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Acute and preventive Approach for effective management of Migraine

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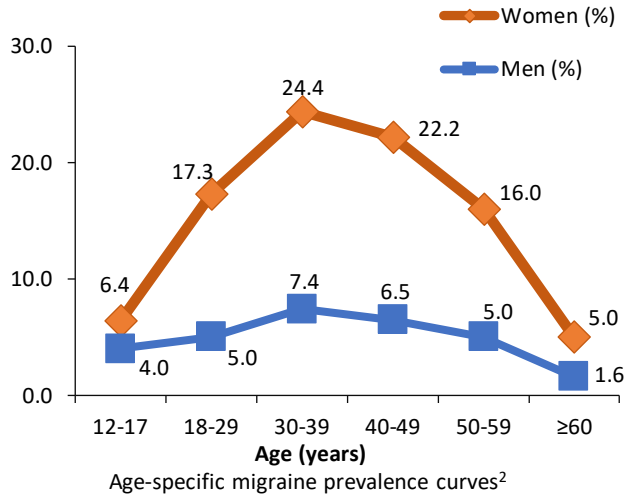
Migraine is a debilitating neurological disorder imposing a high societal burden



Age-specific migraine prevalence curves[2]

Migraine is the 5th leading cause of years lived with disability (DALYs)[1] in MENA

Migraine is 2–3x as common in women as it is in men[2], mostly during their prime working years[3]

Migraine is categorized into:

1) Episodic: <15 headache days per month
2) Chronic: ≥15 headache days per month

- **The most prevalent of all neurological disorders [4]**
- **Current prevalence: >10% of the global population [5]**
- **Only ~10% of migraine patients take current prophylaxis treatment [6]**

1 Global Burden of Disease Study 2015 Collaborators. Lancet. 2016; 2.Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552 3:Lipton RB, Neurology. 2007;68(5):343-349;
4. Edvinsson L. Headache. 2015;55(9):1–7; 5. Stovner et al. Cephalgia 2007;27:193-210 6. Diamond S, et al. Headache 2007;47(3):355–363; 7: Impact of headache in Europe:
a review for the Eurolight project, Lars Jacob Stovner Æ, J Headache Pain (2008) 9:139–146

Globally >10% of population is estimated to suffer from migraine

Globally, headache disorders are common

- Prevalence of headache: **47%**[2]
- Migraine affects **1 in 10 people**[1]

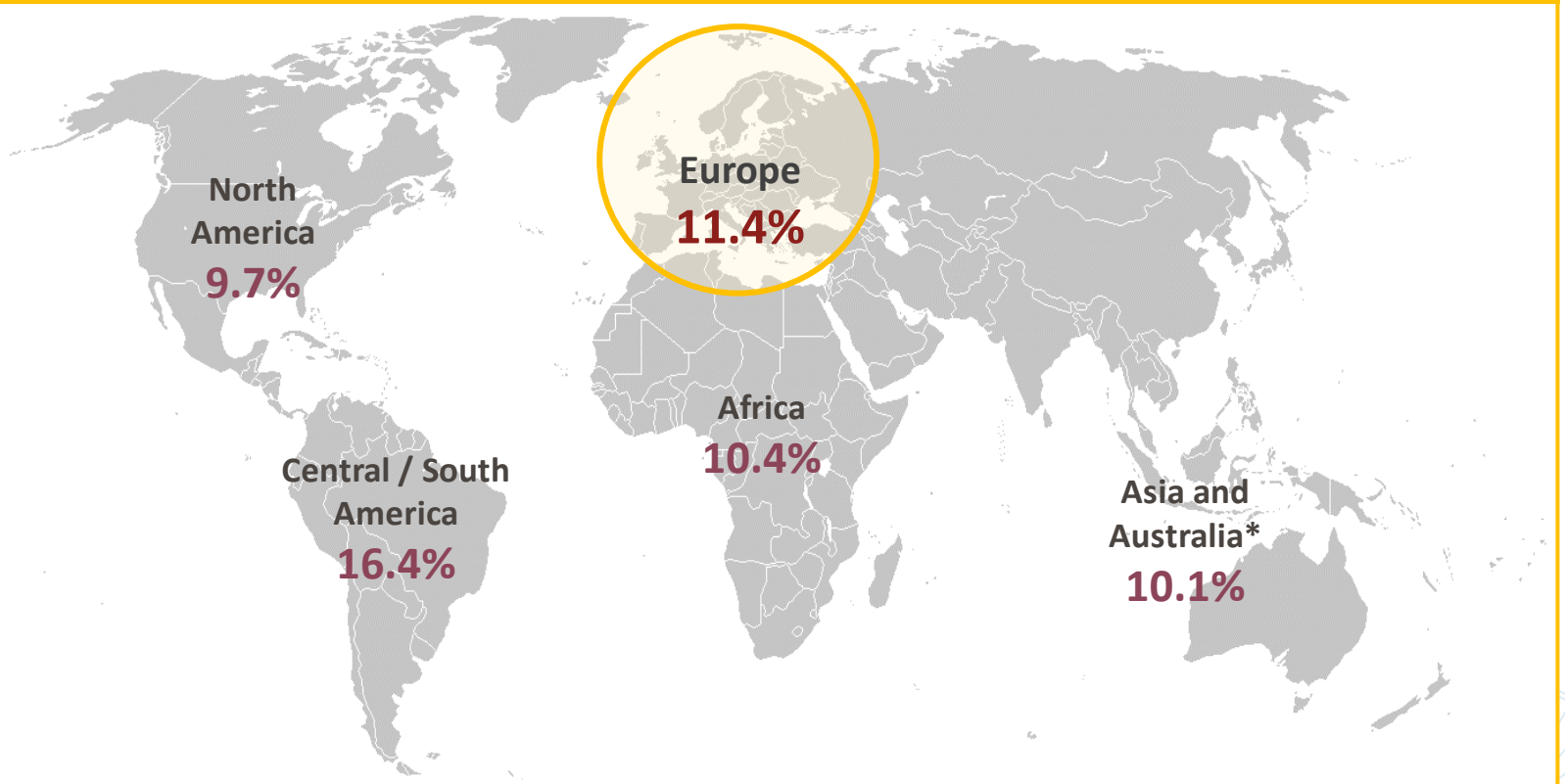
Migraine prevalence is rising worldwide[1,2]

Globally, lifetime prevalence is high:

Headache: **66%**[2]

Migraine: **14%**[2]

Global prevalence of migraine[1]: 11.6%



*Australia was grouped with Asia within this study.

1. Woldeamanuel YW, Cowan RP. J Neurol Sci 2017;372:307–15;
2. Stovner LJ et al. Cephalalgia 2007;27:193–210.

Epidemiology of Headache and Migraine in Gulf Countries

Author (year)	Country	Study duration in months	Study population	Study type	Sample size	Response rate	Prevalence (%)				
							Headache	Migraine	Tension headache	Mixed migraine and tension headache	Unclassifiable headache
Al Rajeh et al. [3]	Saudi Arabia	6	All population	Two-phase community-based study[a]	16,672	–	12.1 (15.9)[b]	5.0	9.5	2.4	–
Jabbar and Ogunniyi [2]	Saudi Arabia	6	Adult population (>15 year old)	Face-to-face questionnaire interviews, door-to-door household visit, community based	5,891	–	8.0	2.6	3.1	2.3	–
Deleu et al. [5]	Oman	24	Population (>10-year old)	Face-to-face questionnaire interviews, door-to-door household visit, community based	1,158	99%	83.6 (78.8)[c]	10.1	11.2	16	62.7
Bener [4]	Qatar	3	Adult population (>15-year old)	Face-to-face questionnaire interviews, cross-sectional primary healthcare clinic based	1,200	76%	72.5	7.9	–	–	–

Benamer HT et al. Epidemiology of Headache in Arab Countries. The Journal of Headache and Pain (2010)

Migraine is underdiagnosed and undertreated

Worldwide:[1]

60%

~50%

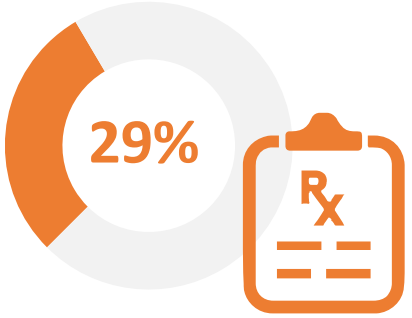
60% of individuals with migraine are not diagnosed by an HCP

About 50% of people with migraine are self-medicating

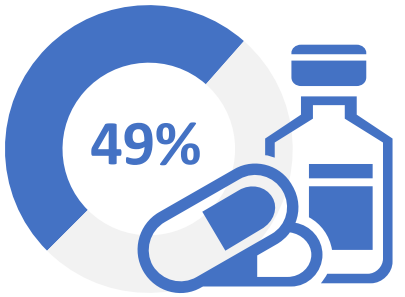
HCP TRAINING TIME ON MIGRAINE IS LIMITED[1]

On average HCPs spend
~4 hours during undergraduate training and
~10 hours of specialist training on headache disorders

IN THE AMPP STUDY OF PATIENTS WITH MIGRAINE IN THE USA:[2]



Used prescription and over-the-counter medication



Used over-the-counter medication only

The majority of patients with migraine self-prescribe medication with only 1 in 8 receiving preventive treatments from an HCP[2]

HCP, Health care professional;
AMPP, American Migraine Prevalence and Prevention.

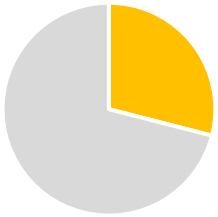
1. WHO Atlas of Headache Disorders and Resources in the World 2011;
2. Diamond S et al. Headache 2007;47:355.

Knowledge regarding diagnosis of migraine and use of prophylactic medication can be limited[1]

Of 18,968 patients with migraine surveyed in 2004 in the AMPP study:[2]

44%

never received a medical diagnosis of migraine

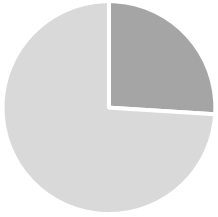


29%

treated attacks with combined prescription and OTC acute medications

49%

treated attacks with OTC medication only



26%

had received prophylactic medication in the past but discontinued treatment

Only **12%**

were current users of prophylactic medication

According to the AMPP study, 39% of patients with migraine should be considered for (13%) or offered (26%) preventive migraine therapy[3]

AMPP, American Migraine Prevalence and Prevention; OTC, over the counter.

