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Views and Perspectives

Chronic Migraine: An Update on Physiology, Imaging, and the Mechanism of Action of Two Available Pharmacologic Therapies

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Several lines of research support the hypothesis that migraine is a spectrum of illness, with clinical symptoms that vary along a continuum from episodic migraine to chronic migraine. Physiologic changes may result in episodic migraine evolving into chronic migraine over months to years in susceptible individuals. With chronification, headache frequency increases, becoming more disabling and less responsive to therapy. Neurophysiologic and functional imaging research has reported that chronic migraine may be associated with severity-specific metabolic, functional, and structural abnormalities in the brainstem. Without longitudinal studies, it is unclear whether these changes may represent a continuum of individual progression and/or are reversible. Furthermore, chronic migraine is associated with larger impairments in cortical processing of sensory stimuli when compared with episodic migraine, possibly caused by more pronounced cortical hyperexcitability.

Progressive changes in nociceptive thresholds and subsequent central sensitization due to recurrent migraine attacks in vulnerable individuals contribute to the chronic migraine state. This may result in changes to baseline neurologic function between headache attacks, evident in both electrophysiological and functional imaging research. Patients experiencing migraine chronification may report increased non-headache pain, fatigue, psychiatric disorders (eg, depression, anxiety), gastrointestinal complaints, and other somatic conditions associated with their long-term experience with migraine pain.

Recent research provides a foundation for differentiating episodic and chronic migraine based on neurophysiologic and neuroimaging tools. In this literature review, we consider these findings in the context of models designed to explain the physiology and progression of episodic migraine into chronic migraine, and consider treatment of chronic migraine in susceptible individuals. Advances in pharmacotherapy provide treatment options for chronic migraine. Of the currently available treatment options, only onabotulinumtoxinA and topiramate have received regulatory approval and have demonstrated efficacy in patients with chronic migraine, although the exact mechanisms of action are not fully elucidated.

Key words: chronic migraine, episodic migraine, pathophysiology, onabotulinumtoxinA, topiramate, literature review

Abbreviations: BOLD fMRI blood oxygen level–dependent functional magnetic resonance imaging, CAMERA Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis, CGRP calcitonin gene-related peptide, fMRI functional magnetic resonance imaging, GABA γ-aminobutyric acid, MEG magnetoencephalography, MRI magnetic resonance imaging, MSPA magnetic suppression of perceptual accuracy, PET positron emission tomography, PREEMPT

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Phase III REsearch Evaluating Migraine Prophylaxis Therapy, SNAP-25 synaptosomal-associated protein, SNARE soluble N-ethylmaleimide–sensitive factor attachment protein receptor, TMS transcranial magnetic stimulation, TRPA1 transient receptor potential cation channel ankyrin subfamily member 1, TRPV1 transient receptor potential cation channel vanilloid subfamily member 1, VAMP vesicle-associated membrane protein

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INTRODUCTION

Migraine is understood to be a spectrum of illness, consisting of episodic and chronic forms. Although chronic migraine typically progresses from episodic migraine, emerging epidemiologic evidence supports unique underlying physiology of the two migraine states.[1-3] In addition, regulatory agencies consider episodic and chronic migraine as unique indications, requiring separate regulatory approval.

In this review, we provide an update of a previous literature review on the physiologic mechanisms underlying chronic migraine, focusing on newly published research retrieved using several key search terms (eg, migraine, pathophysiology, mechanism of action; full list available upon request).[4] First, we examine new neurophysiologic and functional imaging studies that have revealed differences between episodic and chronic migraine, and provide insight into the underlying physiology of migraine in the brain. This research reaffirms our previous findings that the biology of migraine recapitulates the concept of a spectrum disorder with variations along the continuum.

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We then consider these findings in the context of models designed to explain the progression of episodic migraine into chronic migraine. We also briefly discuss new research on the mechanisms of action of two approved migraine prophylactic therapies, onabotulinumtoxinA for chronic migraine, and topiramate for migraine, and consider how these may impact migraine physiology and reduce the burden of illness for the patient. Although novel prophylactic treatments for chronic migraine are currently in development (eg, calcitonin gene-related peptide [CGRP] ligand and receptor targets), this review focuses on those with regulatory approval and demonstrated efficacy. These emerging treatments have been the subject of several recent reviews.[5,6]

MIGRAINE: THE CLINICAL SPECTRUM DISORDER

As initially suggested by Mathew et al over 30 years ago,[7] migraine is currently conceptualized as a continuum from episodic to chronic forms of migraine headache, whereby "chronic" indicates severity or patient-specific symptomatic burden, as opposed to duration of disease. Based on the current classification guidelines,[8] on one end of this continuum is episodic migraine and on the other end is chronic migraine, with variations in headache-day frequency and symptoms along the continuum (Fig. 1).[8,15,16]

Chronic migraine is the most common type of chronic daily headache seen by headache specialists.[17] Globally, approximately 2% of the population experiences chronic migraine; prevalence is 2.5- to 6.5-fold higher in women (1.7%–4.0%) than in men (0.6%–0.7%).[18] Approximately 3% of people with episodic migraine progress to chronic migraine each year;[19] the clinical progression typically occurs gradually, with increasing attack frequency over time.[19-21] However, in some patients, the progression may be abrupt.

