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Chronic disorders with episodic manifestations: focus on epilepsy and migraine

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Abstract

Epilepsy and migraine are chronic neurological disorders with episodic manifestations that are commonly treated in neurological practice and frequently occur together. In this review we examine similarities and contrasts between these disorders, with focus on epidemiology and classification, temporal coincidence, triggers, and mechanistically based therapeutic overlap. This investigation draws attention to unique aspects of both epilepsy and migraine, while identifying areas of crossover in which each specialty could benefit from the experience of the other.

Introduction

Neurological chronic disorders with episodic manifestations (CDEM) are characterised by recurrent attacks of nervous system dysfunction with a return to baseline between attacks. Among the CDEM treated by neurologists, headaches (including migraine) and epilepsy are the most common, each comprising nearly 20% of outpatient neurological visits.¹ Both migraine and epilepsy represent distinct families of neurological disorders with typical constellations of symptoms. Migraine is characterised by recurrent attacks of pain and associated symptoms.² Epilepsy is characterised by recurrent attacks of positive neurological symptoms, often progressing to altered or lost consciousness, and, at times, convulsive features.³

Many challenges face the physician treating these disorders. The sensory, motor, and cognitive characteristics of migraine and epilepsy often overlap. Both disorders can present with headache. Furthermore, as migraine and epilepsy are highly comorbid, many individuals have

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Authors' contributions

SRH, MEB, and RBL contributed equally to the preparation of this manuscript.

Conflicts of interest

SRH is a consultant and speaker for GSK, Novartis, UCB Pharma, and Eisai, and receives research support from Pfizer. MEB is a speaker and receives research support from GSK, OMP, AstraZeneca, Merck, and Pfizer, and also receives research support from UCB, Boehringer, and Forrest. RBL is a consultant and speaker for, and receives research support from, Ortho Neurologics, GSK, Pfizer, Merck, Posen, and Bristol Myers Squibb.

both disorders, further complicating accurate diagnosis. Additionally, the therapeutic options for the disorders overlap.

In this review, we will examine migraine and epilepsy side by side, assessing the points of similarity, as well as the differences, between them.

Classification

As CDEM, both epilepsy and migraine are defined by recurrent attacks with particular features. Epilepsy is defined by recurrent unprovoked seizures encompassing both primary and secondary causes of recurrent attacks. In that sense, epilepsy is more akin to the broader category of headache than to migraine.

Both epileptic and headache disorders have established yet evolving classification systems. The International League Against Epilepsy (ILAE) provides three levels of classification. It classifies seizure types as partial (or focal with or without secondary generalisation) or generalised. Epilepsies are regarded as generalised or localised. The cause can be idiopathic, symptomatic, or cryptogenic.^{3,4} The idiopathic epilepsies are similar to the primary headache disorders in that recurrent attacks occur without an apparent underlying cause, although in many cases the disorders are presumed to be genetic. The symptomatic and cryptogenic epilepsies, like secondary headaches, are attributed to an identified or presumed underlying disorder.

For headache, the International Classification of Headache Disorders, revision 2 (ICHD-2)² defines 14 categories of headache, divided into four primary types and ten secondary forms.² Primary headaches include migraine, tension-type headache, trigeminal autonomic cephalalgias (including cluster headache), and a group of other primary headaches. Migraine is further divided into five major categories, the two most important of which are migraine without aura and migraine with aura.

The ICHD-2 uses a hierarchical approach to classify attacks, with up to four digits for coding (panel 1).⁵ The first digit specifies the major diagnostic type—eg, migraine (1.0). The second digit indicates a subtype within the category—eg, migraine with aura (1.2). Subsequent digits allow more specific diagnosis for some subtypes of headache. Familial hemiplegic migraine, for example, could be coded as migraine (1), migraine with aura (1.2), or, most precisely, as familial hemiplegic migraine (1.2.4). Additionally, the diagnosis of primary headache disorders needs the exclusion of other disorders that might cause the headache—ie, of a secondary headache disorder.

The current concepts of epilepsy classification are evolving; changes have even been proposed for the definition of the term epilepsy itself.⁶ Because epilepsy can potentially be classified on many levels on the basis of the features of individual attacks and the biology and natural history of underlying disorders, the ILAE has a proposed revision to its system with five axes of classification.^{7,8} These proposed axes include a description of ictal symptoms (axis 1); epileptic seizure types (axis 2); clinical syndromes based on various combinations of phenomenology, cause, risk factors, natural history and prognosis, and treatment response (axis 3); cause (axis 4); and degree of impairment (axis 5).

