Clinical Medicine 2015 Vol 15, No 4: 344–50

Integrated care for chronic migraine patients: epidemiology, burden, diagnosis and treatment options

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ABSTRACT

Migraine is a common neurological disorder, characterised by severe headaches. Epidemiological studies in the USA and Europe have identified a subgroup of migraine patients with chronic migraine. Chronic migraine is defined as ≥15 headache days per month for ≥3 months, in which ≥8 days of the month meet criteria for migraine with or without aura, or respond to treatment specifically for migraine. Chronic migraine is associated with a higher burden of disease, more severe psychiatric comorbidity, greater use of healthcare resources, and higher overall costs than episodic migraine (<15 headache days per month). There is a strong need to improve diagnosis and therapeutic treatment of chronic migraine. Primary care physicians, as well as hospital-based physicians, are integral to the identification and treatment of these patients. The latest epidemiological data, as well as treatment options for chronic migraine patients, are reviewed here.

KEYWORDS: Chronic migraine, chronic daily headache, primary care, onabotulinumtoxinA, preventive treatment

Introduction

Migraine is a common neurological disorder, characterised by severe headache attacks that may be debilitating.[1,2] Migraine attacks usually include unilateral headache of a pulsating character, increasing in intensity with physical activity, and often sensitivity to light and sound as well as nausea and vomiting.[3]

Migraine can be incapacitating, and is associated with low health-related quality of life (HRQoL) and high economic burden.[4] Epidemiological studies in the USA and Europe have identified a subgroup of migraine patients with the variant of chronic migraine.[5,6] The International Classification of Headache Disorders (third edition, revised (ICHD-3)) defines chronic migraine as ≥15 headache days per month for ≥3 months, in which ≥8 days per month meet criteria for migraine with or without aura, or respond to treatment specifically for migraine.[1] Phenotypically, migraine features may change with the transition from less-frequent episodic migraine to chronic migraine. Patients with chronic migraine more often have bilateral headache, and their associated symptoms are not as pronounced as they are for those with episodic migraine.[7]

A recent US study showed that, of patients who meet the criteria for chronic migraine, only 20% are properly diagnosed.[8] Treatment options are available for these patients, but only if the patients are properly identified.[9] Once a patient is diagnosed, physicians can focus on eliminating or minimising exacerbating factors and optimising treatment, and thus substantially reduce the global burden of chronic migraine.[10,11]

Optimised treatment of patients with chronic migraine is relatively straightforward, because few agents have proved effective in this population in randomised controlled trials. While some prophylactic medications used for episodic migraine may anecdotally work in chronic migraine, there is a dearth of evidence to support the use in practice. Randomised, placebo-controlled trials have shown that topiramate and onabotulinumtoxinA (BOTOX®) are effective in the prophylaxis of chronic migraine and are superior to placebo.[9] These new preventative treatment options can help chronic migraine patients.

Most patients with *de novo* migraine will make an appointment with their general practitioner as their first point of contact for receiving proper diagnosis, to exclude secondary headache and, if needed, for sufficient attack treatment and medical prophylaxis. Episodic migraine may be appropriately and adequately managed in primary care; however, refractory or chronic patients should be referred to a headache specialist with expertise in the management of difficult-to-treat headache disorders to confirm the diagnosis and begin treatments for chronic migraine patients. A systematic approach to the diagnosis of chronic migraine is warranted and has been proposed: (i) exclude a secondary headache disorder, and (ii) diagnose the primary headache syndrome based on frequency and duration.[12] Many patients with chronic migraine have comorbid depression and anxiety, other chronic pain conditions, and sometimes overuse medications.[13,14] These aggravating factors have to be identified and treated systematically as well. Thus, it is important for primary care physicians and hospital-based physicians to play an integral role in chronic migraine care.