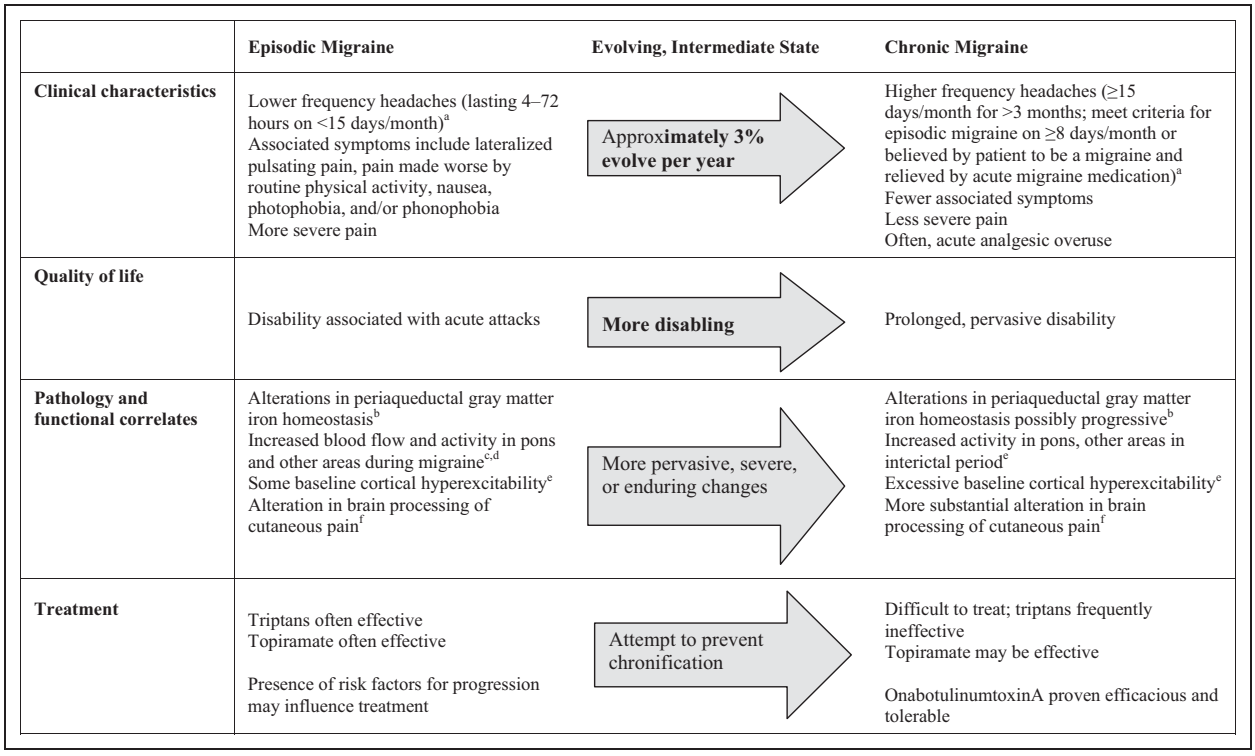

Fig. 1.—Overview of features associated with episodic and chronic migraine.[8] Of note, the ICHD-3b criteria cited here do not differ substantially from the ICHD-2 criteria, which many of the studies cited herein used to define migraine and chronic migraine.[9–13] Source: Adapted and updated from Aurora.[14]

Risk Factors for Clinical Progression.—Several studies have characterized factors associated with migraine progression. Higher risk is reportedly associated with nonmodifiable (eg, female sex, lower socioeconomic status, unmarried)[20] and modifiable (eg, acute headache medication use, caffeine intake, obesity, other pain syndromes, previous head or neck injury, snoring, stressful life events) risk factors.[20] Headache frequency is also an important risk factor for progression.[22] Individuals with ≥4 headache days per month have an exponential increase in the risk of transformation from episodic to chronic migraine.[23] Furthermore, some clinicians have suggested that high-frequency episodic migraine may represent a "pre-chronic migraine" state, which creates an opportunity for identification and early treatment in an effort to prevent further transition into chronic migraine.[24]

The risk of developing migraine may be influenced by genetics, although an association between known migraine-related single-nucleotide polymorphisms and chronification has not been established.[25] Mutations have been identified in genes coding for calcium channels and sodium-potassium pumps among those with familial hemiplegic migraine and episodic ataxia type-2;[26,27] these mutations may cause 5-HT receptor dysfunction and increased synaptic glutamate concentrations, contributing to neuronal hyperexcitability[26] and subsequent cortical spreading depression. Findings from preclinical models[28,29] and human studies suggest that cortical spreading depression is a component of the migraine with aura experience.[30,31] No definitive relation of cortical spreading depression with migraine pain or migraine without aura has yet been demonstrated.[29] While the association between genetic mutations and chronic migraine remains inconclusive, these studies provide support for the general concept of migraine hyperexcitability observed with chronic migraine, as we discuss further in studies of the physiology of visual suppression.