Panel 1: ICHD-2 classification for migraine

1.1

Migraine without aura

1.2

	Migraine with aura
1.3	Childhood periodic disorder
1.4	Retinal migraine
1.5	Complications of migraine
1.6	Probable migraine

Each classification system might be improved by examining features of the other. A similar approach can be readily adapted to the classification of headache disorders. The ICHD-2 does not provide for classification based on phenomenology (axis 1) or headache type (axis 2). Incorporation of classification of headache types, including migraine-like, tension-like, trigeminal autonomic cephalgia-like, and chronic daily headache, independent of cause, would be useful. Conversely, the ICHD-2 has a well-developed system organised by specific cause, which might be useful for the ILAE.

Epidemiology

Similar challenges are presented with the study of the epidemiology of migraine and epilepsy. A diagnosis of epilepsy, by current definition, requires at least two seizures. Migraine without aura, by definition, needs at least five attacks. Rules must be established for definition of incidence (is it the time of the first or fifth migraine attack?) and prevalence. Prevalence is usually defined by the occurrence of at least one attack in the previous year.

Incidence and prevalence

Both epilepsy and migraine are common neurological disorders, although migraine is much more common. The overall incidence of epilepsy in the USA and other developed countries is estimated to be 25–50 per 100 000 person years.^{9,10} Age-specific incidence is highest in the extremes of life; a high incidence in the very young of 100–200 per 100 000 person years⁹ falls to 25 per 100 000 person years during mid-life and peaks again to 100–200 or more per 100 000 person years in elderly people (figure 1). Prevalence studies indicate an overall prevalence of five to six per 1000^{11,12} with the active prevalence in the USA estimated to be 0.6%.¹² The reported incidence and prevalence of epilepsy varies significantly¹³ due, in part, to methodological issues.

The incidence of migraine with aura peaks between ages 12 and 13 years in women (14.1 per 1000 person years), whereas migraine without aura peaks between ages 14 and 17 years (18.9 per 1000 person years).^{14,15} In men, the incidence of migraine with aura peaks several years earlier (6.6 per 1000 person years at 5 years of age). The early age of onset helps to explain why boys have a higher prevalence of migraine than girls (incidence of migraine without aura peaks in boys at 10 per 1000 person years between the ages of 10 and 11 years).^{14,16}

The differences in epidemiological profile between epilepsy and migraine are only partly attributable to differences in detection and definition. For epilepsy, observed changes in behaviour in association with an abnormal electroencephalogram often make diagnosis relatively easy very early in life. If migraine occurs very early in life, it would be difficult to detect since diagnosis relies on reported symptoms. Recurrent idiopathic abdominal pain and

other equivalent syndromes could be an early manifestation of migraine.² They are not, however, usually reported in epidemiological studies of migraine. Another potential characteristic that contributes to the age-profile difference is the exclusion of secondary causes in the definition of migraine. As with epilepsy, the incidence of secondary headaches is raised early in life—attributable to meningitis or brain tumour—and later in life—attributable to stroke, brain tumour, or giant cell arteritis. But these secondary disorders are not classified as migraine and are not included in the description of migraine incidence.

The substantial sex differences reported for migraine (affecting 18% of women and 6% of men; figure 2)^{17,18} are relatively small for epilepsy.¹⁹ Although women with epilepsy often show catamenial patterns, hormonal effects are less of a risk factor for epilepsy per se than a precipitant of attacks. This finding is by contrast with migraine, in which cyclic hormonal factors are thought to contribute to the excess risk of migraine in women, beginning at the age of menarche,²⁰ as well as to individual migraine attacks.

Epilepsy is relatively constant across developed nations and geographic locations.²¹ Rates in developing countries and areas have been reported to be higher than in industrialised nations,^{22–24} although this finding is not consistent and could be associated with issues of methodology.²¹ The prevalence of migraine is highest in the Americas and Europe, intermediate in Africa, and lowest in Asia (figure 3).¹⁷ These differences between epilepsy and migraine could partly reflect definition. In the less developed world, CNS infections such as cysticercosis and CNS malaria are important causes of epilepsy.²² Again, by definition, recurrent headaches attributable to secondary causes are not regarded as migraine.