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Methods

The authors used the results of an extensive and systematic literature search for a review published in *Nature Reviews Neurology*[9] as the basis for this review. PubMed literature search terms included: 'chronic migraine', 'headache', 'transformed migraine', 'chronic daily headache' and 'epidemiology', 'diagnosis', 'burden', and 'treatment approaches'. The search was limited to human studies and publications written in English, with no restrictions on publication date. Results were further limited to studies focusing on information that is relevant to primary care and hospital-based physicians.

Diagnosis of chronic migraine

Proper diagnosis of chronic migraine is important; the recognition of chronic migraine and its initial diagnosis is the responsibility of the physician who is first consulted by the patient. The recent ICHD-3 criteria define chronic migraine as headache on 15 or more days per month over more than 3 months. The headache on more than 8 of these days should meet the criteria for migraine with or without aura and/or should respond to migraine drug treatment,[1] and a secondary cause for chronic headache must have been ruled out.[3,15] A differential diagnosis includes consideration of the following primary headache disorders: chronic tension type headache, hemicrania continua, and new daily persistent headache.[15] Taking a careful history, performing a thorough examination and, when required, diagnostics (eg cerebral magnetic resonance imaging and lumbar puncture) are recommended to exclude secondary causes of chronic headache.[16,17]

The previous version of the International Headache Society (IHS) classification (ICHD-2) noted that medication overuse should be excluded when chronic migraine is diagnosed.[3,15] However, this diagnostic classification often does not apply in the clinical setting. Therefore, Silberstein and Lipton proposed another concept, considering chronic migraine in patients with more than 15 headache days a month and a history of migraine, with or without medication overuse.[1,12] The new IHS classification (ICHD-3), published in 2013, notes that, when a patient is found to overuse medication, diagnoses of both chronic migraine and medication-overuse headache should be given.[1] The establishment of a set of simple diagnostic criteria to aid in identifying chronic migraine patients who will benefit from preventive treatment is useful for clinical practice.[8,18] Thus, modified criteria for diagnosis of chronic migraine, as shown in Table 1,[1] should enable easier diagnosis and may be more realistic for clinical use.[3]

All patients presenting with a history of headache should be assessed for migraine and chronic migraine. Patients often do not recall how many headache days they experience per month, and in most cases they will need to write in a headache diary to capture this information and to identify the number of days with migraine headache. When a patient cannot recall the number of headache days, it might be helpful to ask: 'How many days are you headache free?' or 'Do you feel like you have a headache more often than not?'.[12] It may be useful to ask the patient: 'Do you have any completely headache-free days? If yes, how many per month?'. Patients should be instructed to keep a daily diary that captures headache frequency, severity (with an instruction to include mild headaches), associated symptoms, duration, headache-related disability and acute headache medications.[19] These headache diaries should include a column for pain intensity and one for 'no headache', which will be marked for headache-free days.

A history of episodic migraine is found in many patients with chronic migraine, and many overuse acute headache medications.[20–22] Population- and clinic-based studies have identified several risk factors for chronification from episodic to chronic migraine. These risk factors include: obesity, comorbid depression and anxiety, history of frequent headache (>1 per week), caffeine consumption and medication overuse (ie acute medication such as analgesics, ergots and triptans on more than 10 days per month),[16,21,23] specifically, non-steroidal anti-inflammatory drugs (NSAIDs) or ergots on 15 or more days per month or more and triptans on 10 or more days per month.[14] It is important for the physician to identify patients at risk of chronification, to enable early therapeutic intervention. Once a diagnosis of chronic migraine is made, a treatment plan can be developed. This includes the referral of the patient to a headache specialist, as well as a careful follow-up with the patient in the clinic. Treatment planning will be further discussed in a later section of this review.