1. Katsarava Z et al. Curr Pain Headache Rep 2012;16:86–92;
2. Diamond S et al. Headache 2007;47:355–63; 3. Lipton RB et al. Neurology 2007;68:343–9.

Migraine is costly

EuroLight Project

- Cross-sectional survey in 8 countries (55% of EU adult population)
- Mean per-person annual costs were €1222
- Total annual cost of migraine in EU: **€111 billion**

In the UK

- 25 million days are lost from work or school each year because of migraine, costing £2.25 billion
- The cost to the NHS is **£150 million** per year
- **Despite its economic impact, migraine is the least publicly funded of all neurological illnesses**

SYMPTOMS

Migraine is a distinct neurological disorder

A migraine attack can have up to four phases, which frequently overlap*

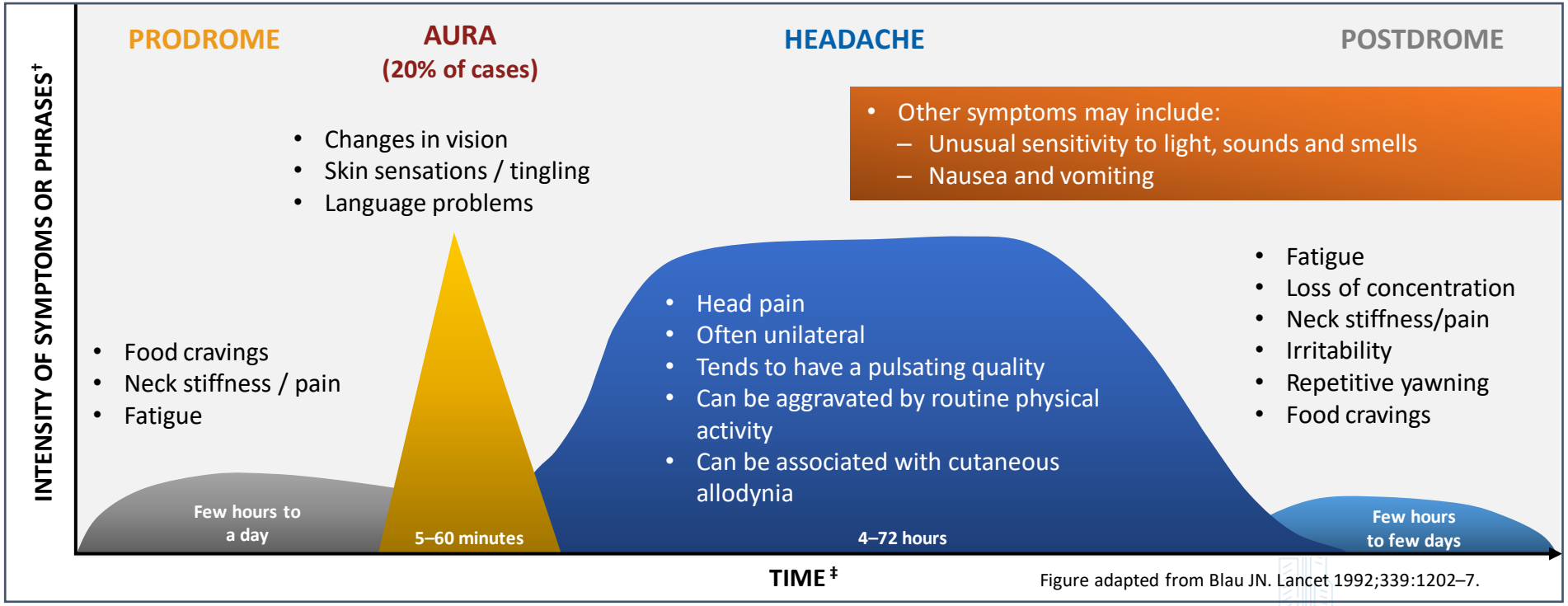
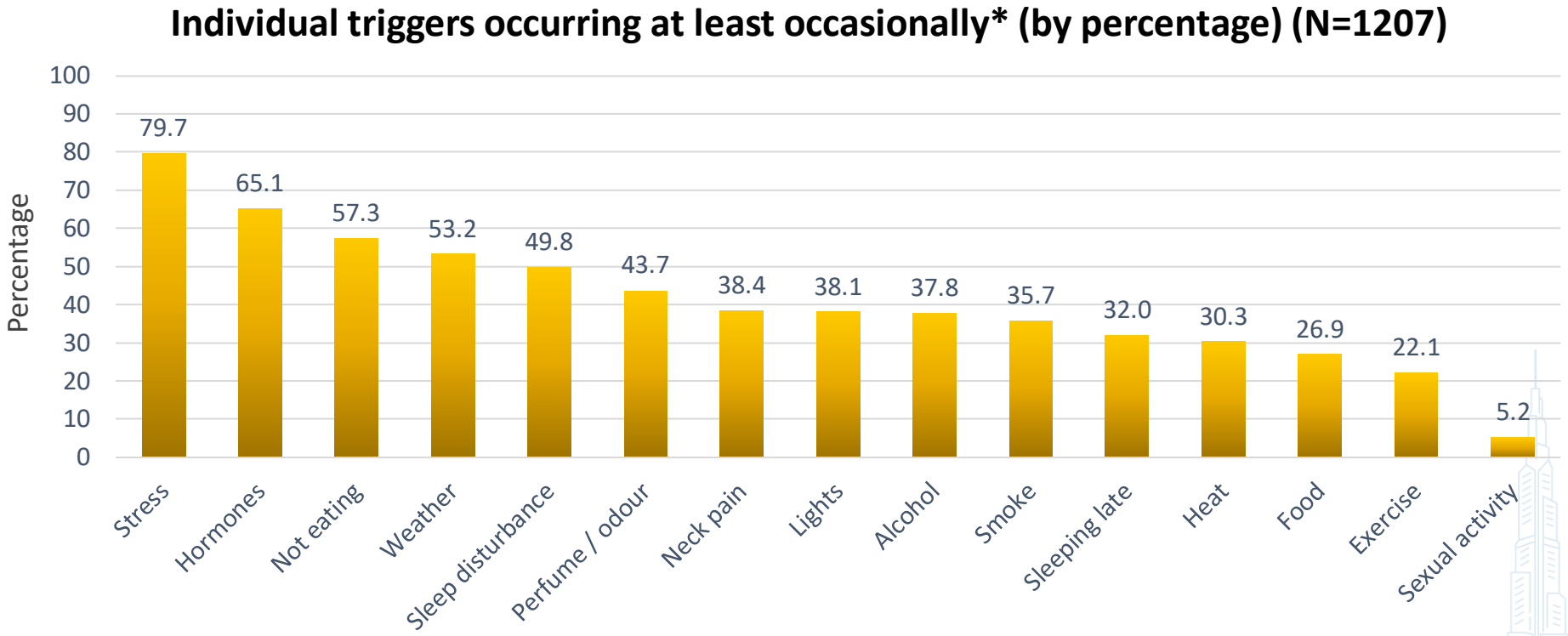


Figure adapted from Blau JN. Lancet 1992;339:1202–7.

*Patients with migraine may not experience all phases and symptoms shown, and not all possible symptoms are listed. † Illustrative only. ‡ Duration per symptom.

Goadsby PJ et al. Physiol Rev 2017:97:553–622;
Headache Classification Committee of the International Headache Society (IHS). Cephalalgia 2018;38:1–211;
Russell MB et al. Int J Epidemol 1995;24:612–8; Viana M et al. Cephalalgia 2013;33:483–90;
Giffin NJ et al. Neurology 2016;87:309–13; Lampl C et al. J Headache Pain 2015;16:566;
Migraine.com, https://migraine.com/migraine-symptoms/, accessed September 2018.

A number of factors are commonly reported by patients as triggers for migraine



- Three quarters of patients report triggers at least occasionally* for an acute migraine attack
- Patients report **stress**, **hormone fluctuations** (in women), **not eating**, **weather** and **sleep disturbance** as the most common triggers
- Triggers are more likely to be associated with a more severe acute migraine attack

Patient management of triggers may be an important aspect of migraine management

*Defined as occurring in >33% of cases.

Kelman L. Cephalalgia 2007;27:394–402.

Migraine significantly impacts quality of life

Significant sleep disturbance

Patients with migraine are ***more than twice as likely*** to have ***poor quality sleep*** and suffer from excessive daytime sleepiness[1–4]

They are also ***more likely to suffer from other sleep-related problems*** (e.g. long sleep latency, daytime dysfunction due to sleepiness, nocturnal sweating and sleep paralysis)[2]

Worsened PR

PRO scores (used to evaluate patient HRQoL) typically ***worsen with increased migraine frequency*** and disease severity[5–7]

Higher risk of certain comorbidities

Approximately ***50–60% of patients with migraine*** suffer from ***comorbid anxiety*** and/or depression[8–10]

For some types of migraine there is evidence of an ***association with other comorbidities*** e.g. chronic stress, bipolar spectrum disorder, ADHD, pre-obesity BMI status, epilepsy and stroke[11–19]

ADHD, adult attention deficit hyperactivity disorder; BMI, body mass index; HRQoL, health-related quality of life; PROs, patient-reported outcomes.

1. Morgan I et al. J Headache Pain 2015;16:18; 2. Karthik N et al. J Neurol Sci 2012;321:73–76; 3. Sadeghniiat K et al. Acta Med Iran 2013;51:784–88; 4. Duman T et al. Ann Indian Acad Neurol 2015;18:298–302; 5. Blumenfeld AM et al. Cephalalgia 2010;31:301–15; 6. Stuginski-Barbosa J et al. Headache 2012;52:400–8; 7. Lipton RB et al. Headache 2016;56:1280–9; 8. Minen MT et al. J Neurol Neurosurg Psychiatry 2016;87:741–49; 9. Buse DC et al. J Neurol 2013;260:1960–69; 10. Breslau N et al. Psychiatry Res 1991;31:11–23; 11. Antonaci F et al. J Headache Pain 2011;12:115–25; 12. Sacco S et al. Eur J Neurol 2015;22:1001–11; 13. Schürks M et al. BMJ 2009;339:b3914; 14. Spector JT et al. Am J Med 2010;123:612–24; 15. Keezer MR et al. Eur J Neurol 2015;22:1038–47; 16. Bigal ME et al. Neurology 2006; 66:545–50; 17. Saunders EF et al. J Clin Psychiatry 2014;75:512–19; 18. Fasmer OB et al. Eur Arch Psychiatry Clin Neurosci 2011;261:595–602; 19. Radat F. Rev Neurol 2013;169:406–12.