Race differences have not been well studied for epilepsy, although increased prevalence has been reported in young black people^{12,25} and elderly African Americans.²⁶ In the USA, migraine is more common in white people than in African Americans and least common in Asians.¹⁷ Finally, the prevalence of migraine is inversely related to socioeconomic status, a pattern also seen in epilepsy.^{17,24}

Comorbidity of migraine and epilepsy

Two disorders are comorbid if they occur in the same person more frequently than by chance alone. Although studies vary, individuals with either migraine or epilepsy are more than twice as likely to have the other disorder. Ottman and Lipton²⁷ assessed the association between migraine and epilepsy from adult participants in the Epilepsy Family Study of Columbia University. Migraine prevalence was 24% among probands with epilepsy, and 26% in the relatives of probands with epilepsy. In the control group of relatives without epilepsy, only 15% had migraine. The sex-adjusted rate ratio for migraine in probands with epilepsy compared with relatives without epilepsy was 2.4. The prevalence of epilepsy in people with migraine varies from 1% to 17%,²⁸ with a median of 5.9%, substantially higher than the population prevalence of epilepsy.

Mechanisms of comorbidity—Ottman and Lipton²⁷ proposed three alternative models to account for the comorbidity of migraine and epilepsy. One possibility is a simple unidirectional causal explanation. For example, migraine could cause epilepsy by inducing brain ischaemia and injury. Under this hypothesis, the incidence of migraine should be raised before, but not after, the onset of epilepsy. Alternatively, epilepsy could cause migraine by activating the trigeminovascular system, in which we would expect an excess risk of migraine after, but not before, the onset of epilepsy. In fact, there is an excess risk of migraine both before and after epilepsy onset, leading to the rejection of both simple unidirectional causal models.²⁷

A second possibility is that shared environmental risk factors might explain this comorbidity. Because the risk of migraine is significantly increased in people with idiopathic or cryptogenic epilepsy, known environmental risk factors cannot account for all of the comorbidity.²⁷

A third possibility is that shared genetic risk factors might account for comorbidity. However, migraine was no more likely in individuals with familial epilepsy than in those without.²⁷ Finally, Ottman and Lipton proposed that an altered brain state (increased excitability) might increase the risk of both migraine and epilepsy²⁹ and account for comorbidity, a hypothesis that draws support from therapeutic similarities.

Temporal coincidence of migraine and epilepsy

Headaches (not necessarily fulfilling criteria for migraine) can occur before (preictal), during (ictal), or after (postictal) a seizure. Additionally, migraine aura can trigger seizures in a condition sometimes termed migralepsy.² Preictal and ictal headaches are often neglected because the seizure overshadows the headache for both patient and physician. Ictal headaches can occur with seizures as the sole or predominant clinical manifestation.³⁰ Isler and colleagues³¹ showed that hemicranial attacks of pain coincided with seizure activity and typically lasted seconds to minutes (hemicrania epileptica); in rare cases, ictal headache can last for hours.

According to the ICHD-2,² migralepsy happens when seizures occur during or within an hour of a migraine aura. Rates of migralepsy reported in populations with comorbid migraine and epilepsy range from 1.7–16%.^{32,33} Reported risk factors for migralepsy included attacks of migraine with aura and catamenial epilepsy.³³

Triggers for migraine and epilepsy

For CDEM, it is useful to distinguish between risk factors for the disease and triggers of particular attacks. Risk factors for a disease increase the probability that the disorder (migraine or epilepsy) will develop in a particular individual. Risk factors common to both epilepsy and migraine include a positive family history, presence of depression, and presence of the other disorder.^{34–38}

By contrast, triggers increase the probability of an attack over a brief period in individuals who have the disease. Putative migraine triggers include endogenous factors (eg, menses) and exogenous factors such as diet (eg, alcohol, especially red wine, and cured meats), changes in weather, as well as changes in sleep.^{39–43} Known trigger factors for epilepsy attacks include poor adherence to medication, sleep deprivation, visual stimulation, alcohol, and menses.^{44–46}

For both epilepsy and migraine, research has generally focused on identifying what initiates attacks rather than what terminates them. This question poses a fruitful area of potentially collaborative exploration.