Table 1. Simplified criteria for chronic migraine diagnosis.[1]

Headache feature	Duration
Headache days	≥15 days/month
Headache days linked to migraine	≥8 days/month
Headache duration	≥4 hours/day

Epidemiology and the burden of chronic migraine

Overall, approximately 12% of the population suffers from migraine, affecting significantly more women than men.[24] Compared with the overall prevalence of migraine, chronic migraine is not as common as episodic migraine; prevalence is estimated at 0.9% to 2.2% among the general population.[5,25] However, chronic migraine is frequently seen in headache centres. Worldwide, up to 45% of patients presenting to headache clinics have daily or near-daily headaches.[26–33] Therefore, chronic migraine should be understood as a disabling, underdiagnosed and undertreated disorder.[8]

HRQoL is considered to be important for determining the burden of a condition,[34] and different patient questionnaires can evaluate this measure.[35,36] To assess the burden of disease and functioning in daily activities, the Migraine Disability Assessment (MIDAS) or the Headache Impact Test-6 (HIT-6™) can be used in the clinical setting for both episodic and chronic migraine patients.[37,38] Both of these measures are validated questionnaires, available in numerous languages, that may be used in the office to measure the burden of disease and may detect changes during a course of treatment. Chronic migraineurs have been shown to have significantly more severe disability (MIDAS grade IV) compared with episodic migraineurs (78 vs 23%; p=0.001),[4] demonstrating the large burden that chronic migraine places on the patient.

The results of the International Burden of Migraine Study (IBMS) demonstrated that patients with chronic migraine had lower HRQoL than those with episodic migraine.[4] Persons with chronic migraine are also more likely to suffer from severe disability, such as inability to work, attend social functions, and perform routine chores.[4] The American Migraine Prevalence and Prevention (AMPP) Study also sheds light on the burden of chronic migraine: compared with those with episodic migraine, chronic migraineurs miss nearly three times as many family activities due to headache.[8] Nearly 60% of chronic migraineurs report reduced household work productivity for 5 or more days over 3 months.[8] Nearly 75% of chronic migraineurs reported that headache symptoms negatively affected their work. Furthermore, patients with chronic migraine reported working at approximately half of their full effectiveness when experiencing headache symptoms; and migraine adversely affects attendance and increases absenteeism. Patients with chronic migraine missed more days and had more days where their productivity was reduced due to headache than those with episodic migraine.[39] As a result, chronic migraine has an enormous socio-economic impact.[4,40,41] The IBMS showed that chronic migraine patients in the USA visit primary care physicians two times more often than episodic migraine patients (48 vs 26.4%).[4,40,41] Chronic migraineurs are significantly more likely to visit accident and emergency (A&E) and their primary care physician than patients with episodic migraine.[4,40,41] This has a wider effect on the healthcare system. In a recent study of chronic and episodic migraine medical costs in five European countries, including the UK, France, Germany, Italy and Spain, patients with chronic migraine had greater disability and more prevalent psychiatric disorders compared with those with episodic migraine.[42] Chronic migraine participants also had more visits to healthcare providers, A&E, and hospitals, and more diagnostic tests. Additionally, medical costs were three times higher for patients with chronic migraine than for those with episodic migraine.[42]

Several neurological and medical comorbidities are common among persons with chronic migraine,[18,43–46] such as obesity, ischaemic stroke, cardiovascular disease, sleep disorders, chronic pain disorders, frequent low back pain, asthma and allergic rhinitis.[43–46] These comorbidities can influence the effects of migraine and impact disease prognosis, treatment and clinical outcomes.[18,47] Prevalence of psychiatric comorbidities, including depression, anxiety, and post-traumatic stress disorder (PTSD), is higher in patients with chronic migraine than in those with episodic migraine.[48–51] Furthermore, there is a linear relationship between the number of headache days and the degree of depression and anxiety measured by questionnaires. When the number of headache days reaches the chronic variant, the linearity is lost and all patients suffer from a high impact of psychiatric impairment.[52]

Treatment options

It is common practice for many physicians to prescribe preventive medications for chronic migraine that are approved/recommended for episodic migraine (eg beta-blockers).[53] However, there are new treatment options in this area that deserve attention and can improve patients' quality of life.[9] For frequent migraine, preventive treatments should be used.[19]