Indicators of Progression to Chronic Migraine.—Neurological changes have been implicated in migraine progression in two models of migraine.[19,32] Cady et al view neurological changes underlying progression from the perspective of increased levels of anxiety, depression, fatigue, gastrointestinal disorders, and nonheadache pain between migraines, which occur after years of episodic migraine attacks.[32] This is not surprising, considering the widespread central impact of migraine. Bigal and Lipton propose that reduced nociceptive thresholds and changes in pain pathways that underlie allodynia and central sensitization may represent physiologic correlates of progression, while stroke and radiographic white matter lesions may provide anatomic signs of progression.[19] In support of these models, chronic migraine has been associated with frontal lobe neuropsychologic dysfunction,[33] altered cortical pain processing,[34] and brainstem vascular malformations.[35] Furthermore, Noseda et al mapped single trigeminovascular neurons that project to the posterior, lateral posterior, and lateral dorsal thalamic nuclei and found that they ultimately connected with auditory, ectorhinal, insular, parietal-association, retrosplenial, somatosensory, and visual cortices, which influence affect, memory, motor control, sensory perception (ie, auditory, olfactory, visual), and spatial orientation.[36]

Chronic stimulation of central pain pathways during repeated migraine attacks may increase central sensitization by decreasing nociceptive thresholds.[13,19,37] As Bigal and Lipton's model proposes, cutaneous allodynia may serve as an indicator of migraine progression, as it is believed to signify central sensitization, wherein second-order brainstem trigeminal neurons are increasingly sensitive to innocuous input.[38]

Cutaneous allodynia is common in people with migraine. Burstein et al reported that non-noxious stimuli during a migraine attack produced a pain reaction among 79% of patients with migraine seen at a medical center; all patients in his study experienced episodic migraine attacks 1–6 times per month for at least the previous 3 years and some also experienced frequent tension-type headaches.[38] Later studies confirmed this finding in individuals with episodic as well as chronic migraine;[37,39,40] however, one study reported greater allodynia severity among individuals with chronic migraine than those with episodic migraine,[39] and another found that individuals who met the criteria for episodic migraine with aura or chronic migraine showed a higher frequency of cutaneous allodynia than people with episodic migraine without aura.[40] One interpretation for these differences is that individuals who experience aura exhibit more persistent or severe central sensitization than those with episodic migraine without aura. Zappaterra et al found that patients with chronic headache (defined as headache >15 days per month, including chronic tension-type headache and medication overuse headache that started as transformed migraine) show higher rates of acute and interictal allodynia and increases in pathological mean cutaneous pain threshold scores relative to those with episodic headache (including episodic migraine with and without aura and episodic tension-type headache).[41] Together with observations of lower pain thresholds in individuals with chronic migraine (as opposed to episodic migraine)[13] and atypical cortical processing of cutaneous nociceptive input,[34,42] these findings support the hypothesis of physiologic progression involving disrupted central pain mechanisms.

Clinically Important Differences between Episodic and Chronic Migraine.—Important distinctions exist along the continuum between episodic and chronic migraine (Fig. 1). Chronic migraine imparts a substantially greater burden with disability scores nearly twice as high among individuals with chronic versus those with episodic migraine.[1,43] Patients with chronic migraine experience higher rates of comorbidities, including impaired sleep, mental health disorders (especially anxiety and depression), and gastrointestinal dysfunction.[20,44-48] Chronic migraineurs also experience an increased frequency of emergency department visits,[49] greater economic burden,[50] and suffer greater detriments to their work, school, home, social, and leisure activities.[1,43] This biological disability is often further confounded by some pharmacotherapies that may be accompanied by intolerable side effects;[51] treatment with more tolerable drugs, which may be successful

Table 1.—Neurophysiological and Functional Imaging in Migraine

Technique	Episodic Migraine	Chronic Migraine	Interpretation/Implication
Neurophysiological Techniques			
Magnetic Suppression of Perceptual Accuracy (MSPA)	Letter reporting accuracy decreased by magnetic pulse, but not as much as in controls†	Letter reporting accuracy not decreased by magnetic pulse, in contrast to episodic migraine and controls†	Intracortical inhibitory mechanisms may be more impaired in chronic migraine than episodic migraine, leading to a greater increase in baseline cortical excitability†
Magnetoencephalography (MEG)	Intermittent excitability associated with migraine attack‡‡	Persistent excitability during and between attacks‡‡	Different pathophysiologic mechanisms underlie episodic and chronic migraine‡‡
Functional Imaging Techniques			
Positron Emission Tomography (PET)	Increased activity in brainstem (pons) and selected cortical areas during migraine‡,§	Increased activity in pons, right temporal cortex; decreased activity in selected cortical areas, caudate nuclei; all findings in the interictal period†	Certain brain regions (eg, pons, rostral medulla) may be overactive during attacks‡,§ of episodic migraine but continuously overactive† in chronic migraine
		Activity in dorsal rostral pons, anterior cingulate cortex, and cuneus correlated with pain scores; activity in anterior cingulate cortex and pulvinar correlated with paresthesia scores¶	Pulvinar, cingulate and cuneus activity likely linked to affective component of pain; pons activity may be associated with migraine pathophysiology¶
Magnetic Resonance Imaging (MRI; relaxation rates R2, R2' and R2*)	Significant increase in R2' and R2* values in periaqueductal gray matter vs controls, not different from chronic migraine††	Significant increase in R2' and R2* values in periaqueductal gray matter vs controls, not different from episodic migraine††	Iron homeostasis in the periaqueductal gray may be persistently impaired in migraineurs, perhaps caused by repeated attacks††
	No differences in R2' and R2* values in red nucleus and substantia nigra vs controls††	Significant decrease in R2' and R2* values in periaqueductal gray matter, red nucleus, and substantia nigra compared with the episodic migraine and controls††	May be due to hyperoxia associated with head pain during an attack††

†Ref. 12.
‡Ref. 10.
§Ref. 11.
¶Ref. 56.
††Ref. 9.
‡‡Ref. 57.

in episodic migraine, is frequently unsuccessful in patients with chronic migraine.