Identification of triggers—Risk factors for epilepsy and for the primary and secondary headache disorders have been extensively studied. There has been little progress in the study of trigger factors. Understanding trigger factors is crucial, because people with migraine or epilepsy are eager to understand what initiates their attacks, and for both migraine and epilepsy, trigger management can potentially reduce attack frequency and enhance self-efficacy. Identification of trigger factors might also provide clues to the neurobiological mechanisms that lead to the transition to the ictal state in people who have migraine or epilepsy. On the other hand, misidentification of triggers can lead to unhelpful and unnecessary changes in

lifestyle. Therefore, robust methods to identify triggers are necessary both for clinical practice and research.

There are several approaches to the study of triggers of migraine and epilepsy. The most common approach relies on patient self-report. Patients are asked to enumerate their triggers from a prespecified list.⁴⁷ In a study, 88% of respondents believe that Chinook weather exacerbates their headaches;⁴⁰ in a rigorous diary study, this finding was proven in only 20% of patients.³⁹ For this reason, self-reported triggers provide information about patient beliefs and should be viewed as hypothesis generating.

For some exogenous triggers, it is possible to undertake clinical trials to expose patients to trigger factors or to placebo and then follow them for the development of an attack. During in-patient epilepsy monitoring, sleep deprivation and medication withdrawal are often studied as putative triggers.⁴⁸ For migraine, exposure to aspartame, alcohol, chocolate, and nitroglycerin have been studied in blind randomised trials.^{49,50} Although these studies usefully identify group differences, multiple blinded exposures are necessary to identify individual differences in trigger susceptibility—a design that is rarely feasible.

Most endogenous triggers (ie, menses, stress) cannot be studied through randomised exposure. In this context, diary studies have many advantages for assessing trigger factors of seizures and migraine. Exposure to the putative trigger and seizure or headache characteristics can be recorded on a daily basis. Thus, multiple triggers can be temporally linked to attacks within the same person. As there are striking individual differences in trigger factors, these designs allow the investigator to study the effect of trigger factors within individuals and in the population. Temporal lag between exposure and attack can also be studied.

Hormonal changes as a trigger—Diary studies have been used to assess the temporal association of the menstrual cycle to both migraine and epilepsy.⁵¹ Menstruation-related seizures are characterised by a cyclical occurrence of seizures in relation to the menstrual cycle.⁵² Prevalence varies from 12.5%⁵³ to more than 70%,⁵¹ depending on the stringency of the criteria chosen, with a third of women exhibiting a twofold increase in seizures during a particular phase of the cycle. The pathophysiology of catamenial epilepsy, although not clearly delineated, probably relates generally to a cyclical balance between the proconvulsant effects of oestrogens⁵⁴ and the anticonvulsant effects of progesterone.^{55,56} Progesterone effects are probably mediated in part through effects on inhibitory GABA_A receptors⁵⁷ and are most noted during progesterone withdrawal.

Menstruation is a robust trigger for migraine without aura. The association has been shown in clinical and population-based diary studies.^{58,59} By contrast with the findings in epilepsy, human experimental evidence in migraine suggests that the predominant trigger is oestrogen withdrawal.^{60,61} Attacks related to menstruation are frequently more severe and disabling than those not related to menses.

Treatment

Epilepsy and migraine are fundamentally different disorders, mandating significant differences in approach to treatment. There is a striking underlying mechanistic similarity common to both disorders, neuronal hyperexcitability.^{62,63} Many of the treatments for both disorders target this characteristic. This therapeutic overlap allows each specialty to learn lessons from the other, both in terms of specific treatments and therapeutic strategies.

Goals of treatment

The traditional goal of epilepsy treatment, for the patient to be seizure-free, has expanded to include no seizures and no side-effects, in recognition that side-effects of the antiepileptic drugs can be as disabling as seizures.⁶⁴ By contrast, clinicians treating patients with migraine recognise that a similar goal of migraine-free is not generally feasible.⁶⁵ For migraine, the goal is to reduce pain and disability and heighten function. Although treatment of both migraine and epilepsy is aimed at eliminating attacks, reducing disability, and improving quality of life, seizures present a health and safety risk that migraines typically do not. Even a single seizure precludes driving for 3–12 months. Because the consequences of a single seizure are more enduring than the consequence of a single migraine, the need for complete control is greater for epilepsy.

Acute and preventive treatment

Treatment modalities in epilepsy and migraine fall into two categories: acute treatments, given in the immediate setting of an attack; and preventive treatments, given interictally (typically daily) to prevent attacks. Similarities and differences in treatment choices for epilepsy and migraine reflect pathophysiological differences and also potential underuse of treatment.