Table 2. Recommended preventive treatment in episodic and chronic migraine.[54–66]

Episodic migraine	Chronic migraine
Antiepileptic drugs	Antiepileptic drugs
– Valproate	– Topiramate
– Topiramate	
Antidepressants	Botulinum toxins
– Amitriptyline[a]	– OnabotulinumtoxinA (BOTOX®)
Beta-blockers	
– Metoprolol	
– Propranolol	
Calcium channel blocker	
– Flunarizine	

[a]additional evidence is needed; however, in a subgroup analysis of 58 subjects who had headaches ≥17 days/month (fitting Silberstein–Lipton criteria), more patients taking amitriptyline than placebo showed ≥50% improvement in headache frequency at 8 and 16 weeks. Amitriptyline might be helpful for comorbidity in patients treated with other chronic migraine therapies.[78]

Most recommended drugs have proven efficacy only in episodic migraine (Table 2).[54–66] The only oral medication that has been assessed in chronic migraine is topiramate.[63,64] In randomised, double-blind, placebo-controlled trials, topiramate was effective for preventive treatment of chronic migraine, even in patients with medication overuse. In chronic migraine patients, topiramate treatment resulted in a statistically significant mean reduction of migraine/migrainous headache days versus placebo.[63,64] MIDAS questionnaires also showed improvement with those taking topiramate compared with those receiving placebo.[63] OnabotulinumtoxinA (BOTOX) is the only therapy specifically approved for the prophylaxis of headache in adults with chronic migraine,[67] based on evidence from the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT I and II) clinical trials, the largest trials in chronic migraine patients.[61,62,68] In PREEMPT, onabotulinumtoxinA reduced multiple symptom dimensions, such as headache days and episodes, migraine days and episodes, total cumulative hours of headache and headache severity.[61,62,68] In addition, onabotulinumtoxinA significantly reduced headache-related disability and significantly improved functioning and quality of life.[69] It demonstrated a clinically significant decline in disability as measured by HIT-6 scores that were above 2.3, the established clinically meaningful between-group minimally important difference.

HRQoL is often measured by the Migraine-Specific Quality of Life questionnaire (MSQ), a 14-item questionnaire designed to measure the ways that migraines affect or limit patients' daily performance over the preceding 4 weeks across three domains: role restrictive (RR), role preventive (RP), and emotional function (EF). Specifically, RR assesses how migraines limit daily social- and work-related activities, RP measures how migraines prevent these activities, and EF gauges the emotions associated with migraine. In PREEMPT, onabotulinumtoxinA

treatment also improved quality of life for each of the three MSQ functional domains: RR, RP and EF.[69]

The PREEMPT trials were criticised for including patients who were suffering from medication overuse. However, headache classification has recently changed. The current ICHD-3 (beta) recommends making the diagnosis of medication overuse in addition to chronic migraine.[1] Moreover, the PREEMPT studies, as well as the clinical experiences after approval, revealed that therapy with onabotulinumtoxinA is not less effective in patients suffering from medication overuse.[70] In addition, it has been noted that the significant difference between the onabotulinumtoxinA group and the placebo group in the PREEMPT trials was only moderate at the end of the treatment period. However, the open-label extension of the studies showed increasing efficacy over time.[71] It is important to note that most of the patients with chronic migraine were refractory to first-line prophylaxis before they were treated with onabotulinumtoxinA. PREEMPT was designed to compare onabotulinumtoxinA with placebo, with regulatory purposes in mind. In real life, the placebo effect is added to the drug effect. Therefore, the results seen with onabotulinumtoxinA are impressive for this severely affected population.