Steps to successful migraine management

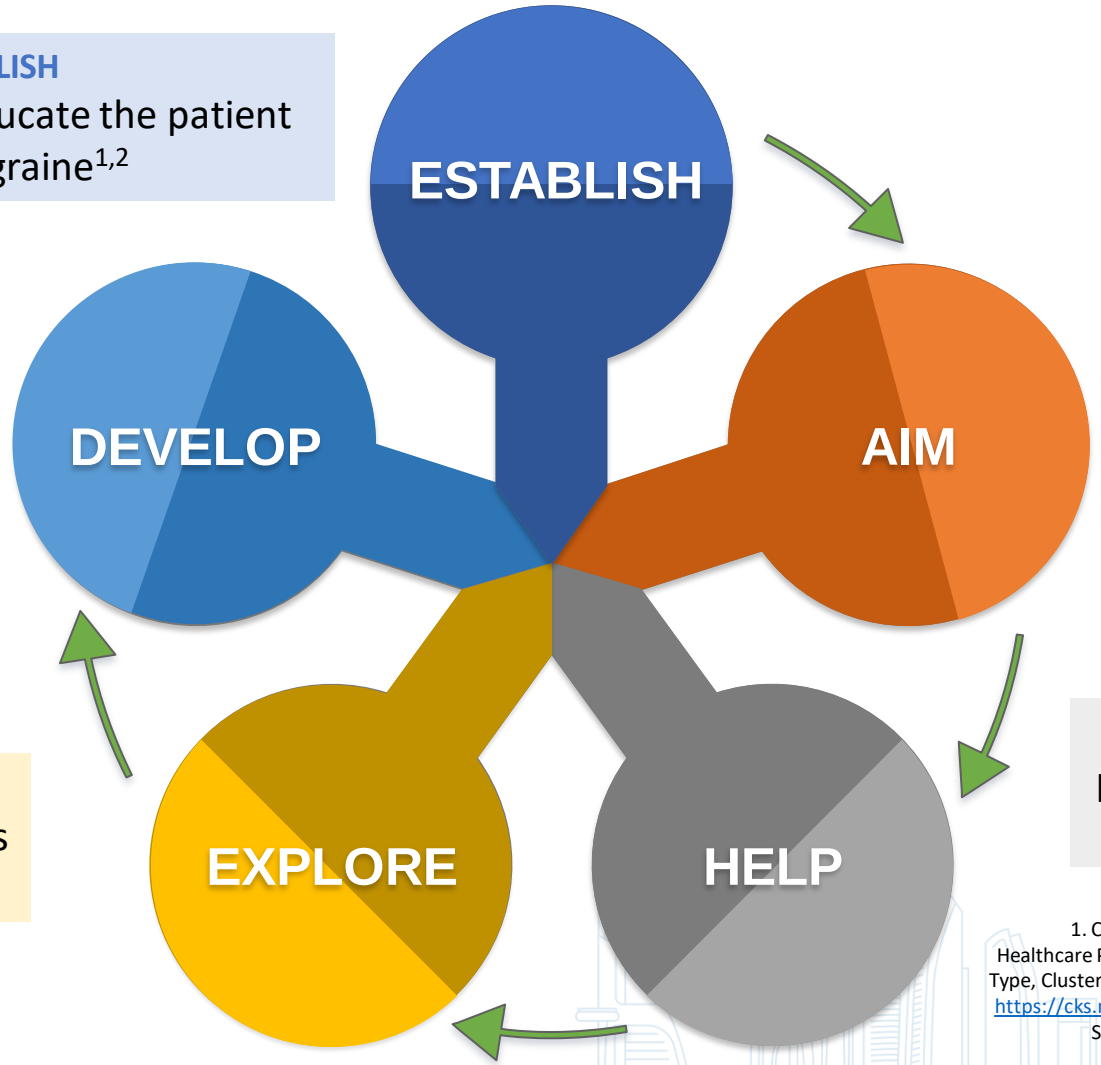
1. ESTABLISH
a relationship and educate the patient on their migraine[1,2]

2. AIM
for a correct and timely diagnosis[2]

3. HELP
patients identify and avoid their migraine triggers[2,3,5]

4. EXPLORE
behavioural management strategies to minimise the onset of migraine[3]

5. DEVELOP
a pharmacological treatment plan, specific to the patient's individual needs and goals[3,4]



1. Cottrell CK et al. J Fam Pract 2002; 51: 142–7; 2. BASH Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache 3rd edition (1st revision) 2010; 3. https://cks.nice.org.uk/migraine#!scenario (Accessed August 2018); 4. Silbertstein SD. CNS Spectrums 2017;22:4–12; 5. May A, Schulte LH. Nat Rev Neurol 2016;12:455–64.

Potential factors to consider when initiating migraine therapy

Are the patient and HCP aware of the treatment goals?	Treatment should reduce attack frequency, severity, disability and improve quality of life[1–3]
Will the patient benefit from acute or prophylactic therapy or both?	Patients that have >4 migraine days / month should be encouraged to use prophylactic therapy[4]
Has the patient previously failed multiple prophylactic therapies?	Patients commonly discontinue therapy due to lack of efficacy and intolerable side effects;[5,6] patients should be educated on new treatment options, including the availability of anti-CGRP mAbs[7]
Does the patient use contraindicated drugs / suffer from comorbidities?	Treatment plans should be individualised to each patient, consider whether a single medication can manage both conditions[4]
Has the patient previously been misdiagnosed?	Misdiagnosis is associated with chronification; patients should be encouraged to use prophylactic therapy[8]

CGRP, calcitonin gene-related peptide; HCP, healthcare professional; mAbs, monoclonal antibodies.

1. Silberstein SD. Neurology. 2000;55:754–62; 2. Evers S et al. Eur J Neurol. 2006,13:560–72; 3. Estemalik E, Tepper S. Neuropsychiatr Dis Treat 2013;9:709–20; 4. Silberstein SD. Continuum (Minneap Minn) 2015;21:973-89; 5. Blumenfeld AM et al. Headache 2013;53:644–55; 6. Hepp Z et al. Cephalalgia 2015;35:478–88; 7. Ashina M et al. Cephalalgia 2018;38:1611–21; 8. D'Amico D et al. Neuropsychiatr Dis Treat 2008;4:1155–67.

Pharmacological strategies for migraine treatment

Migraine can be treated using two strategies – acute and prophylactic treatments

Acute treatment

Characteristics:

- Abortive or symptomatic
- First choice for initial treatment
- May provide symptom relief

Possibility for:

- Moderate or inconsistent benefits
- Tolerability issues
- Medication overuse headache

Prophylactic treatment

May reduce:

- Frequency, severity and duration of attacks
- Disability
- Health care resource utilisation (including cost)

Efficacy can be limited:

- Includes therapies repurposed from other therapeutic areas
- Most are associated with issues of patient adherence

Giamberardino MA, Martelletti P. Expert Opin Emerg Drugs. 2015;20:137–147.

Key recommendations from treatment guidelines

MIGRAINE IS FIRST TREATED WITH ACUTE THERAPIES (E.G. ANALGESICS) TO ABORT MIGRAINE ATTACKS; PROPHYLAXIS IS CONSIDERED, DEPENDENT ON FREQUENCY, USING DRUGS REPURPOSED FROM OTHER THERAPEUTIC AREAS[1–3]

Diagnosis migraine (± aura)

Acute treatment (evidence level)

- Analgesics (A-EFNS)
- Triptans (A-EFNS)
- Anti-emetics (B-EFNS)
- Ergot alkaloids (EFNS / A-AHS / AAN*)
- Some combinations (EFNS)

Goal for acute treatment:[2]
- To abort migraine attacks
- Pain relief and improvement after 2 hours
- Sustained pain relief within 24 hours and consistent efficacy in 2–3 attacks

Prophylactic treatment (evidence level)

EPISODIC MIGRAINE

- Beta blockers: metoprolol, propranolol (A-EFNS / AHS / AAN), timolol (A-AHS / AAN)
- Anti-epileptics: valproic acid (A-EFNS), topiramate (A-EFNS / AHS / AAN)
- Calcium channel blocker: flunarizine (A-EFNS)
- Antidepressant: amitriptyline (B-EFNS / AHS / AAN)
- Candesartan, lisinopril (C-EFNS / AHS / AAN), methysergide (C-EFNS), gabapentin (C-EFNS / U-AHS / AAN)

CHRONIC MIGRAINE

* OnabotulinumtoxinA has not been found effective in episodic migraine[4]

OnabotulinumtoxinA is recommended for treatment of chronic migraine; patients should preferably have tried 2–3 other migraine prophylactics previously (H,S-EHF)[4]

Goal for prophylactic treatment:
- To reduce the frequency and severity of attacks[2,5]
- Reduction by 50% of migraine attacks within 3 months[2]

Prophylaxis should be considered when:[2]
- QoL, work or school attendance are severely impaired
- Frequency of attacks ≥2 per month
- Migraine attacks do not respond to acute treatment
- Occurrence of frequent, very long or uncomfortable auras

Choice of prophylaxis is largely made on a patient-by-patient basis, considering comorbidities and side effects[2]

*Evidence level A applies to dihydroergotamine (DHE) nasal spray.
Evidence levels: A, first choice with evidence of efficacy; B, second choice, with less efficacy or more side effects; C, possible efficacy; H, high quality of evidence; S, strong recommendation; U, inadequate evidence.
AAN, American Academy of Neurology; AHS, American Headache Society; EFNS, European Federation of Neurological Societies; EHF, European Headache Federation; QoL, quality of life.

1. Marmura MJ et al. Headache 2015;55:3–20; 2. Evers S et al. Eur J Neurol 2009;16:968–81; 3. Novartis Press Release, May 2018. https://www.novartis.com/news/media-releases/novartis-and-amgen-announce-fda-approval-aimovigtm-erenumab-novel-treatment-developed-specifically-migraine-prevention, accessed September 2018; 4. Bendtsen L et al. J Headache Pain 2018;19:91; 5. Garza I, Swanson JW. Neuropsychiatr Dis Treat 2006;2:281–91.

Overview of acute pharmacological therapies in the treatment of migraine[1,2]

Goals of acute migraine treatment:	Specific acute migraine treatments:	
To relieve migraine-related disability, pain and other symptoms and to abort migraine attacks	• Triptans	• Dihydroergotamine mesylate
Principles of acute migraine treatment:	**Non-specific acute migraine treatments:**	
• Treating the headache as early as possible to reduce migraine-associated pain and disability • Personalising acute treatment to the individual and their migraine to increase effectiveness • Restricting medication to 2–3 days per week to prevent medication overuse headache	• NSAIDs • Analgesics	• Antiemetics

NSAIDs, non-steroidal anti-inflammatory drugs.