MIGRAINE NEUROPHYSIOLOGY AND IMAGING FINDINGS

Emerging evidence supports the existence of both structural[52-55] and functional brain alterations in migraine. Important advances into the pathogenesis and pathophysiology of migraine have been afforded by neurophysiologic tests (eg, magnetic suppression of perceptual accuracy [MSPA], magnetoencephalography [MEG], transcranial magnetic stimulation [TMS]), functional imaging (eg, functional magnetic resonance imaging [fMRI], blood oxygen level–dependent [BOLD] fMRI, positron emission tomography [PET], perfusion

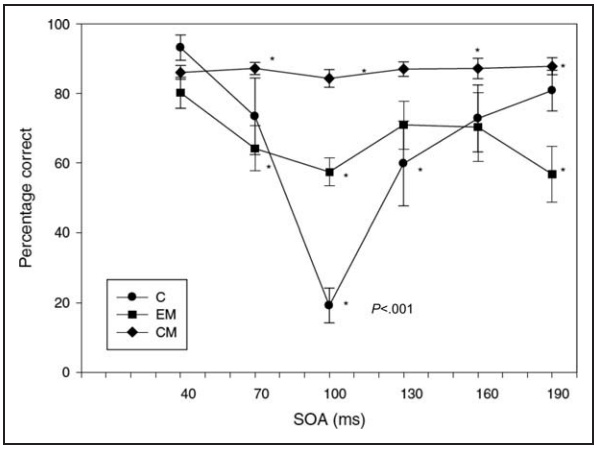

Fig. 2.—Cortical excitability as measured by magnetic suppression of perceptual accuracy. *$P < .001$. Stimulus onset accuracy is the time between the appearance of the letter trigram and the delivery of the TMS pulse. Bars show standard errors. Source: Aurora et al.[12]

weighted imaging), and structural imaging (eg, magnetic resonance imaging [MRI]). The research summarized below discusses some insights from these approaches (Table 1).

Neurophysiologic Studies.—*Cortical Hyperexcitability.*—MSPA utilizes TMS to investigate cortical excitability in migraine.[58] During the MSPA test, a series of 3 letters (trigram) is flashed briefly on a computer screen. Each trigram is followed by a 40- to 190-ms interval, after which a single high-intensity magnetic pulse is delivered to the occipital skull via a stimulation coil. Participants are asked to report which letters were flashed in each trigram.

In people without migraine, response profiles show a U-shaped function, in which letter-reporting accuracy is high at short (40 ms) and long (190 ms) intervals, but no better than chance for mid-range (100 ms) intervals (Fig. 2). Among migraineurs, marked differences in perceptual accuracy are reported between those with episodic and chronic migraine, with chronic migraineurs demonstrating no measurable difference in perceptual accuracy throughout the range of TMS pulse intervals (Fig. 2), and episodic migraineurs showing decreased letter-reporting accuracy at the mid-range intervals (most pronounced at 100 ms), though less pronounced than those without migraine.[12,58] The neural basis of these results may be attributed to inhibitory neurons that are activated at the mid-range intervals[59] in people without migraine, impairing perceptual accuracy; however, increased baseline cortical excitability caused by impaired intracortical inhibitory mechanisms may make perceptual suppression more difficult in those individuals with migraine.[60] These findings suggest a continuum of cortical excitability, wherein people with episodic migraine exhibit increased cortical excitability over those without migraine, and people with chronic migraine exhibit an even greater degree of cortical excitability over episodic migraineurs and nonmigraineurs.[12,58]

Cortical excitability has also been studied using MEG. Patients with chronic migraine demonstrated persistent cortical excitability between migraine episodes. This differs from the intermittent excitability and potentiation observed in episodic migraine and suggests different, or more extreme, effects in the patient with chronic migraine.[57,58,61] This finding, combined with MSPA research, suggests central inhibitory dysfunction in chronic migraine, with increased cortical hyperexcitability as a significant factor underlying the transformation of episodic migraine into chronic migraine.

Functional Imaging Studies.—*Activation During and Between Migraine Episodes.*—Several PET studies have examined cerebral activation during migraine attacks.[10,11] Weiller et al found increased blood flow in the cingulate, auditory and visual association cortices, and brainstem; injection of the acute migraine medication sumatriptan relieved headache pain and light and sound sensitivity, and only the brainstem remained activated.[10] In a PET study of migraine evoked via glyceryl trinitrate infusion, Afridi et al noted increased pons activation during and after an episode compared with the baseline premigraine state; other structures (eg, cingulate, insula, cerebellum, prefrontal cortex, putamen) were active during the attack, but not after it was fully controlled with sumatriptan.[11] They also reported concordance between the side of pons activation and the laterality of the migraine, and suggested that pain lateralization during a migraine may be attributed to lateralized pons dysfunction.[11] In view of the central role of the trigeminal pathway in chronic migraine, pontine activation is not

unexpected. Another PET study among chronic migraineurs reported that interictal glucose metabolism increased in the pons and right temporal cortex, but decreased bilaterally in the medial frontal, parietal, and somatosensory cortices, as well as caudate nuclei.[12] These results suggest that the normal inhibitory capacity of the cortex is reduced in people with chronic migraine,[12] although no such activation of the pons between attacks has been reported among those with episodic migraine.