Acute treatment—Both seizures and migraines are self-limited, but seizure duration is typically brief (median attack duration 1–2 min), whereas the duration of migraine is usually hours to days (median attack duration 24 h).^{2,17} As a result, seizures generally do not need acute treatment. Acute antiepileptic drugs are prescribed for only a few patients with epilepsy, typically in the setting of a history of prolonged seizures, seizure clusters, or status epilepticus. By contrast,⁶⁵ according to recent guidelines, virtually all people who have migraines need acute treatment.

There is only a small overlap in acute treatment for the two disorders, seen mainly in the setting of prolonged ictus, either status epilepticus or status migrainosus, for which intravenous valproic acid may be used.⁶⁶ Benzodiazepines, the mainstay of acute treatment of seizures, are rarely used for migraine. Widely used acute agents in migraine include triptans, which have no known antiepileptic properties and can indeed reduce seizure threshold,⁶⁷ as well as non-steroidal antiinflammatory drugs and analgesics.

Preventive treatment—Preventive antiepileptic drug treatment for seizures is generally not indicated until after a second unprovoked seizure.^{68–70} Nearly every patient with epilepsy is maintained on preventive treatment. By contrast, preventive treatment for migraine, which should be considered in patients with more than 2 days of headache-related disability per month or more than 4 days of migraine, seems to be significantly underused. Estimates from the American Migraine Prevalence and Prevention Study suggest that 40%⁷¹ of migraine sufferers meet those criteria, whereas only 13% receive preventive treatment.

A significant crossover exists between preventive treatment of epilepsy and migraine.^{65,67} This therapeutic cross-fertilisation is almost entirely from epilepsy to migraine and not from migraine to epilepsy. To explain this difference the points of convergence and divergence of mechanisms need to be examined.

Epilepsy can be regarded as a disorder of hyperexcitability, whereas migraine is both an excitatory disorder and a disorder that affects pathways of neurovascular inflammation.⁶⁵ The initiating feature of both disorders, hyperexcitability, can be regarded as a point of convergence, and antiepileptic drugs developed in animal models of epilepsy therefore have proven efficacy in migraine. However, the excitatory events in migraine are believed to be proximal, whereas the neurovascular events that lead to pain production are more distal, a point of mechanistic

divergence.⁶⁵ Thus the animal models used to screen for migraine drugs have focused on agents that inhibit neurovascular inflammation, especially triptans.^{65,72} These drugs would typically not be expected to have an effect on seizures. Similarly, the migraine preventives identified by clinical observation, such as beta blockers and calcium channel blockers, have little efficacy in epilepsy.

Epilepsy and migraine as disorders of hyperexcitability

Both epilepsy and migraine are deemed to be disorders of neuronal hyperexcitability. Acute attacks arise in the setting of an abnormal interictal substrate.^{62,63} Although this concept is long accepted in epilepsy, for migraine the hyperexcitability hypothesis was put forward by Welch and has garnered increasing support over the past two decades.⁶² In migraine, cortical and brainstem activation give rise to activation of ascending and descending pathways, perimeningeal vasodilatation, and neurogenic inflammation.⁷² Various causes for hyperexcitability of the migrainous brain have been suggested. These include low concentrations of GABA and magnesium, high concentrations of glutamate, mitochondrial abnormalities, dysfunctions related to nitric oxide, or a calcium channelopathy.^{73,74}

To that end, the antiepileptic drugs, also referred to as neuromodulators, are used for both disorders (table 1). Although antiepileptic drugs are the mainstay of preventive treatment for epilepsy, they comprise only one class of effective treatment for migraine prophylaxis, implicating other mechanisms of migraine that might not be present in epilepsy.

There are 24 agents approved for the chronic treatment of epilepsy in the USA. Although choice of antiepileptic drug in epilepsy is complex and beyond the scope of this review, factors relevant to the treatment decision include age, seizure type, epilepsy syndrome, comorbidities, drug–drug interactions, and childbearing status.⁷⁵ Apart from phenobarbital and carbamazepine, all currently available antiepileptic drugs were initially used, or specifically designed, to treat epilepsy. Once approved for epilepsy, however, many of these drugs showed efficacy for other disorders, including migraine (panel 2).