1. Silbertstein SD. CNS Spectrums 2017;22:4-12; 2. Tepper SJ. Continuum (Minneap Minn) 2012; 18:807-22; 3. Silberstein SD. Continuum (Minneap Minn) 2015;21:973-989; 4. BASH Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache 3rd edition (1st revision) 2010.

Acute treatment use in migraine

- ✓ Up to **40% of patients are dissatisfied with their acute treatment**; reasons for dissatisfaction include: lack of treatment success and safety / tolerability concerns[1]
- ✓ Only **22% of patients use a migraine-specific acute treatment**, this contributes to the socioeconomic burden and can promote migraine chronification[2,3]
- ✓ Initial treatment is selected **based on individual patient needs**; the patient should be treated early in the attack with an **adequate dose and formulation** of the medication[4,5]
- ✓ **NSAIDs and triptans** are standard treatments and can be used individually or in combination[4,5]
- ✓ Ideally, acute therapy should be restricted to **no more than 2 to 3 days per week** to **avoid medication overuse**[4]

NSAIDs, non-steroidal anti-inflammatory drugs.

1. Bigal M et al. Headache 2007;47:475–9; 2. Bigal M et al. Cephalalgia 2009;29:891–897;
3. Lipton RB et al. Neurology 2007;68:343–9; 4. Öztürk V. Noro Psikiyatr Ars 2013;50:S26–9; 5. Marmura MJ et al. Headache. 2015;55:3–20.

Limitations of acute treatment

- ✓ Long term use of acute medication is **associated with medication overuse headache** and the **transformation from episodic to chronic migraine** (chronification)[1]
- ✓ Acute therapeutics **temporarily abort headache symptoms** and **do not prevent reoccurrence**[2]
- ✓ **Inconsistent efficacy** and **slow onset of action**[2]
- ✓ Use is **limited by contraindications** (e.g. patients with CV disease or CV risk factors)[3]
- ✓ Use is **restricted to 2–3 days** / week to prevent medication overuse headache[4]

CV, cardiovascular.

1. Diener HC et al. Dtsch Arztebl Int 2018;115:365–70;
2. Lipton RB et al. Headache 2004;42:S3–9;
3. BASH Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache 3rd edition (1st revision) 2010;
4. Öztürk V. Noro Psikiyatr Ars 2013;50:S26–9.

Unmet needs associated with traditional acute treatments

Tolerability issues

Up to 43% of patients experience AEs within 24 hours[1]

Recurrence

67% to 82% of patients experience **return of pain** within 24 hours[2]

MOH

Overuse of many traditional acute therapies can cause MOH[3,4]

CV contraindications

Approximately 2.6M in the US[5]

AE, adverse event; CV cardiovascular; MOH, medication overuse headache.

1. Derry CJ et al. *Cochrane Database Syst Rev*. 2012;2012(2):CD008615. 2. Cameron C et al. *Headache*. 2015;55(suppl 4):221-235.
3. Schwedt TJ et al. *J Headache Pain.* 2018;19(1):38 4. Rosen N, Duarte RA. *Pract Neurol (Fort Wash PA)*. May 2021. Accessed May 16, 2021.
https://practicalneurology.com/articles/2021-may/medication-overuse-headache-2 5. Buse DC et al. *Headache*. 2017;57(1):31-44.

There is an unmet need in available prophylactic migraine treatments

Medications with more than once-daily dosing have lower levels of compliance[1]

Many patients rely on acute medications that, when overused, are ineffective and associated with MOH[2]

Current prophylactics are frequently not well tolerated and can be associated with a range of side effects. This can pose-a risk to the patient and potentially lead to treatment discontinuation[2,3]

Finding the right treatment for patients with comorbidities is challenging and current therapeutics are often not suitable[2]

MOH, medication overuse headache.

1. Osterberg L, Blaschke T. N Engl J Med 2005;353:487–97;
2. Giamberardino MA et al. J Pain Res 2017;10:2751–60; 3. Hepp Z et al. Cephalalgia 2015;35:487–88.

Prophylactic treatment for migraine

Treatment goals

- Click to edit Master text styles
  - Second level
    - Third level
      - Fourth level
        - Fifth level

Eligible patients

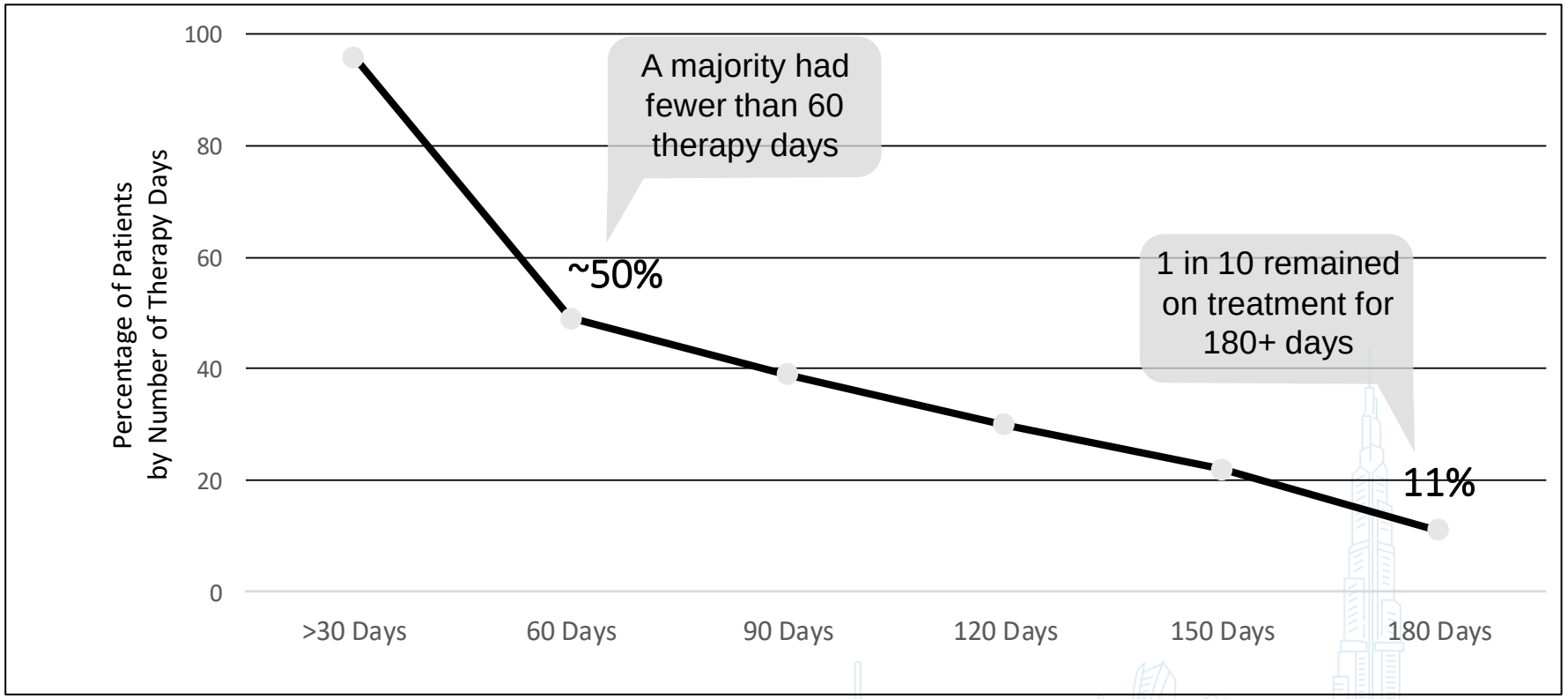
- Prophylactic therapy is recommended in patients with migraine who[1,4,5]:
  - Suffer from ≥4 migraine attacks per month
  - Over use acute medication
  - Experience significant disability from migraine

Real-world challenges

- Prophylactic therapy is underused[6]
- Adherence to prophylactic therapies is poor[7]
  - Up to 80% of patients with migraine are non adherent within 1 year
- Patients frequently discontinue prophylactic therapies[4,8]
  - The most common reasons for discontinuation include side effects and limited efficacy[4]

1. Silberstein SD. Neurology 2000;55:754–62; 2. Devine J et al. J Headache Pain 2007;8:105–13; 3. Wertz DA et al. Curr Med Res Opin 2009;25:499–503; 4. Blumenfeld AM et al. Headache 2013;53:644–55; 5. Silberstein SD. Continuum 2015;21:973–89; 6. Lipton RB et al. Neurology 2007;63:343–49; 7. Hepp Z et al. Cephalalgia 2015;35:478–88; 8. Hepp Z et al. Cephalalgia 2017;37:470–85.

Patients' adherence to migraine-preventive treatment*[1]



*Includes total of **antidepressants, antiepileptics, and beta blockers**. Patients were followed for at least 180 days after index prescription initiation of preventive treatment. The median number of therapy days was consistent across classes: 60 for antidepressants, 79 for antiepileptics, and 60 for beta blockers.

1. Berger A, et al. *Pain Pract.* 2012;12:541-549.

Currently available prophylactic pharmacological treatments for migraine*

Consideration should be given to the following prior to prescription of prophylactic medication[1]:	
Efficacy[1]	• Limited efficacy can reduce patient adherence to treatment programme
Safety[1]	• Adverse event profiles or treatment regimes that the patient finds unacceptable can limit uptake and perseverance
Concurrent mediation[2]	• Drug interactions should be considered when selecting treatment options e.g. topiramate can reduce the efficacy of contraceptives
Pregnancy[3]	• Some drugs are unsuitable for use in pregnant or lactating women e.g. topiramate is associated with increased risk of birth deformities
Comorbidities[4]	• Comorbidities may prevent some patients from taking certain prophylactics e.g. valproic acid may not be suitable for patients with hepatic dysfunction
Lifestyle[1]	• Some aspects of an individual patient's lifestyle can make particular therapies unsuitable, for example: – Drugs that can cause difficulty with memory may not be suitable for a teacher (e.g. topiramate) – Drugs that can cause somnolence may not be suitable for a taxi driver (e.g. amitriptyline)

EPISODIC AND CHRONIC MIGRAINE[5]

- **Beta blockers**
  e.g. Metoprolol, propranolol, timolol
- **Anticonvulsants**
  e.g. Topiramate
- **Calcium channel blockers**
  e.g. Flunarizine
- **Antidepressants**
  e.g. Amitriptyline
- **CGRP monoclonal antibodies[6–8]†**
  e.g. Rimegepant, Erenumab, Galcanezumab
- **Other[5]**
  e.g. Candesartan, lisinopril

CHRONIC MIGRAINE ONLY[7]

- **Other[9]**
  e.g. OnabotulinumtoxinA

!