Brainstem Activation.—Recent evidence implicates rostral brainstem activation during migraine episodes. Several rostral brainstem nuclei (eg, periaqueductal gray, raphe nucleus, locus coeruleus) are known to modulate sensory information; therefore, dysfunction in these nuclei has been proposed to contribute to sensory abnormalities observed during migraine episodes (eg, throbbing headache, sensitivity to light and sound).[62] Chronic dysfunction among these nuclei may contribute to increased headache frequency, and potentially migraine chronification.[62]

Studies using fMRI have identified activity in the red nucleus and substantia nigra during spontaneous migraine-related visual aura and visually triggered migraine.[63,64] Although these areas are best known for their roles in motor function, they are also involved in sensory processing and pain.[65-67] Another study using BOLD-fMRI has also associated spontaneous visual aura with changes consistent with cortical spreading depression, beginning in the extrastriate cortex and progressing to the occipital cortex.[68] This result is supported by a MEG clinical trial in which visually triggered aura was associated with MEG-direct current shifts typical of those observed during cortical spreading depression.[69]

Structural Observations.—Dysmodulation of the pain system in the brainstems of migraineurs has been demonstrated using neurophysiologic and functional imaging studies, which indicate that chronic migraine is associated with progressive abnormalities in the periaqueductal gray matter,[61] and possibly other brain regions as well.[70,71] Convincing evidence is mounting that suggests that repeated migraines are associated with iron accumulation in periaqueductal gray matter,[9] globus pallidus,[70,71] red nucleus, and putamen.[71] All of these areas are involved in central pain processing and proposed migraine physiology. Iron accumulation during an attack may catalyze free radical injury, which may be increasingly impactful with repeated attacks. High-resolution MRI was used to map iron homeostasis as an indicator of brain function in the periaqueductal gray matter during migraine episodes among individuals with chronic migraine/chronic daily headache and between attacks in individuals with episodic migraine.[9] Results showed significant impairment in iron homeostasis in the periaqueductal gray of both migraine groups compared with the control group (nonmigraineurs), but no difference between the episodic and chronic migraineurs.[9] These results support the notion that repeated migraine attacks may impair periaqueductal gray function, resulting in elevated iron concentrations, and that this structure may contribute to migraine episodes through dysregulation of the trigeminovascular nociceptive system.[9] Another MRI study showed increased iron deposits in people with migraine, but not controls, in 3 deep nuclei, putamen, globus pallidus, and red nucleus, suggesting a disturbed central antinociceptive neuronal network.[71] Further evidence of iron accumulation in migraine has been identified in the basal ganglia; this study showed that people with chronic migraine displayed more iron accumulation than those with episodic migraine when evaluated by T2 MRI.[70]

Mainero et al demonstrated that repeated migraine attacks increase functional connectivity between the periaqueductal gray and brain regions involved in pain modulation (eg, prefrontal cortex, anterior cingulate, amygdala), potentially reducing the ability to inhibit pain response, and increasing hyperexcitability.[72] Volumetric MRI (voxel-based morphometry) studies have demonstrated a reduction in the gray matter in pain network structures, and increased density of brainstem structures in patients with chronic migraine.[52,73] Kim et al reported a positive correlation between reductions in gray matter volume and increased headache duration and lifetime headache frequency.[52] A separate study identified the sites of gray matter reduction to be involved in pain circuitry.[73]

The MRI CAMERA (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis)

cross-sectional study provided further evidence for structural anomalies in the brains of people with migraine. In this study population of 295 migraineurs and 140 age- and sex-matched controls, those with migraine had higher incidence of lesions (eg, subclinical infarcts in the cerebellum/posterior circulation, brainstem hyperintense lesions) and experienced frequent syncope and orthostatic insufficiency/intolerance.[53,74] An updated analysis from this study found that frequent syncope and orthostatic intolerance were independent risk factors for subclinical lesions in both migraineurs and controls (ie, independent of migraine status).[74] Nonetheless, female migraineurs without frequent syncope or orthostatic intolerance still remained at 2-fold higher risk for substantial deep white matter hyperintense lesion load.[74] CAMERA also found an increased risk of brain lesions and iron accumulation in those with a longer disease duration or higher migraine frequency, although longitudinal studies are needed to determine whether these lesions have relevant functional correlates and gradually accumulate over time.[53] In sum, the investigators in CAMERA are re-evaluating their study population 8 years after the initial study to determine how these physiologic changes modulate over time.[53]

These studies suggest that migraine is associated with progressive structural abnormalities in the periaqueductal gray matter and associated deep nuclei, and the affected structures may be functionally impaired in migraine and/or central to the dysregulated trigeminal nociceptive network. Although the role of iron accumulation in the development of chronic migraine remains unclear, several studies have suggested that increased duration since diagnosis and headache frequency may influence overall iron deposition,[70,71] or alternatively be an epiphenomenon. Nevertheless, it is not clear whether these findings correlate with attack frequency, chronicity, and/or migraine-specific symptomatology (eg, aura), and whether the iron signals are dynamic and potentially reversible with therapy.