Two antiepileptic drugs, valproic acid and topiramate, are approved for both migraine prophylaxis and treatment in epilepsy.^{76–79} Valproic acid increases concentrations of GABA in synaptosomes and in the brain by inhibiting the enzyme GABA acid transaminase responsible for degradation of GABA; enhances the postsynaptic response to GABA; increases potassium conductance, producing neuronal hyperpolarisation; turns off the firing of the 5-HT neurons of the dorsal raphe nucleus, which are implicated in controlling head pain; and reduces central trigeminal activation, as shown by reduced C-Fos activation in the trigeminal nucleus caudalis. Valproic acid also has peripheral activity outside the brain, including reduction of experimental neurogenic inflammation in the trigeminal vascular system, which is mediated by GABA_A receptor agonism.⁸⁰ Topiramate, in turn, has multiple mechanisms of action and can affect the activity of some types of voltage-activated sodium and calcium ion channels, GABA_A receptors, and the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) or kainate subtype of glutamate receptors.⁸¹ Topiramate also inhibits some isozymes of carbonic anhydrase (CA) and exhibits selectivity for CA II and CA IV.^{81,82} The effects of topiramate on voltage-activated sodium and calcium ion channels, GABA_A receptors, and AMPA or kainate receptors have been suggested to be regulated by protein phosphorylation,⁸² which has implications for the combination of pharmacological properties of topiramate.

Why don't all antiepileptic drugs work for migraine? To explain disparities between efficacies of these drugs in migraine needs a detailed understanding of pharmacological similarities and differences between drugs as well as insights into the specific mechanisms of each disorder. This area needs future exploration. Although large scale studies are absent thus far, other antiepileptic drugs reported to show migraine efficacy in uncontrolled studies include

gabapentin,⁸³ levetiracetam,^{84,85} tiagabine,⁸⁶ and zonisamide.⁸⁷ Of note, lamotrigine has been reported to be effective for treatment of migraine aura, but not headache (table 2).^{90,96}

Patients with migraine seem to tolerate antiepileptic drugs with fewer side-effects than do patients with epilepsy, which could be partly related to lower target doses in migraine (table 1). The dosing schedules in trials of topiramate for epilepsy were higher than those of migraine trials; subsequently, the recommended dose for epilepsy is 200–400 mg per day, compared with 100 mg per day for migraine prophylaxis.

Because patients with epilepsy are typically maintained on antiepileptic drugs for many years, long-term side-effects noted in this population should be similarly considered in patients with migraine receiving antiepileptic drug maintenance treatment. The risk of bone loss in association with long-term use of valproic acid is a particular example.⁹⁷

Concomitant treatment—In the spirit of parsimony (the principle that entities should not be multiplied needlessly),⁹⁸ it is tempting to treat concomitant diagnoses with a single drug, as has been recommended. This approach can reduce side-effects of polypharmacy, and can even be particularly effective, as has been reported with the use of valproic acid for migraine prophylaxis in children with epilepsy.⁹⁹ Regulatory studies showed that 100 mg per day of topiramate is an effective monotherapy for both epilepsy and migraine, although this finding might not indicate the necessary dose for concomitant treatment. Although the attempt to treat comorbid disorders with one drug has potential merit, caution must be exercised to avoid undertreating one of the disorders.

Panel 2: Approved non-epilepsy indications for antiepileptic drugs

Carbamazepine
 Trigeminal neuralgia
 Bipolar disorder
 Clonazepam
 Panic disorder
 Valproate semisodium
 Migraine prevention
 Manic episodes associated with bipolar disorder
 Gabapentin
 Postherpetic neuralgia
 Lamotrigine
 Maintenance treatment of bipolar 1 disorder to delay time to occurrence of mood episodes
 Phenobarbital
 Hypnotic/sedative
 Topiramate
 Migraine prevention

Epilepsy as a structural disorder

A critical difference between epilepsy and migraine is in the consideration of focal epilepsy as a structural disorder. Focal epilepsy is typically characterised by one or more brain regions that are epileptogenic, or able to produce seizures.⁶³ Therefore, in epilepsy, there may be cortical generators that are amenable to surgical resection. For migraine, there is a cortical generator for aura, and possibly a brainstem generator for pain production, neither of which is amenable to resection.⁷²