Not all drugs are licensed in all countries for the treatment of migraine Please always refer to your own local Prescribing Information before prescribing

†CGRP monoclonal antibodies are not included in the 2009 EFNS guidelines; however, erenumab was first approved in the US for migraine prophylaxis in May 2018 and fremanezumab and galcanezumab in September 2018.

1. D'Amico D et al. Neuropsychiatr Dis Treat 2008;4:1155–67; 2. Reddy DS. Expert Rev Clin Pharmacol 2010; 3:183–92; 3. Vecesi L et al. Exp Opin Drug Saf 2015;14:667–81; 4. Epilim® (sodium valproate) Summary of Product Characteristics, August 2018; 5. Silberstein SD. Continuum (Minneap Minn) 2015;21:973–89; 6. AIMOVIG® (erenumab) Summary of Product Characteristics, July 2018; 7. AJOVY® (fremanezumab) US Prescribing Information, September 2018; 8. EMGALITY™ (galcanezumab) US Prescribing Information, September 2018; 9. Bendtsen L et al. J Headache Pain 2018;19:91.

Unmet need in migraine prophylactic treatment

For some patients, prophylactic migraine medications may reduce migraine frequency and severity[1,2]

However, prophylactic treatment is often **underused**, as approximately two thirds of eligible patients do not receive it[3]

In addition, oral prophylactic treatment can be associated with **poor patient adherence** and high rates of **switching** and **discontinuation**[1,4,5]

Common reasons for oral prophylactic discontinuation include **lack of efficacy** and **intolerable side effects**[1]

Prophylactic medication may reduce acute medication use and reduce the risk of disease chronification[6]

1. Mitsikostas DD, Rapoport AM. BMC Med 2015;13:279; 2. Blumenfeld AM et al. Headache 2013;53:644–55;
3. Lipton RB et al. Neurology 2007;63:343–9; 4. Hepp Z et al. Cephalalgia 2015;35:478–88; 5. Hepp Z et al. Cephalalgia 2017;37:470–85;
6. Manzoni GC et al. Neurol Sci 2013;34(Suppl. 1):S57–60.

New Therapy in the Preventive Care of Migraine

Calcitonin Gene-Related Peptide (CGRP)

- Role of CGRP in migraine pathogenesis
- Monoclonal antibodies (mAbs) in treatment of migraine

- Efficacy, safety, and tolerability in the prevention of episodic and chronic migraine

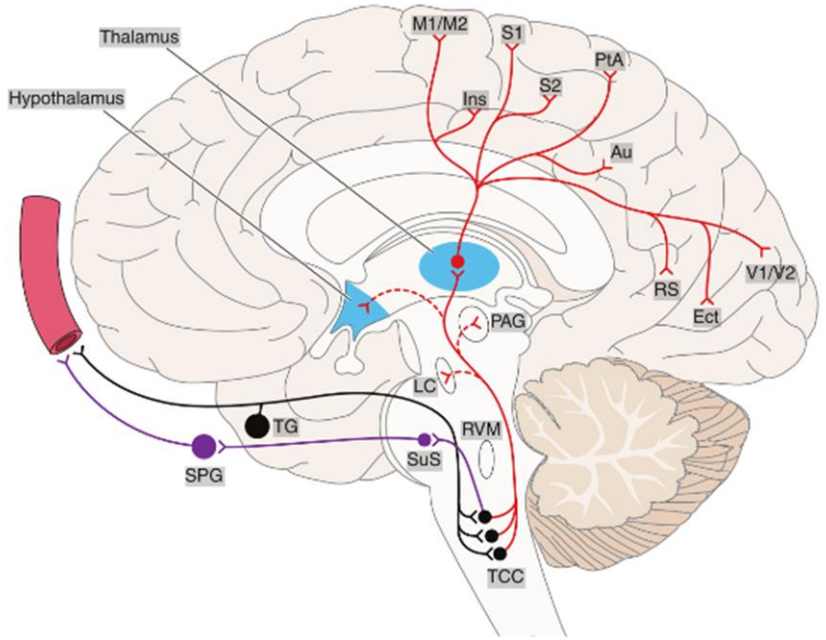
CGRP and Migraine

Actions

- *Vasodilation*
- *Inflammation*
- *Sensory neurotransmission*
- *Pain perception, modulation, and sensitization*

CGRP and Migraine

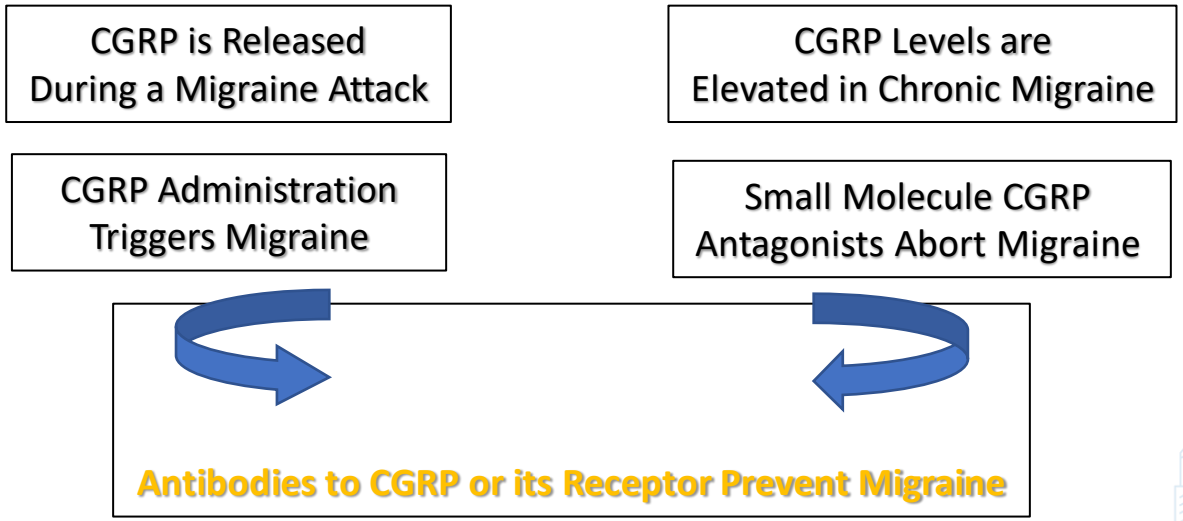
Vasodilation
CGRP



sensitization
CGRP

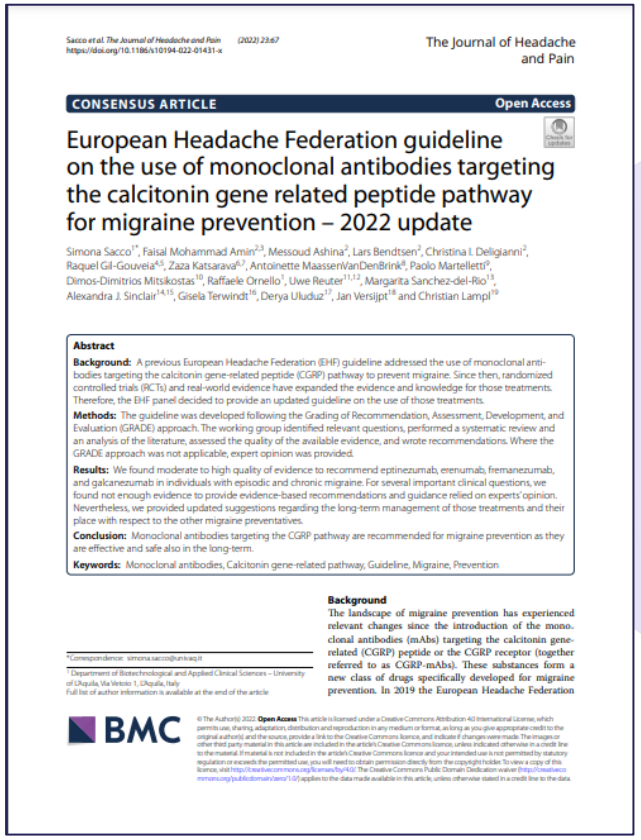
CGRP
transmission
Central sensitization

CGRP plays a pivotal role in migraine



[1]Goadsby PJ, et al. *Ann Neurol.* 1990; 28:183-187. [2]Goadsby PJ, et al. *Brain.* 1994;117(Pt 3):427-434. [3]Hansen JM, et al. *Cephalalgia.* 2010;30(10):1179-1186.
[4]Cernuda-Morollon E, et al. *Neurology.* 2013;81(14):1191-1196. [5]Olesen J, et al. *N Engl J Med.* 2004;350:1104-1110. [6]Ho TW, et al. *Neurology.* 2008;70:1304-1312

Expert consensus statement - Updated EHF guidelines on the use of CGRP mAbs for migraine prevention



Sacco et al. The Journal of Headache and Pain (2022) 23:67
https://doi.org/10.1186/s10194-022-01431-x

The Journal of Headache and Pain

CONSENSUS ARTICLE Open Access

European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update

Simona Sacco[1*], Faisal Mohammad Amin[2,3], Messoud Ashina[2], Lars Bendtsen[2], Christina I. Deligianni[2], Raquel Gil-Gouveia[4,5], Zaza Katsarava[6,7], Antoinette MaassenVanDenBrink[8], Paolo Martelletti[9], Dimos-Dimitrios Mitsikostas[10], Raffaele Ornello[1], Uwe Reuter[11,12], Margarita Sanchez-del-Rio[13], Alexandra J. Sinclair[14,15], Gisela Terwindt[16], Derya Uluduz[17], Jan Versijpt[18] and Christian Lampl[19]

Abstract

Background: A previous European Headache Federation (EHF) guideline addressed the use of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway to prevent migraine. Since then, randomized controlled trials (RCTs) and real-world evidence have expanded the evidence and knowledge for those treatments. Therefore, the EHF panel decided to provide an updated guideline on the use of those treatments.

Methods: The guideline was developed following the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. The working group identified relevant questions, performed a systematic review and an analysis of the literature, assessed the quality of the available evidence, and wrote recommendations. Where the GRADE approach was not applicable, expert opinion was provided.