In a recent, real-life prospective study, 254 adults with chronic migraine were injected with onabotulinumtoxinA following the PREEMPT protocol. OnabotulinumtoxinA significantly reduced the number of headache and migraine days, increased the number of headache-free days, and improved patients' quality of life in a real-life clinical setting. These results among patients seen in a typical tertiary headache centre support the findings of the PREEMPT clinical programme.[72]

A headache specialist or neurologist with experience in prescribing and injecting onabotulinumtoxinA should treat patients with chronic migraine. Choice of medication (onabotulinumtoxinA, topiramate or other preventive medication – Table 2) should be made while taking concomitant diseases into account. It is also important to follow requirements for reimbursement.

Practical approach to patient care: primary care and hospital-based physicians as point of care

The vast majority of chronic migraine sufferers (87.6%) had previously sought care from a health professional.[8] Most (73.6%) had consulted a physician at least once over the previous year. Most patients who had consulted a physician met with a primary care physician (80.1%). Neurologists were the second most commonly consulted physicians (41.6%). Of these patients, 26.9% saw headache or pain specialists.[8] Primary care or hospital-based physicians are the first point of care for patients, and should continue to manage patients after they have been referred to headache specialists.

In the case of chronic migraine, the headache specialist will confirm the diagnosis and decide on the appropriate therapy. It is important for all physicians who are treating the patient to understand the treatment plan, in order to monitor the patient's response to treatment. The physician's role in patient management should include monitoring as well as continual assessment of the patient's HRQoL (Fig 1). Physicians may want to stress the importance of compliance with the new

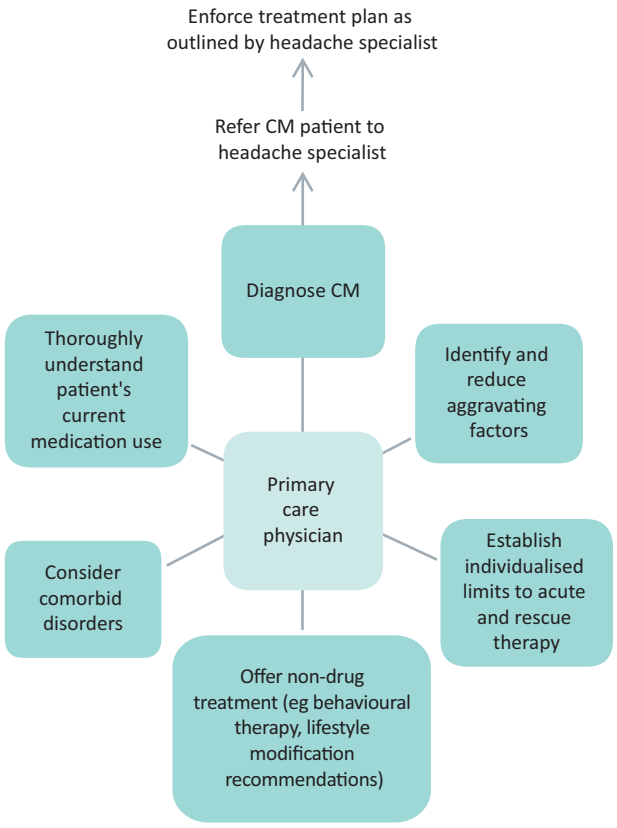

Fig 1. Primary care and the hospital-based physician's role in CM management. CM = chronic migraine.

treatment plan determined by the headache specialist and explain to patients that benefit occurs over time and cannot be expected immediately.[17] Preventive therapy for migraines may take up to 6 to 8 weeks to begin to demonstrate efficacy, and up to 6 months before full efficacy is established.[17] Patients receiving onabotulinumtoxinA therapy should be asked to fill out a headache diary and encouraged to continue at least two treatment cycles of onabotulinumtoxinA treatment before they decide whether the treatment is 'working'. In the PREEMPT clinical program, patients continued to improve after up to five injection cycles, and those who had five cycles had greater resolution of symptoms than those who stopped at three cycles.[73] Support and close follow-up are essential for patients, particularly in the first 3 months of treatment.