In epilepsy, surgical procedures are directed to the epileptogenic zone. This area can be identified through extensive neurophysiological, structural, and functional testing; if available for resection, surgical removal of the epileptogenic zone can render the patient seizure free.¹⁰⁰ In migraine, surgical procedures are either directed towards reducing the effect of triggers, or reducing afferent or efferent outflow in the pain expression pathway.¹⁰¹

Surgery—About 35–40% of patients with epilepsy¹⁰⁰ are intractable to medical treatment. Of these, around 2000 patients per year in the USA are estimated to undergo resective surgery¹⁰² (most commonly an anterior temporal lobectomy) to remove the epileptogenic zone (table 3).^{103,104} Successful surgery can be curative; 66% of patients are estimated to be seizure-free or have only auras¹⁰² after anterior temporal lobectomy, although continuation of antiepileptic drug treatment after surgery is recommended.¹⁰⁵ Other surgical procedures (ie, corpus callosotomy, multiple subpial transections) are restricted to specific circumstances.

Migraine is regarded as intractable to pharmacological treatment in just a few individuals. Migraine by definition does not have structural pathology, although there are secondary forms of migraine-like headache (ie, arteriovenous malformations). A brain-stem generator for migraine has been postulated on the basis of PET studies during and between attacks. However, this generator is not amenable to surgical approaches.⁷²

Surgical repair of cardiac abnormalities, including patent foramen ovale⁹² and atrial septal defect,⁹³ is an emerging point of interest in migraine treatment that could have implications for epilepsy management. Theoretically, paradoxical cerebral emboli or right–left shunts could lead to hypoxia or increase vasoactive amines, which in turn increase neuronal excitability and result in migraine. Not yet addressed is whether a similar mechanism operates in epilepsy.

Stimulation, injections, and blocks—Although the concept of stimulation of neural structures for the treatment of epilepsy is not new, the first Food and Drug Administration approved device for the treatment of epilepsy was the vagal nerve stimulation system, in 1997,¹⁰³ which has proven efficacy in the add-on treatment of intractable epilepsy (table 3). Other stimulation trials, including deep brain stimulation, are ongoing. Vagal nerve stimulation has been reported to be efficacious in the treatment of chronic migraine;¹⁰⁴ rigorous clinical trials are needed.

Blocking both the afferent and efferent pathways of pain modulation has been an approach in migraine treatment. Afferent approaches include: occipital nerve block and stimulation, cervical root block, correction of intranasal trigeminal contact points, and deactivation of trigger points.⁶⁵ Efferent approaches, including trigeminal ganglion block, are rarely undertaken.

Complementary medicine

The use of complementary and alternative medicine, defined by the National Institutes of Health as a group of diverse medical and health-care systems, practices, and products that are not presently judged to be part of conventional medicine (NCAAM), is anecdotally widespread

for both migraine and epilepsy. Many modalities of complementary and alternative therapy have been used in the treatment of epilepsy or migraine;^{90,91,94,95} none has clearly shown efficacy for both. Few rigorous data are available, although randomised controlled trials of herbs and vitamins for migraine prophylaxis have been done (table 2).^{94,96} Shared mechanisms suggest that crossover of treatment should potentially be considered.

Conclusions

Epilepsy and migraine are CDEM linked by their symptom profiles, comorbidity, and treatment. The presence of one disorder increases the probability that the other is also present. Because of its greater prevalence, migraine is expected in almost a quarter of patients with epilepsy, whereas epilepsy is expected in 1–2% of migraine sufferers.

Much effort has been devoted to descriptive aspects of each disorder, including development of classification schemes, epidemiological investigations, and identification of risk factors and triggers. Epidemiological and classification differences between the disorders are in part explained by the definition of migraine as a primary process, whereas much of epilepsy is secondary or symptomatic. The classification of the epilepsies might improve by consideration of specific causes, whereas the classification of headache disorders needs a categorisation of headache types, akin to the classification of seizures.

Risk factors and trigger factors must be distinguished. As the exploration of these issues is in its infancy, each area stands to benefit from examining the strategies of the other.

Search strategy and selection criteria

Only articles published in English were reviewed. Data were searched during a 4 month period between March and June, 2005, on PubMed with the following keywords: epilepsy, migraine, antiepileptic drugs, classification, incidence, prevalence, neuromodulation, catamenial epilepsy, temporal lobectomy, vagal nerve stimulation, patent foramen ovale, valproate, topiramate. Papers from 1985 onwards were searched. Additionally, many articles were chosen from the extensive files of the authors. Abstracts and reports from meetings were used only if they presented new relevant information.

