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## Headache in people with epilepsy

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### Abstract

Epidemiological estimations indicate that individuals with epilepsy are more likely to experience headaches, including migraine than individuals without epilepsy. Headaches can be temporally unrelated to seizures, or can occur before, during or after an episode; seizures and migraine attacks are mostly not temporally linked. The pathophysiological links between headaches (including migraine) and epilepsy are complex and have not yet been fully elucidated. Correct diagnoses and appropriate treatment of headaches in individuals with epilepsy is essential, as headaches can contribute substantially to disease burden. Here, we review the insights that have been made into the associations between headache and epilepsy over the last 5 years, including information on the

26 pathophysiological mechanisms and genetic variants that link the two disorders. We also discuss the current best  
27 practice for the management of headaches co-occurring with epilepsy and highlight future challenges for this area  
28 of research.

## 29 **[H1] Introduction**

30 The hallmark of epilepsy is an enduring predisposition to seizures accompanied by neurobiological, cognitive  
31 and psychological comorbidities<sup>1</sup>. Epileptic seizures are defined as the disruption of normal neuronal functioning  
32 owing to excessive or synchronous neuronal activity, leading to an epileptic event that is discernible by the person  
33 and/or by an observer<sup>1</sup>. An analysis for the Global Burden of Disease Study 2016 estimated that >50 million  
34 people worldwide had active epilepsy, that is, they had continuing seizures or were receiving epilepsy treatment<sup>2</sup>.  
35 The origin and cause of seizures can vary. The International League Against Epilepsy (ILAE) scheme<sup>3</sup> classifies  
36 seizures as either “focal”, meaning that seizures originate at a specific location in one hemisphere; “generalised”,  
37 denoting seizures that engage bilaterally distributed networks; or “unknown”, for seizures with an undefined  
38 origin. The ILAE classifies epilepsy as either “focal”, “generalised”, “focal and generalised”, or “unknown”,  
39 depending on the type of seizures that occur<sup>3</sup>. The same scheme also classifies epilepsy according to aetiology,  
40 including “structural” (for example, associated with a brain tumour or gliosis), “genetic”, “metabolic” (for  
41 example, associated with mitochondrial disease), “infectious”, “immune” or “unknown”<sup>3</sup>. The category  
42 “unknown” includes genetic, metabolic and structural causes that have not yet been identified.

43  
44 Headaches are among the commonest disorders globally — the Global burden of Disease Study 2017 estimated  
45 that there were > 3 billion individuals with headache across 195 countries and territories<sup>4</sup>. The International  
46 Classification of Headache Disorders 3 (ICHD-3)<sup>5</sup> distinguishes between primary headaches — including  
47 migraine, tension-type headache (TTH) and trigeminal autonomic cephalalgias — and secondary headaches,  
48 which are attributable to other disorders or substances. TTH, which affects >2 billion people globally<sup>4</sup>, is a poorly  
49 defined featureless headache that lacks the characteristic features of other primary headaches and is usually  
50 bilateral and pressing (non-pulsating)<sup>5</sup>. TTH can last for 30 minutes to seven days, is not usually aggravated by  
51 routine physical activity and is not accompanied by nausea, vomiting or photo-phobia or phonophobia<sup>5</sup>.

52 Global migraine prevalence is ~1.3 billion and the disorder is 3–4 times more common in women than men<sup>4</sup>.  
53 Migraine is a heterogeneous brain disorder, typically characterised by recurrent attacks of mostly severe unilateral  
54 pulsating headache lasting 4–72 hours, accompanied by nausea, vomiting and/or hypersensitivity to sensory  
55 stimuli, and a range of other sensory and cognitive symptoms<sup>5</sup>. In about 30% of individuals with migraine, the  
56 pain is preceded — and in rare cases accompanied or followed by — a migraine aura, consisting of transient focal  
57 neurological symptoms. Symptoms of migraine aura are usually visual but may involve tactile, motor and/or  
58 speech disturbances<sup>6</sup>. Some individuals have auras without headache<sup>7</sup>.

59 Here, we review the link between epilepsy and headaches, starting with the epidemiology of the two disorders.  
60 We then discuss the diagnosis and classification of headaches in epilepsy and provide an overview of the current  
61 understanding of the underlying pathophysiological mechanisms. Last, we discuss the clinical management of  
62 co-existing headaches and epilepsy. We focus on evidence published between 2015 and 2020 to provide a view  
63 of recent progress in the field, and we also provide a timeline of key publications from before 2015 (Fig. 1.).