Results: We found moderate to high quality of evidence to recommend eptinezumab, erenumab, fremanezumab, and galcanezumab in individuals with episodic and chronic migraine. For several important clinical questions, we found not enough evidence to provide evidence-based recommendations and guidance relied on experts' opinion. Nevertheless, we provided updated suggestions regarding the long-term management of those treatments and their place with respect to the other migraine preventatives.

Conclusion: Monoclonal antibodies targeting the CGRP pathway are recommended for migraine prevention as they are effective and safe also in the long-term.

Keywords: Monoclonal antibodies, Calcitonin gene-related pathway, Guideline, Migraine, Prevention

Background

The landscape of migraine prevention has experienced relevant changes since the introduction of the monoclonal antibodies (mAbs) targeting the calcitonin gene-related (CGRP) peptide or the CGRP receptor (together referred to as CGRP-mAbs). These substances form a new class of drugs specifically developed for migraine prevention. In 2019 the European Headache Federation

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Full list of author information is available at the end of the article

In individuals with migraine who require preventive treatment, EHF guidelines suggest mAbs targeting the CGRP pathway to be included as a first line treatment option

Migraine Management

- Migraine management should involve both acute and preventive treatment

Acute treatment

- Taken at the first sign of attack
- Minimizes and relieves emerging symptoms as they occur

Preventive treatment

- Taken regularly by those with frequent migraine attacks
- Proactively reduces migraine frequency, severity and duration

- Mayo Clinic. Migraine disease and treatment. https://www.mayoclinic.org/diseases-conditions/migraine-headache/diagnosis-treatment/drc-20360207 (last accessed October 2021).

Abbvie – Offering solutions for every migraine patient.

Acute treatment

UBRELVY®
(ubrogepant) tablets 50mg 100mg

Preventive treatments

AQUIPTA™
(atogepant) tablets

BOTOX® 50U 100U 200U
Botulinum Toxin Type A

* Indicated for chronic migraine only

1. Ubrelvy Prescribing information. 2. Aquipta Prescribing Information 3. Botox Prescribing information

Introducing UBRELVY® for acute treatment for migraine

UBRELVY® is indicated for the acute treatment of migraine with or without aura in adults[1]

UBRELVY® was the first drug in the Gepant class to receive FDA approval for the acute treatment of migraine[1]

UBRELVY® is a Gepant that blocks the binding of CGRP to it's receptor[1] and, therefore, antagonises CGRP receptor function[1]

10 NOW AVAILABLE PACK

1. Ubrelvy Prescribing information

Impact of UBRELVY® on pain associated with migraine up to 24 hours after dose, compared with placebo

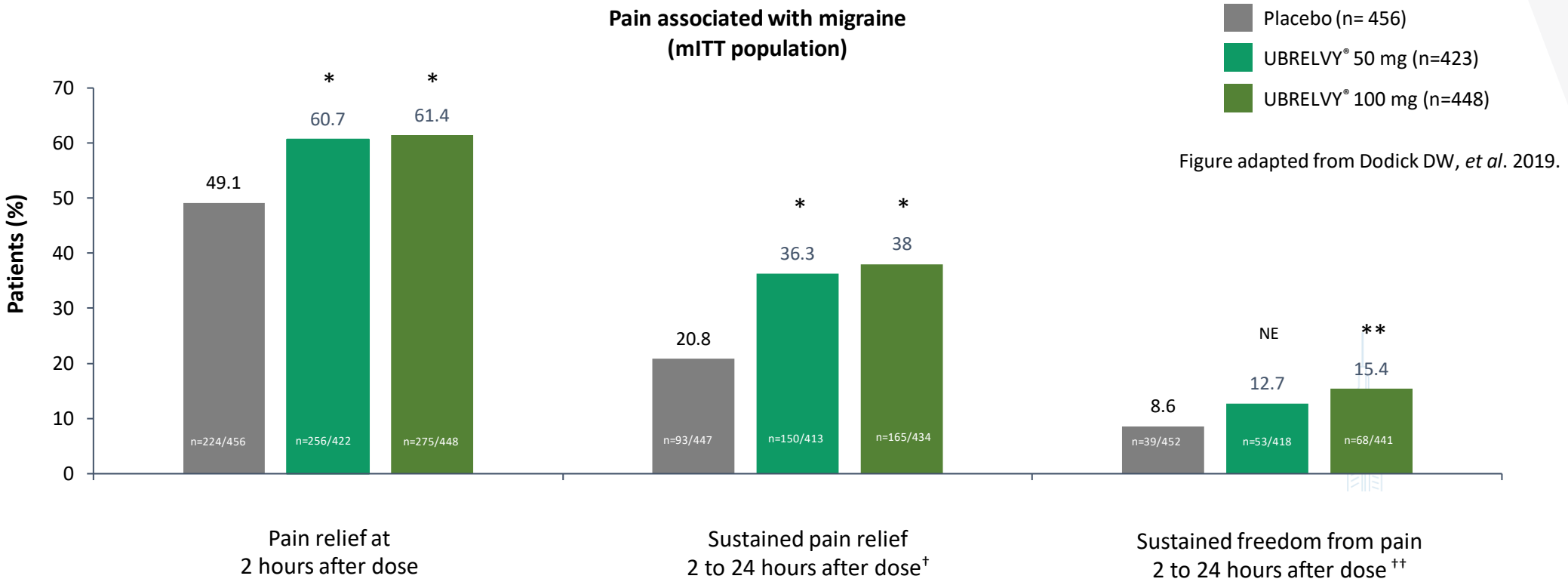


Figure adapted from Dodick DW, *et al*. 2019.

GEPANTS ACUTE TREATMENT LANDSCAPE

	Ubrogepant	Rimegepant
Acute treatment of migraine with or without aura[1-2]	✓	✓
Oral administration[1-2]	✓	✓
Optional second dose[1-2] **(For Unpredictable / Persistent attacks)**	✓	✗
Multiple dosing strengths available[1-2] **(Tailored approach for different patitents Profiles**	✓	✗
Prodrome clinical evidence[3]	✓	✗
studied in Combination with mABs CGRP RA and Botulinum Toxin	✓	✗

No conclusion regarding comparative safety or efficacy can be drawn from this information

1. Ubrelvy Prescribing Information. 2. Nurtec Prescribing Information. 3. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the acute treatment of migraine when administered during the prodrome (premonitory phase): results from a phase 3, randomized, double-blind, placebo-controlled, crossover study. Abstract presented at: 2023 AAN Annual Meeting; April 22-27, 2023; Boston, MA.

~70% of People With Migraine Reported Experiencing Prodrome Symptoms of a Migraine Attack1,2

In a US study of approximately 2000 people with migraine[2]

UBRELVY Has Been Studied in Patients With Migraine Who Recognized Prodrome Symptoms of a Migraine Attack 1 to 6 Hours Before the Headache Phase[1]

During the screening period,

77% of patients (n=911)

reliably identified their prodrome symptoms‡

The 5 most common pre-headache symptoms experienced during the screening period were§:

- **57%** Sensitivity to light
- **50%** Tiredness/sleepiness/fatigue
- **42%** Neck pain/stiff neck
- **34%** Sensitivity to sound
- **28%** Dizziness/light-headedness/vertigo/imbalance

*Other pre-headache symptoms may include irritability, yawning, increased need to urinate, food cravings, difficulty speaking or reading, nausea, visual disturbances, numbness and tingling. Pre-headache symptoms may vary between individuals and from attack to attack.[1]

1. American Migraine Foundation. Published January 18, 2018. Accessed February 2023. https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/ 2. Lipton RB, et al. Poster presented at: 64th Annual Scientific Meeting of the American Headache Society, June 9-12, 2022; Denver, CO.

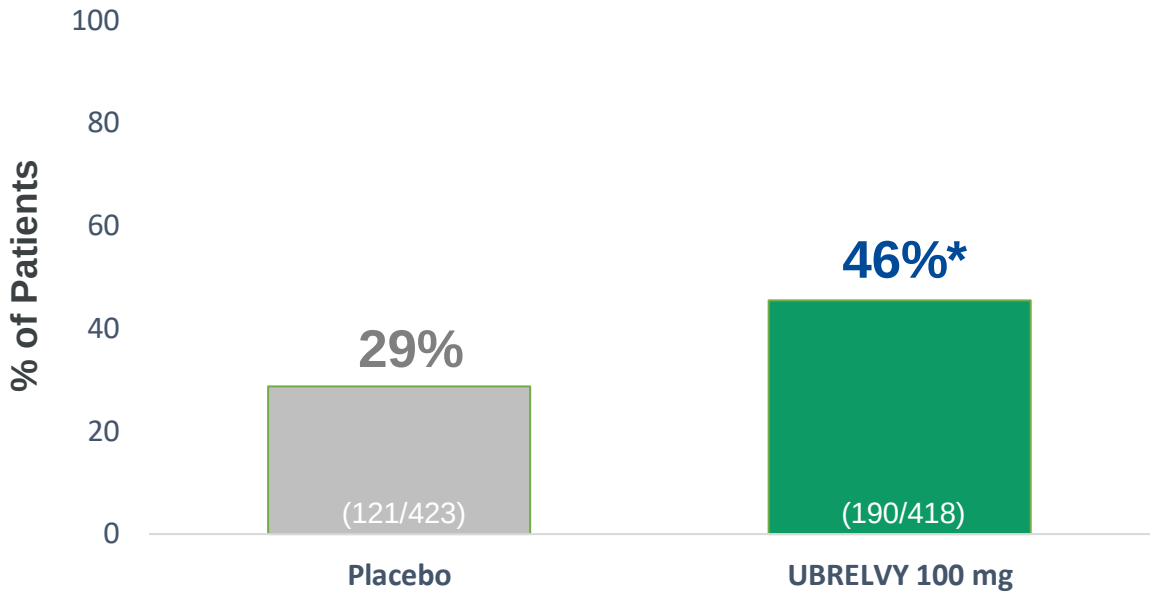
‡77% value based on 911 participants who had evaluable data. Of the 1087 patients who were screened for eligibility, 290 failed screening due to qualifying event criteria, including investigator judgment.

§Based on 920 participants who entered eDiary data and includes a total of 4802 qualifying events during the screening period.[1]

1. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the acute treatment of migraine when administered during the prodrome (premonitory phase): results from a phase 3, randomized, double-blind, placebo-controlled, crossover study. Abstract presented at: 2023 AAN Annual Meeting; April 22-27, 2023; Boston, MA.