Similarly, shared mechanisms offer potential for therapeutic fertilisation. This crossover includes therapeutics with proven efficacy for both disorders, such as neuromodulators, related to epilepsy and migraine being disorders of hyperexcitability. Less explored is the potential cross fertilisation of other modalities of treatment shown to be successful in each disorder, including both traditional and less conventional approaches.

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Figure 1.
Age-specific incidence rate, cumulative incidence rate, and prevalence rate of epilepsy in Rochester, Minnesota (1935–74) Reproduced from *Epilepsia* by permission of Blackwell Publishing.

Figure 2.
Adjusted prevalence of migraine by age, from a meta-analysis of studies using IHS
criteria Reproduced from *Epidemiology of Pain* by permission of IASP Press.

Figure 3.
Adjusted prevalence of migraine by geographic area and sex, from a meta-analysis of studies using IHS criteria Reproduced from *Epidemiology of Pain* by permission of IASP Press.

Table 1

Antiepileptic drugs used for migraine

	Antimigraine dose	Antiepileptic dose
Valproate semisodium tablets ^{*†}	500–1500 mg	750–4000 mg
Gabapentin tablets [*]	300–3000 mg	600–3600 mg
Levetiracetam tablets	1500–4500 mg	1000–3000 mg
Topiramate tablets ^{*†}	50–100 mg	50–400 mg
Zonisamide capsules	100–400 mg	100–400 mg

^{*} Evidence for moderate efficacy from at least two well designed placebo-controlled trials

[†] Approved by the Food and Drug Administration for migraine treatment.

Table 2

Evidence for non-conventional preventive treatments for migraine and epilepsy

	Epilepsy	Migraine	Postulated mechanisms
Biofeedback	Efficacy of neurofeedback (electroencephalographic biofeedback) in uncontrolled and few controlled series, no evidence from large randomised controlled trial ⁹⁰	Efficacy of biofeedback/relaxation techniques in uncontrolled and few controlled series ⁹¹	Suppress negative slow cortical potentials, increase sensorimotor rhythm to normalise ⁹⁰ electroencephalogram
Embolism source repair	No evidence	Evidence from series, no evidence from randomised controlled trials ^{92,93}	Increased neuronal excitability due to hypoxia, decreased vasoactive amines ^{92,93}
Botulinum toxin	No evidence	Evidence from randomised controlled trial ⁹⁴	Antinociceptive effect on trigeminal ganglion neurons; possible role of muscular factors
Coenzyme Q10	No evidence (other than in mitochondrial disorders)	Efficacy in one randomised controlled trial ⁹⁵	Improved energy metabolism via mitochondria mechanisms
Riboflavin	No evidence (other than in mitochondrial disorders)	Evidence from randomised controlled trial ⁹⁴	Improved energy metabolism via mitochondria mechanisms
Herbs	Mistletoe, kava, skullcap, melatonin investigated: no evidence from randomised controlled trials	Petasites: evidence from randomised controlled trial ⁹⁶	Calcium channel regulation; inhibition of peptide-leucotriene biosynthesis

Table 3
Evidence for conventional preventive treatments for migraine and epilepsy

	Epilepsy	Migraine	Postulated mechanisms
Valproate semisodium	Proven efficacy in randomised controlled trials ⁹⁰	Proven efficacy in randomised controlled trials ⁷⁶	Neuronal hyperpolarisation through increased potassium conductance, enhanced postsynaptic response to GABA, decreased serotonergic firing in dorsal raphe ^{79,80}
Topiramate	Proven efficacy in randomised controlled trials ⁹¹	Proven efficacy in randomised controlled trials ^{77,78}	Numerous mechanisms proposed, including blockage of voltage gated sodium channels, increased GABA-induced currents, inhibition of L-type calcium channels ^{81,82}
Resective surgery	Proven efficacy in randomised controlled trials ¹⁰⁷	Not done	Removal of epileptogenic zone
Vagal nerve stimulation	Proven efficacy in randomised controlled trials ¹⁰³	Efficacy in uncontrolled series ¹⁰⁴	Numerous mechanisms proposed, including effect on NTS, decreased interictal spikes, altered thalamic blood flow, altered CSF neurochemistry ¹⁰³

NTS=nucleus tractus solitarius