden of disease, barriers to care, current evidence-based treatment recommendations, and highlighting the role for the newest preventive therapies in migraine management, pharmacists have the information to make more informed decisions and better advise patients about the treatment of migraine and, in particular, why, how, and when preventive therapy should be initiated.

Table 4 Summary of considerations for acute treatment and overview of acute treatments with established efficacy [5]

Treatment considerations for acute treatment
<i>Offer all patients with migraine acute treatment</i>
<i>Use evidence-based acute treatment</i>
Treat at first sign of pain
<i>For patients with severe nausea or vomiting, choose a non-oral route of administration</i>
Subcutaneous or intranasal sumatriptan
Intranasal or intramuscular ketorolac
Subcutaneous or intranasal dihydroergotamine
Rectal administration of antiemetics such as prochlorperazine
<i>Consider tolerability of acute medication and comorbid conditions</i>
NSAIDs cardiovascular and gastrointestinal tolerability
Avoid triptans and ergotamines in patients with coronary artery disease, peripheral vascular disease and uncontrolled hypertension
<i>Consider use of a self-administered rescue treatment</i>
Consider for patients with a history of nonresponse or variable response to their acute treatment
<i>Avoid medication overuse</i>
Advise patients to avoid using acute medications for > 2 headache days per week
Consider preventive medication for patients with ≥ 6 monthly headache days (see Table 2)
Acute medications with established efficacy [5]
Triptans
Calcitonin gene-related peptide receptor antagonists (gepants: ubrogepant, rimegepant) ^a
Ergotamine derivatives
5-HT _{1F} receptor agonists (ditans: lasmitidan) ^a
NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
Opioids (butorphanol) ^b
Combination medications

^aNot approved at the time the AHS consensus statement was developed

^bUse is not recommended in migraine

Take home messages

- Pharmacists are in a position to identify patients with migraine who may benefit from further physician assessment and preventive therapies.
- Pharmacists can educate patients on the benefits of preventive medications for migraine, and what to realistically expect from their treatment.

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