Summary of Neurophysiologic, Functional, and Structural Imaging Findings.—Taken together, findings from studies using a range of techniques suggest persistent changes in certain brain structures among chronic migraineurs, while fewer or transient changes occur in individuals with episodic migraine, supporting the spectrum model of migraine. It is not clear whether any of these changes were present before clinical symptoms and reflect a fundamental biology of susceptibility, or alternatively, are the signature of consequent abnormalities in pain signaling. Nevertheless, whether pathophysiologic epiphenomenon or etiologic, clear abnormalities are observed on a population basis, suggesting that migraine itself is associated with abnormalities and that, in particular, episodic migraine and chronic migraine may form a continuum. A goal of future research would be to further elucidate how these differences manifest between episodic and chronic migraine, including identifying if any of these changes to brain structures are reversible. In the long run, future research should identify means of preventing the transition to chronic migraine in susceptible individuals.

Insights into the Physiology of Migraine.—Our view is that migraine is a "system disorder" associated with both peripheral and central dysfunction;[75] linear constructs are over-simplistic in describing the complex disorder we know clinically as migraine. The nidus of attack onset has not been established, and is likely multifactorial within individuals and heterogeneous across the affected populations. Several possible scenarios suggest extracranial origins of intracranial pain, as well as intracranial origins of extracranial pain, both resulting in local release of proinflammatory mediators.[76] The imaging and neurophysiology findings support the premise that cortical dysfunction and hyperexcitability are important components of migraine, which may be caused by peripheral sensitization of the trigeminal nerve and the upper cervical afferents.[14,28,29] Repeated stimulation of trigeminal fibers may cause increased release of nociceptive neurotransmitters and neuropeptides (eg, CGRP, glutamate, substance P, neurokinin A),[28,29] and/or upregulation of ion channels or sensory receptors (eg, transient receptor potential cation channel ankyrin subfamily member 1 [TRPA1], transient receptor potential cation channel vanilloid subfamily member 1 [TRPV1]) on nociceptive nerve endings.[76,77] These events can sensitize peripheral

neurons (ie, meningeal and dural trigeminal sensory afferents) and promote central sensitization,[76,78] which is pervasive in chronic migraine.[14]

In chronic migraine, central sensitization, observable by the development of cutaneous allodynia, is associated with dysfunctional activity of central trigeminal sensory neurons,[76] including spontaneous firing, firing in response to innocuous stimuli, and a reduced firing threshold.[19,32,78] This aberrant activity may be mediated by increased descending facilitation, impaired descending inhibition of nociceptive activity within the trigeminal cervical complex from key brainstem pain modulatory centers,[29] or heightened peripheral nociceptive input (ie, peripheral sensitization). Central sensitization likely contributes to maintaining the pain referral patterns in the trigeminal nerve and the upper cervical afferents[29] as well as the persistent pain of chronic migraine.[19,28] Individuals with chronic migraine display persistent cortical hyperexcitability,[14] often resulting in cutaneous allodynia (ie, central sensitization) even during the interictal period.[39,41]

Careful immunohistochemistry tractology studies revealed that the trigeminal nucleus has direct, single neuronal connections to thalamus, hypothalamus, amygdala, and other deep nuclei.[31,79-81] Through these pathways and further projections to cortex, peripheral trigeminal stimulation via a sensitized trigeminal nucleus, may contribute to autonomic, limbic and other migraine-associated dysfunction, in addition to cortical spreading depression. Emerging evidence supports a neurolimbic pain model of migraine, in which ascending and descending connections between the periaqueductal gray and limbic system influence the occurrence of migraine attacks.[75] Indeed, evidence suggests that the periaqueductal gray also regulates mood and emotion along with the limbic system, and this interaction may explain the common occurrence of psychiatric comorbidities (eg, depression, anxiety) in people with migraine, especially those with chronic migraine.[75]

TREATMENT OPTIONS

OnabotulinumtoxinA[82] is the only prophylactic treatment globally approved specifically for chronic migraine, and has demonstrated efficacy for up to 56 weeks in the large-scale PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) trials.[83-86] Although not specifically licensed for chronic migraine, orally administered topiramate[87] is an effective prophylactic treatment for patients with migraine,[47,88,89] and may be effective in patients with chronic migraine.[90] To understand how these therapies may affect the underlying migraine physiology, we have summarized their mechanisms of action.

Onabotulinumtoxin A Mechanism of Action.— Normally, neuronal stimulation initiates a series of intracellular events that leads to a neuropeptide-containing vesicle fusing with the nerve cell membrane. This process is facilitated by interaction between proteins on the vesicle (ie, vesicle-associated membrane protein [VAMP/synaptobrevin]) and on the internal membrane surface (eg, synaptosomal-associated protein [SNAP-25]), which together form the soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) complex.[76,91,92] The SNARE complex is fundamental to vesicular trafficking and fusion of the vesicle with the membrane. The molecular biological mechanism of action of onabotulinumtoxinA is well established, whereby it inhibits fusion of intracellular vesicles with the nerve membrane[93] by cleaving SNAP-25.[94] By impairing intraneuronal vesicular fusion, onabotulinumtoxinA modulates neuropeptide release and downregulates receptors and ion channels important in nociception.[76,92] This mechanism is important in the current notion of migraine prevention via disrupting the cascade of events that leads to peripheral and central sensitization, as described below.