Prodrome: Trial Results[1]

Absence of Moderate to Severe Headache Pain
Within 24 Hours After Dosing



Limitation: This study evaluated a subset of the migraine population who could reliably predict the onset of a migraine attack (per clinician judgment) within a short time window. Patients should be carefully assessed on their ability to accurately predict the onset of a migraine attack and progression to the headache phase.

mITT=477 participants. The mITT population consists of all randomized participants with at least 1 assessment of headache occurrence within 24 hours after taking double-blind study intervention for at least 1 qualifying event during the double-blind treatment period.

*P<0.0001 vs placebo.

1. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the acute treatment of migraine when administered during the prodrome (premonitory phase): results from a phase 3, randomized, double-blind, placebo-controlled, crossover study. Abstract presented at: 2023 AAN Annual Meeting; April 22-27, 2023; Boston, MA.

In addition to the primary endpoint, all three secondary endpoints met statistical significance:

- Absence of moderate/severe headache within 48 hours
- Ability to function normally over 24 hours post dose
- Absence of any intensity headache within 24 hours post dose

mITT=477 participants. The mITT population consists of all randomized participants with at least 1 assessment of headache occurrence within 24 hours after taking double-blind study intervention for at least 1 qualifying event during the double-blind treatment period.

*TEAEs reflect any adverse events reported within 48 hours after taking UBRELVY or placebo.

TEAEs=treatment emergent adverse events.

1. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the acute treatment of migraine when administered during the prodrome (premonitory phase): results from a phase 3, randomized, double-blind, placebo-controlled, crossover study. Abstract presented at: 2023 AAN Annual Meeting; April 22-27, 2023; Boston, MA.

AQUIPTA: Only Oral Gepant for Preventing of Both Episodic and Chronic Migraine

RECOMMENDED DOSES[1]

The recommended dosage of AQUIPTA for episodic and Chronic migraine is **60 mg** taken once daily.[1]

No injections[1]
No titration needed
Taken orally, with or without food[1]
One Pill, Once a Day1

AQUIPTA PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE

- **1 to 2 hours** time to peak plasma concentrations (T_{max})[1]
- **11 hours** elimination half-life[1]
- **AQUIPTA 60 mg was designed to block CGRP receptors for 24 hours**—pharmacologically active plasma concentrations maintained for 24 hours[2]*

The clinical significance of these data is not known.

*Based on the steady state inhibition of human capsaicin-induced dermal vasodilation, a pharmacodynamic measure of CGRP blockade, EC_{90}=13.6 nM.

Please see full Prescribing Information for Usage and Dose Modifications for Drug Interactions and Use in Specific Populations.

EC_{90}=the 90% maximal effective concentration.

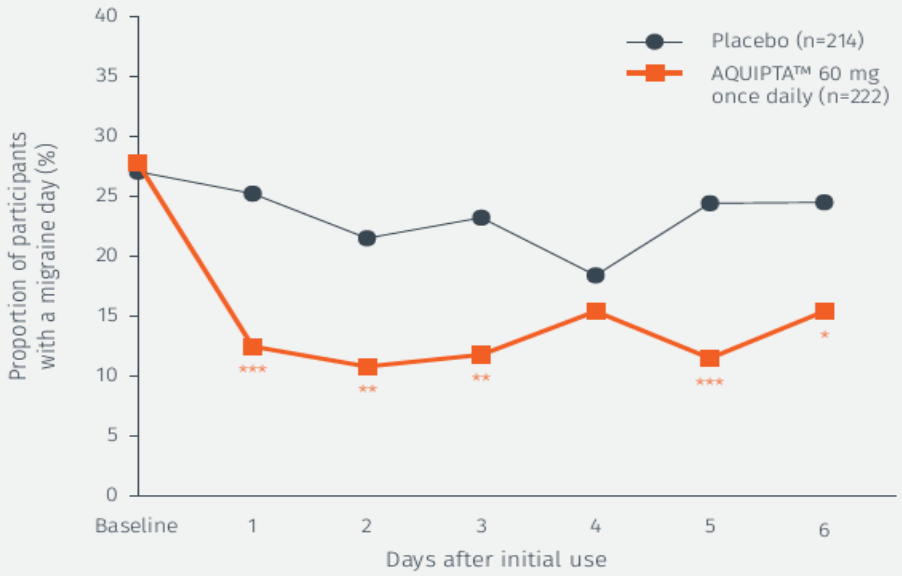
1. ae-atogepant60mgtablets-spc-august 2023 (v1.0)
2. Banerjee P, et al. Poster presented at: CGRP 2022 10th International CGRP Family Peptides Conference; April 11-12; Virtual.

AQUIPTA offers prevention Starting Day 1

CHOOSE PREVENTIVE MEDICATION THAT IS QUICK

IN THE ADVANCE STUDY, AQUIPTA™ OFFERS THE POSSIBILITY OF MIGRAINE-FREE DAYS AS EARLY AS DAY 1

Proportion of participants with a migraine each day during the first week of treatment (mITT population)[a1]



Adapted from Schwedt TJ, et al.[1]

*p<0.05; **p<0.01; ***p<0.001.

AQUIPTA™ - once daily demonstrated treatment benefits with significant reductions as early as:[1]

Day 1
AFTER THE FIRST DOSE[†]

87.7%
of patients treated with AQUIPTA™ **did not have a migraine.**

[†] Day 1 data: 12.3% of AQUIPTA™ 60 mg patients had a migraine day vs. 25.2% of placebo patients.

Week 1
SIGNIFICANT REDUCTION[§]

54%
migraine day reduction from baseline with AQUIPTA™

VS.

15%
with placebo

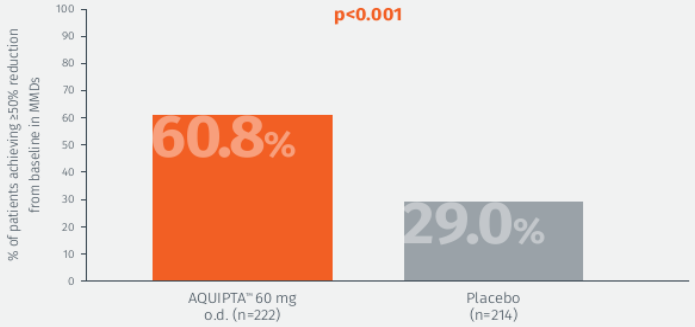
[§] Week 1 AQUIPTA™ 60 mg: Baseline Weekly migraine days was 1.9; change from baseline: -1.03. Week 1 placebo: Baseline Weekly migraine days was 1.9; change from baseline: -0.29.

[a] Day 0 excluded, as migraine attacks occurring prior to study drug administration were included

Effective Prevention for EM and CM Patients who still search of control over Migraine:

AQUIPTA™ ACHIEVED MORE MIGRAINE-FREE DAYS VS. PLACEBO ACROSS 12 WEEKS*[1]

Proportion of patients achieving a ≥50% reduction from baseline in mean MMDs across 12 weeks treatment [1]



Adapted from Ailani J, et al. N Engl J Med. 2021;385:695–706.

Migraine-free days across 12 weeks

60.8%

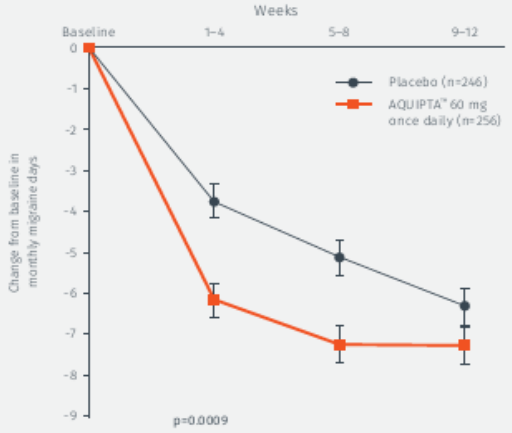
of participants treated with AQUIPTA™ responded with a ≥ 50% reduction in MMDs. (odds ratio: 3.8; 95% CI: 2.6–5.7)[1]

* AQUIPTA™ was evaluated for the prophylaxis of migraine in patients with 4–14 migraine days per month. The ADVANCE study enrolled patients who met ICHD criteria for a diagnosis of migraine with or without aura. Patients with myocardial infarction, stroke, or transient ischaemic attacks within 6 months prior to screening were excluded.[1,2]

AQUIPTA™ THE ONLY CGRP APPROVED FOR CHRONIC MIGRAINE PATIENTS

CHOOSE MIGRAINE PREVENTION THAT'S EFFECTIVE[1]*

Change from baseline in mean monthly migraine days across 12 weeks[1]



Placebo (n=246): -5.1 days from 18.9 baseline

AQUIPTA™ 60 mg o.d. (n=256): -6.8 days from 19.2 baseline

Adapted from Pozo-Rosich P, et al. Lancet. 2023;402(10404):775-785.

mITT population.

MEAN DIFFERENCE FROM PLACEBO: -1.8 DAYS (95% CI: [-2.9]–[-0.8])

35.4%

significant reduction from baseline in mean monthly migraine days for patients receiving AQUIPTA™ across 12 weeks treatment[1]

vs.

26.8%

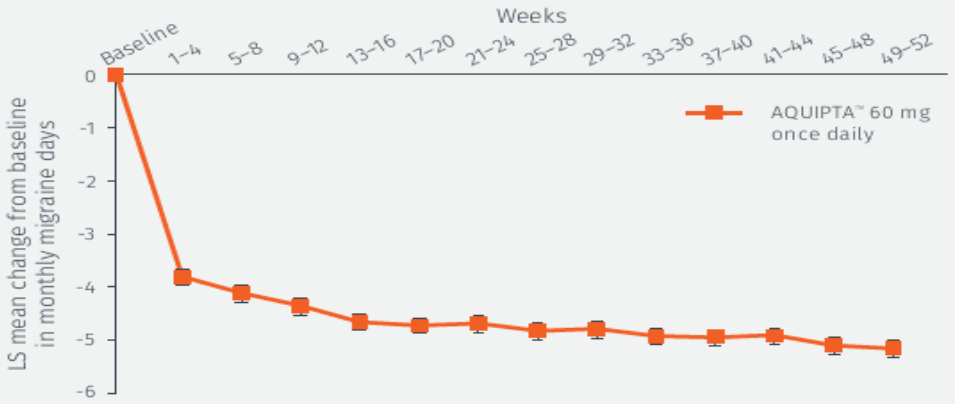
with placebo

* AQUIPTA™ was evaluated for the prophylaxis of chronic migraine. The chronic migraine study (PROGRESS) enrolled patients who met ICHD criteria for chronic migraine. Patients with myocardial infarction, stroke, or transient ischaemic attacks within 6 months prior to screening were excluded.[1]

AQUIPTA provide Sustained reduction of MMDs and AMDs over 52 weeks

CHOOSE MIGRAINE PREVENTION THAT'S SUSTAINED*[1]

Change from baseline in mean monthly migraine days across 1 year[1]



Adapted from Ashina M. et al. Headache. 2023;63(1):79-88.