Additionally, physicians should try to identify and reduce aggravating risk factors, such as triggers of migraine or other behavioral habits that may have contributed to the patient's headaches.[74–76] Risk factors that may be modifiable through health interventions include obesity and medication overuse. It is important to control for concomitant medications the patients may be taking in addition to what was recommended by their headache specialist, to exclude undesirable pharmacological interactions. At each appointment, the goal should be to thoroughly understand the patient's current medication use; as many as 73% of chronic migraine patients

Box 1. Important components of chronic migraine management.

- Complete and correct diagnosis
- Referral to headache specialist/neurologist to confirm CM diagnosis and provide a treatment plan
- Management of overuse of acute headache pain medications; providing limits to acute and rescue therapy
- Patient education about CM and importance of treatment compliance
- Explaining realistic expectations to patients
- Consideration of important exacerbating factors
- Treatment of comorbid conditions
- Non-pharmacotherapy, including trigger management and behavioural therapy
- Monitoring of the patient's response to treatment plan (use of headache diary and HRQoL tools such as MIDAS and HIT-6)

CM = chronic migraine, HIT-6 = headache impact test-6; HRQoL = health-related quality of life; MIDAS = migraine disability assessment.

overuse acute headache medications.[20,22] It is important to establish limits to acute and rescue therapy. It is recommended that use of NSAIDs and triptans be limited to <15 days/month and <10 days/month, respectively; barbiturates and ergots should be avoided when possible in patients with frequent attacks.[77] It is also hoped that physicians can help patients to find a way to modify their response to stressful life events that may be contributing to their headaches.[7] Patients may also be encouraged to engage in regular exercise, establish regular mealtimes and sleep schedules, and limit or eliminate caffeine consumption. These lifestyle modifications can be beneficial for some patients.[16] Also, coexistent and comorbid medical disorders should be considered,[9] and physicians should address cases of depression, anxiety and sleep disturbances.[16] Thus, multimodal treatment concepts are superior to simple drug treatment in severely affected patients. Box 1 contains the key components of chronic migraine management for physicians.

Conclusion

Chronic migraine is associated with higher burden of disease, more severe psychiatric comorbidity, greater use of healthcare resources, and higher total costs than episodic migraine. Therefore, there is a strong need to improve diagnosis and therapeutic treatment of chronic migraine. Further studies are necessary, not only to provide supporting evidence for reduction in headache frequency, but also for impact on quality of life, psychiatric comorbidities, and resource allocation within the healthcare system. Easy-to-use standard questionnaires – such as MIDAS or HIT-6 – should be included in the assessment of chronic migraine patients, to determine the burden of disease and to evaluate the effects of prescribed therapy. Treatment should also take into consideration psychiatric and other comorbidities, which are more frequent in chronic than in episodic migraine patients. ■

Disclosures

HCD received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Addex Pharma, Allergan, Almirall, Autonomic Technologies, AstraZeneca, Bayer Vital, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Coherex, CoLucid, GlaxoSmithKline (GSK), Grünenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Medtronic, Menerini, Minster, MSD, Neuroscore, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brümmer, Sanofi, St Jude and Weber & Weber. Financial support for research projects was provided by Allergan, Almirall, AstraZeneca, Bayer, GSK, Janssen-Cilag, MSD and Pfizer. Headache research at the Department of Neurology in Essen is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF) and the European Union. HCD has no ownership interest and does not own stocks of any pharmaceutical company. DH has received a scientific grant from Grüenenthal. CG received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Desitin, Allergan, Boehringer Ingelheim, Berlin Chemie AG, MSD, Astellas, Complen Health, and St Jude. CG has no ownership interest and does not own stocks of any pharmaceutical company.

Acknowledgement

The authors would like to thank Allergan Inc, for funding editorial support in the preparation and styling of this manuscript by IMPRINT Publication Science (New York, NY, USA).

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