In chronic migraine, maladaptive pain responses to peripheral chemical or mechanical stimuli result in the peripheral release of neurotransmitters and neuropeptides (eg, CGRP, glutamate, substance P) and/or activation/upregulation of ion channels and receptors on peripheral meningeal nociceptors.[76,91] Peripheral stimulation may also result in the release of proinflammatory cytokines, which activate mast cells and contribute to regional neuroinflammation. The effect of receptor upregulation is to lower the nociceptor threshold for stimulation (the hallmark of peripheral sensitization). As peripheral sensitization builds in chronic migraine,

it contributes to central sensitization and the development of cutaneous allodynia or hyperalgesia.[76,95]

OnabotulinumtoxinA blocks the release of inflammatory neuropeptides from stimulated trigeminal sensory neurons.[76,77,91,96,97] In vitro, onabotulinumtoxinA inhibits substance P release[98] and reduces stimulated, but not basal, release of CGRP.[99] A preclinical bladder pain model demonstrated that onabotulinumtoxinA inhibits CGRP release from afferent nerve terminals and significantly reduces pain responses after exposure to acetic acid.[100] Receptors such as TRPV1 have been shown to mediate CGRP release, thus leading to neuronal hyperexcitability.[101] In the rat formalin-pain model, onabotulinumtoxinA demonstrated inhibition of several of the neurophysiologic and neurochemical effects of formalin (eg, glutamate release, Fos-like immunoreactivity, evoked activity of wide dynamic-range neurons), which are regarded as measures of nociceptive processing.[102] A rat migraine model demonstrated that onabotulinumtoxinA administered into craniofacial muscles decreased the effects of glutamate by reducing the mechanical sensitivity of temporalis muscle nociceptors and decreasing blood perfusion, and may attenuate the provoked release of CGRP from muscle nociceptors.[103] An in vitro study demonstrated that onabotulinumtoxinA prevents and reverses mechanosensitization in C-type, but not Aδ-type, meningeal nociceptors.[76] The authors suggest that onabotulinumtoxinA accomplishes this effect either by associating with select C-type meningeal nociceptor ion channels or by reducing cell surface expression of these channels and/or associated receptors, such as TRPV1 and TRPA1.[76] A follow-up study in an animal model of chronic migraine showed that extracranial administration of onabotulinumtoxinA reduces intracranial responsiveness to TRPV1 and TRPA1 activation 7 days after administration, presumably by inhibiting docking of synaptic vesicles containing TRPV1 and TRPA1 receptors thereby preventing their membrane insertion.[104] Surface expression of other receptors, such as P2X3, may also be inhibited by onabotulinumtoxinA.[105] Recent clinical data demonstrating a peripheral action of anti-CGRP monoclonal antibodies[106-108] and CGRP receptor antagonists[109] support the notion that onabotulinumtoxinA neuromodulates pain through a peripheral mechanism. In fact, onabotulinumtoxinA has recently been shown to reduce serum CGRP concentration in patients with chronic migraine (pretreatment median, 74.1 pg/mL; 1 month post-treatment median, 51.9 pg/mL, $P < .001$).[110] Interestingly, one month after treatment, CGRP levels significantly decreased in patients defined as onabotulinumtoxinA responders (pretreatment median, 76.9 pg/mL; post-treatment median, 52.5 pg/mL; $P = .003$) but not non-responders (pretreatment median, 50.5 pg/mL; post-treatment median, 51.9 pg/mL; $P > .05$).

Topiramate Mechanism of Action.—It is thought that topiramate has dual effects on neurotransmission – enhancing inhibitory effects while minimizing excitatory effects, both of which are implicated in migraine physiology. The pharmacologic mechanisms underlying this antimigraine activity may include regulation of cell membrane ion channels (voltage-gated sodium and calcium channel blockage, potassium channel activation), modulation of neurotransmitter release (inhibition of glutamate, enhancement of γ-aminobutyric acid [GABA]-evoked currents), and inhibition of some carbonic anhydrase isozymes and kainate-evoked currents.[111,112] Studies have demonstrated topiramate's inhibitory effect on excitability in motor and visual cortices.[113-115] Based on this broad mechanism of action, topiramate may prevent the development of cortical spreading depression by reducing nociceptive transmission and generally inhibiting neuronal hyperexcitability.[116] Similarly, topiramate has demonstrated cognitive adverse events, which are likely a reflection of the central inhibitory effects. Pooled analyses of clinical trial results suggest that preventive topiramate treatment in patients with episodic migraine may reduce the risk of headache-day increase, which in some cases may prevent migraine chronification.[23]

In summary, the antinociceptive effect of onabotulinumtoxinA has been demonstrated to directly inhibit peripheral sensitization by preventing the release of neurotransmitters and neuropeptides as well as inhibiting membrane expression of relevant ion channels/receptors in the periphery, thereby inhibiting the development of, or attenuating, central sensitization.[76,77,96] Support for this mechanism

of action comes from clinical studies demonstrating suppression of cutaneous allodynia, an indicator of central sensitization, after onabotulinumtoxinA injection in the periorbital skin.[117,118] Topiramate is postulated to both enhance inhibitory and minimize excitatory neurotransmission, and may reduce the risk of progression to chronic migraine; however, this drug is not currently approved for use specifically in people with chronic migraine.