* Data from an open-label safety study that randomised 744 patients 5:2 to receive either AQUIPTA™ 60 mg (n=546) or standard of care migraine prevention medication (n=198). Adults from the previous Phase 2b/3 trial, who re-established study eligibility, and de novo patients were included. Participants had 4–14 migraine days in the 28-day baseline period. Efficacy measures, changes from baseline in least squares mean monthly migraine days, moderate/severe headache days, mean monthly acute medication use days and the proportion of responders based on reductions in monthly migraine days and evaluated using the mITT population (n=521 AQUIPTA™-treated patients) and a mixed-effects model for repeated measures. Efficacy endpoints for long-term efficacy evaluation were not classified as primary, secondary, or additional endpoints. Clinical efficacy outcomes were only collected from the AQUIPTA™ arm by electronic diary (eDiary) data.[1]

Reduction in migraine days over 52 weeks was consistent with AQUIPTA™ [1]

WEEKS 1-4
52.1%
reduction vs. baseline
AQUIPTA™ 60mg: **3.8** fewer mean monthly migraine days (from **7.3** baseline)[1]

→

WEEKS 49-52
71.2%
reduction vs. baseline
AQUIPTA™ 60mg: **5.2** fewer mean monthly migraine days (from **7.3** baseline)[1]

A reduction in the use of acute medication was also observed with AQUIPTA™ [1]

WEEKS 1-4
61%
reduction vs. baseline
The mean number of monthly acute medication use days was reduced by **4.0 days** at weeks 1–4 from baseline **6.6 days.**

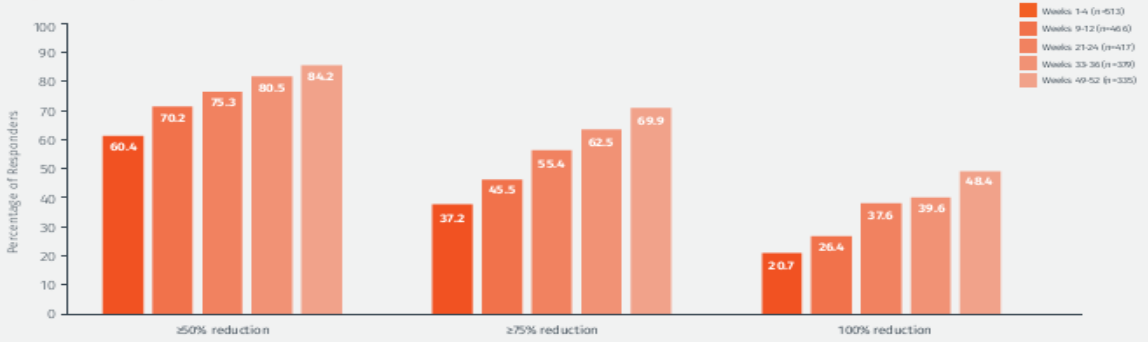
→

WEEKS 49-52
74%
reduction vs. baseline
AQUIPTA™ 60 mg showed a reduction of **4.9** acute medication use days per month from baseline **6.6 days.**

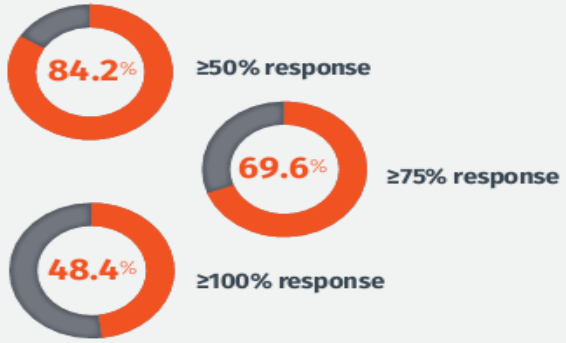
AQUIPTA Offer a chance of Migraine Freedom up to 100% Reduction of MMDs

AQUIPTA™ PROVIDED THE CHANCE MIGRAINE FREEDOM IN APPROXIMATELY HALF OF ALL PARTICIPANTS WITHIN 1 YEAR[1]

Proportion of responders with ≥50%, ≥75%, and 100% reduction in monthly migraine days (mITT population)[1]

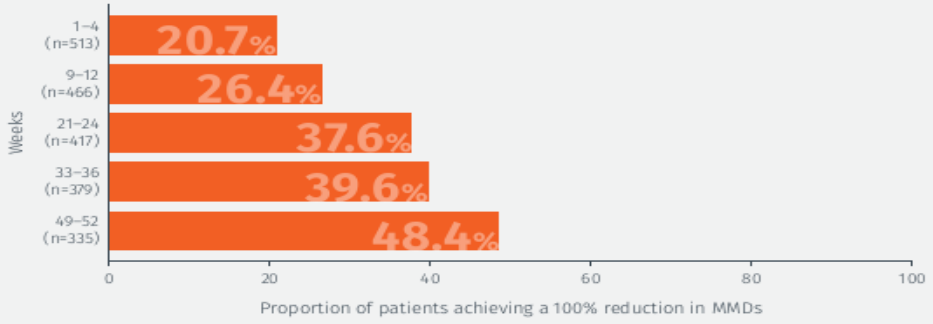


Response to atogepant at 1 year



OFFER YOUR PATIENT THE CHANCE OF GETTING FREE MIGRAINE DAYS WITH 100% REDUCTION[1*]

Proportion of patients achieving 100% reduction from baseline in MMDs across 52 weeks treatment[1]



Adapted from Ashina M, et al. Headache. 2023;63(1):79–88.

In patients who completed the treatment period:

48.4%

of patients (162/335) receiving AQUIPTA™ 60 mg o.d. experienced migraine freedom, or 100% response in Weeks 49–52[1]

* Data from an open-label safety study that randomised 744 patients 5:2 to receive either AQUIPTA™ 60 mg (n=546) or standard of care migraine prevention medication (n=198). Adults from the previous Phase 2b/3 trial, who re-established study eligibility, and de novo patients were included. Participants had 4–14 migraine days in the 28-day baseline period. Efficacy measures, changes from baseline in least squares mean monthly migraine days, moderate/severe headache days, mean monthly acute medication use days and the proportion of responders based on reductions in monthly migraine days and evaluated using the mITT population (n=521 AQUIPTA™-treated patients) and a mixed-effects model for repeated measures. Efficacy endpoints for long-term efficacy evaluation were not classified as primary, secondary, or additional endpoints. Clinical efficacy outcomes were only collected from the AQUIPTA™ arm by electronic diary (eDiary) data.[1]

AQUIPTA Safety Profile.

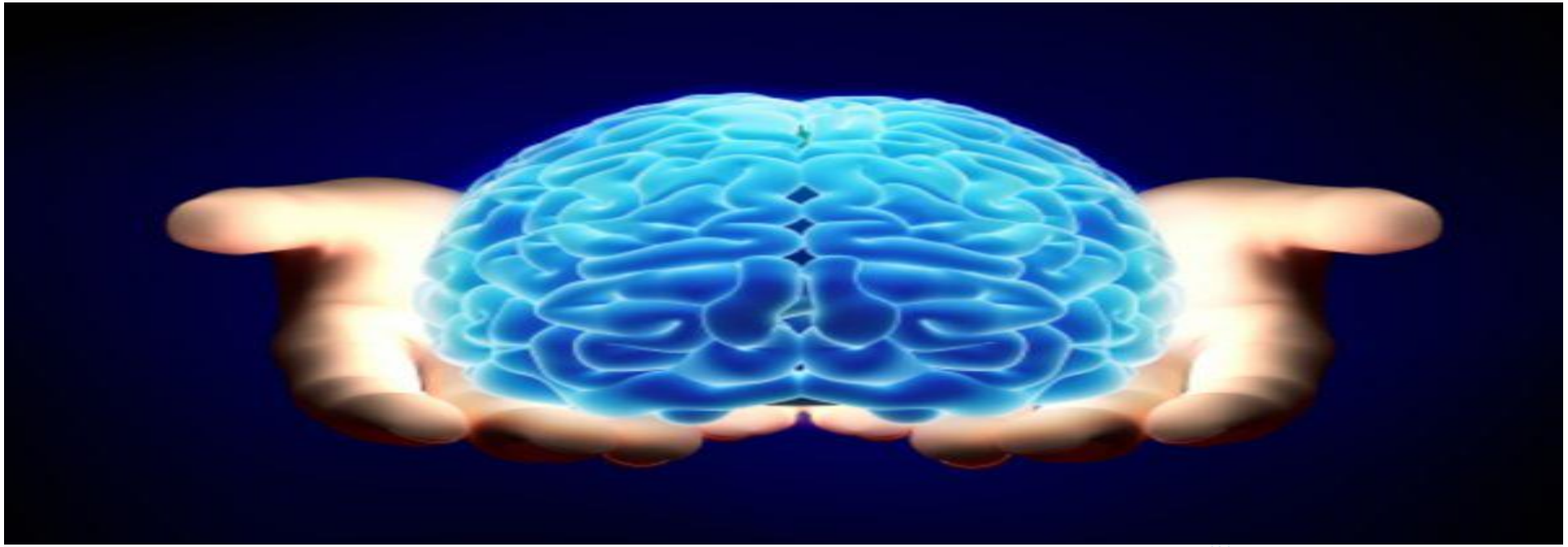
AQUIPTA™ IS WELL TOLERATED ACROSS PATIENTS[1]

The safety of AQUIPTA™ was evaluated in 2,657 patients with migraine who received at least one dose of AQUIPTA™.[1]

Of these, 1,225 patients were exposed to AQUIPTA™ for at least 6 months and 826 patients were exposed for 12 months.*[1]

- The most commonly reported adverse drug reactions were **nausea (7%), constipation (7%) and fatigue/somnolence (5%)**[1]
- The majority of cases were **mild, and none were serious**[1]
- The adverse reaction that most commonly led to **discontinuation** was nausea **(0.6%)**[1]

* In 12-week, placebo-controlled clinical studies, 678 patients received at least one dose of AQUIPTA™ 60 mg once daily, and 663 patients received placebo.[1]



Thanks

شـــكـــراً

Shukran