64

## 65 **[H1] Epidemiological evidence**

66 Headaches, especially migraine, and epilepsy frequently co-exist in the same individuals. A meta-analysis of  
67 population-based studies of migraine in people with epilepsy published between 1996 and 2012 indicated that  
68 lifetime migraine prevalence was 52% greater in people with epilepsy than in people without epilepsy<sup>8</sup>. The  
69 lifetime epilepsy prevalence was also 79% greater in people with migraine than in people without migraine. A  
70 more recent meta-analysis (including studies published between 2004 and 2019) estimated a 49% prevalence of  
71 unspecified headache among people with epilepsy<sup>9</sup>. Additional evidence has confirmed the findings of these  
72 meta-analyses regarding the co-existence of epilepsy and headache (Table 1)<sup>10–19</sup>. In these studies, ≤79% of  
73 individuals with epilepsy reported experiencing headaches. The most common headache types in individuals with  
74 epilepsy were migraine (reported by ≤25% of participants) and TTH (reported by ≤40% of participants)<sup>10,13,14,16,18</sup>.  
75 Women with epilepsy tended to report migraine more often than men with epilepsy<sup>11,12,16,18,20</sup>. No clear  
76 relationship between headache type and epileptic focus location, seizure type, seizure frequency, or use of anti-  
77 seizure medication was identified in these recent studies<sup>13,16</sup>. One older study reported that peri-ictal headaches  
78 were ipsilateral to the epileptic focus in temporal epilepsy, but not in extra-temporal epilepsy<sup>22</sup>. Some researchers

79 have suggested that the association between headache and epilepsy is stronger in individuals with genetic forms  
80 of epilepsy than those with non-genetic forms, and stronger in children than in adults<sup>23</sup>, One study reported a  
81 negative correlation between headache frequency and age of epilepsy onset<sup>11</sup> comparative meta-analytic evidence  
82 to support this finding is lacking.

### 83 ***[H2] Limitations of epidemiological studies***

84 Epidemiological studies have offered important insights into the relationship between epilepsy and headache but  
85 can be subject to biases, which might influence findings. First, the case-ascertainment method used often  
86 influences study findings, for example, studies that use self-report questionnaires tend to show a stronger  
87 association between headache and epilepsy than those that rely upon a physician's assessment<sup>8</sup>. This disparity  
88 might be caused by the fact that few validated instruments exist for self-diagnosis of epilepsy or headaches<sup>24</sup> —  
89 studies often use their own, unvalidated instruments<sup>8</sup>, the accuracy of which is unknown. How questions are  
90 formulated can influence the responses; for example, the results of one study suggested that people with epilepsy  
91 were three times more likely to report headaches preceding seizures when asked closed-ended questions than  
92 when asked open-ended questions<sup>25</sup>.

93 Second is the effect of recall bias on findings<sup>26</sup>. Evidence indicates that, compared with healthy individuals,  
94 individuals with a pre-existing condition are more likely to report additional symptoms<sup>26</sup>. This observation might  
95 explain why individuals with epilepsy report migraine more often than individuals without epilepsy<sup>8</sup>. Conversely,  
96 seizures can be associated with amnesia, which would make it difficult for the individual to recall what happened  
97 just prior, during or after the seizure, thus preventing the reporting of comorbidities such as headache<sup>27</sup>.  
98 Additionally, seizures are often conspicuous events and could overshadow less apparent complaints like  
99 headache, especially in children. Consequently, individuals with epilepsy might perceive headaches as  
100 “mundane” and thus not report them unless directly asked.

101 Third, physicians might not be aware that headaches are common in individuals with epilepsy<sup>27-29</sup>, which could  
102 introduce misclassification bias<sup>26</sup>. This type of bias could occur when the health provider is more or less attentive  
103 to comorbidities contingent on whether the individual has a debilitating condition. A serious ailment might  
104 prompt physicians to look for other associated conditions. However, an individual might be so ill that “milder”  
105 symptoms or diseases are overlooked or seen as part of the significant condition. We hypothesize that this bias

106 could explain why studies based on physician assessment show a lower association between epilepsy and  
107 headaches than studies based on self-assessment<sup>8</sup>.

108 Last, although studies that use insurance data or International Classification of Diseases codes have the advantage  
109 of physician-diagnosed data from large cohorts of individuals, the use of codes and insurance labels can be  
110 influenced by local policies. The choice of codes used might be influenced by financial or insurance-related  
111 factors, also resulting in biases. Despite these various sources of bias, epidemiological studies are essential in  
112 ascertaining the overlap between different conditions. Designing studies that are totally free of bias is impossible  
113 but bias can be reduced during the data collection phase and taken into account when interpreting results.