Implications.—Clinical, neurophysiologic, and functional imaging studies increasingly support the hypothesis that enduring and pervasive alterations can occur in the brains of individuals with chronic migraine, whereas the changes underlying episodic migraine are predominantly intermittent, occurring during migraine attacks. Migraine should be considered a spectrum disorder with chronic migraine being considered unique from episodic migraine, although its relationship (primarily as a predisposing condition) is acknowledged. Evidence is building that the neuroplastic changes observed during the transition from episodic to chronic migraine also occur in other forms of chronic pain (eg, fibromyalgia, low back pain).[119]

Given the disability associated with chronic migraine and the substantial interference of this condition with everyday activities, patients with episodic migraine who have risk factors for progression (eg, frequent attacks, acute headache medication use, obesity, snoring, stressful life events) should be monitored closely for headache frequency and chronification.[120] Without effective treatment, continued migraine attacks can be associated with structural changes.[119] The risk of progression may potentially be reduced through a combined treatment approach in patients at risk of chronification (eg, acute migraine treatments to reduce migraine attack severity, prophylactic medications to decrease migraine frequency). Clinically, treatment of migraine-related inflammatory symptoms may reverse peripheral and central sensitization; however, medication (eg, triptans) overuse may also increase sensitivity to triggers, potentially increasing the likelihood of sensitization.[119] Furthermore, switching triptan regimens may be associated with increased headache-related disability in some cases.[121] Therefore, the concept of appropriate interventional therapy forms the basis of the notion that effective treatment of chronic migraine has the promise of reversing the underlying pathophysiology. Some evidence suggests that modifying some risk factors[122-124] can move a patient from a chronic migraine pattern to an episodic migraine pattern. However, modification of risk factors, when possible, or the use of effective therapy, has not been prospectively demonstrated to prevent chronification.

Patients with chronic migraine require effective, tolerable treatments that provide pain relief, while avoiding serious or intolerable side effects. Treatments that are effective for patients with episodic migraine are not necessarily effective for those with chronic migraine (and vice versa), which may be expected based on the pathophysiologic differences in these conditions noted in this and other articles.[125] Abortive medications (eg, triptans) are often effective in patients with episodic migraine, as is the prophylactic medication topiramate, which in one pooled analysis showed reduced risk of increase in headache days, potentially preventing chronification in some patients (see above).[23] Consistent with this notion, prophylaxis with an effective treatment may revert a patient's headache frequency down the continuum from chronic to episodic migraine; this was recently demonstrated in a 2-year open-label prospective study of patients receiving headache prophylaxis with 195 U of onabotulinumtoxinA every 3 months (±1 week) during a 2-year period.[126] OnabotulinumtoxinA has been shown to be an effective prophylactic treatment for patients with chronic migraine (≥15 headache days per month) in double-blind, placebo-controlled clinical trials,[83,86] a prospective real-life data analysis,[127] and a 2-year open-label prospective study,[126] and may reduce healthcare visits (ie, emergency department, urgent care, hospitalizations) associated with chronic migraine.[128] Evidence-based guidelines concluded that episodic migraine (<15 headache days per month) was not responsive to onabotulinumtoxinA treatment;[129] however, the treatment paradigm utilized in the registration clinical trials (PREEMPT) has not been systematically assessed in patients with <15 headache days per month. Although the

classification of episodic and chronic migraine is dichotomized at 15 headache days per month, this distinction is primarily empiric, and the pathophysiology and likely treatment responsiveness may be ambiguous at the intersection,[24] as would be expected in a complex biologic system disorder. The next phase of research should aim to assess whether treatments for chronic migraine work in individuals with high-frequency episodic migraine, to more precisely define a headache-day frequency threshold for the pathophysiologic shift.

CONCLUSION

As a complex spectrum disorder, the recurring migraine clinical and pathophysiological features may evolve over time, due to decreased nociceptive thresholds in vulnerable individuals, the hallmark of peripheral and central sensitization. Neurophysiological and functional imaging studies show changes in baseline neurologic function between migraine attacks in people with chronic (as opposed to episodic) migraine, and suggest that chronic migraine is associated with progressive brain dysfunction.

Differences in physiology between episodic and chronic migraineurs highlight the need for state-specific and effective treatments for these patient populations. Topiramate is an effective option for patients with migraine, and has been suggested to prevent chronification.[23] For those who have already progressed to chronic migraine, onabotulinumtoxinA is an effective prophylactic option that can interrupt the clinical signs attributed to the pathological cascade of events causing peripheral sensitization, via direct inhibition of the peripheral release of neurotransmitters and neuropeptides, and surface expression of relevant membrane receptors, which then indirectly blocks central sensitization. The clinical trial data have shown that, for some patients, onabotulinumtoxinA reduces the number of headache days per month into the range seen with episodic migraine,[83-86] and it is appealing to consider that by effectively decreasing the frequency of chronic migraine to the range of episodic migraine, this prophylactic treatment might mitigate the chronification pathophysiology seen in patients with chronic migraine. Notwithstanding ambiguity at the intersection, further research into underlying differences between episodic and chronic migraine will continue to advance science, and likely provide further effective treatments.

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