## 114 ***[H2] A bidirectional relationship***

115 Whether epilepsy and headaches have a “bidirectional” association — meaning that the occurrence of one  
116 influences the onset of the other and vice versa — remains unknown. To date, most studies of the association  
117 between epilepsy and headaches have been cross-sectional, so do not allow for such assessments. To assert that  
118 a relationship between two conditions is bidirectional, a precise determination of condition B's onset in relation  
119 to condition A is required, and thus costly and labour-intensive longitudinal studies are needed. One such study  
120 evaluated the risk of developing subsequent epilepsy when first diagnosed with migraine and found that  
121 individuals with migraine and those who had migraine and sleep disorders, cognitive disorders, anxiety or  
122 depression were more likely to develop epilepsy than healthy individuals<sup>30</sup>. This cohort was followed-up for a  
123 mean period of 12 years, and the relative risk of developing epilepsy was found to be 2.3 times higher in men  
124 than in women<sup>31</sup>. Risk was increased by older age, low-income status and comorbidities, especially head trauma.  
125 For example, the risk of developing epilepsy was 4.6 times higher in men with migraine and a history of head  
126 trauma than in men with migraine and no history of head trauma<sup>31</sup>. These studies are longitudinal, but only  
127 assessed the risk of developing epilepsy in people with migraine and do not provide information on whether or  
128 not the relationship is truly bidirectional. Multi-centre prospective, long-term studies with clear diagnostic criteria  
129 will be vital to shed light on the complex relationship between epilepsy and headache and help identify individuals  
130 at risk of developing severe or chronic forms of either condition.

## 131 **[H1] Diagnosis and classification**

132 Headaches that co-occur with epilepsy can be classified according to their temporal relationship to seizures (Fig.

133 2). Interictal headaches occur > 24 hours before and > 72 hours after epileptic seizures. Peri-ictal headaches,  
134 including migraine, occur shortly before, during or just after an epileptic seizure and can present a diagnostic  
135 challenge. The distinction between epilepsy and peri-ictal headaches is often apparent, the conditions can  
136 sometimes overlap either temporally or in terms of symptoms. These temporally classified types of headache  
137 (pre-ictal, post-ictal, ictal and interictal headache) can occur in the same individual (table 1).

138 Accurate classification of epilepsy and headache is important for initiating adequate, timely and appropriate  
139 treatment and requires a good description of the symptoms and their temporal relationships. The ILAE seizure  
140 classification scheme does not include a class of seizures with symptoms that overlap with headaches. However,  
141 the ICHD-3 includes several categories of seizure-related headaches<sup>5</sup> (Box 1): migraine aura-triggered seizure  
142 (section 1.4.4), ictal epileptic headache (section 7.6.1) and post-ictal headache (section 7.6.2).

## 143 ***[H2] Pre-ictal headaches***

144 Headaches that occur < 24 hours before a seizure and last until seizure onset have been defined as pre-ictal<sup>11</sup>.  
145 According to the ICHD-3<sup>5</sup>, the existence of pre-ictal headaches is controversial<sup>5</sup>, even though they have been  
146 reported in several studies<sup>32–35</sup>. The issue is that an EEG recording of the headache event is mandatory for the  
147 diagnosis of pre-ictal headache — for a headache to be pre-ictal, it must not be accompanied by ictal epileptic  
148 discharges on the EEG — and the studies cited above did not include an EEG recording of the event<sup>32–35</sup>.  
149 Headache concomitant with ictal epileptic discharges should be classified as ictal epileptic headache (see below).  
150 A classification of pre-ictal headache is not given in the ICHD-3<sup>5</sup>, but the comments section calls for more studies  
151 to establish the existence, prevalence and features of this type of headache. The results of cohort studies suggest  
152 that possible pre-ictal headaches (without EEG confirmation) occur in 1–10% of people with epilepsy<sup>10,12–15,19,21</sup>  
153 — (Table 1) the headache is migraine-like in 30–60% of these individuals and tension-type in ~20%<sup>10–15,17,19,21</sup>.  
154 In a video-EEG study, 25 of 831 (6.3%) individuals with epilepsy reported pre-ictal headache without epileptic  
155 discharges on the EEG<sup>17</sup>. Five had “headache as a seizure aura”, which should be classified as “ictal epileptic  
156 headache”, see below<sup>17</sup>.

## 157 ***[H2] Migraine-aura triggered seizures***

158 The term aura is used to describe subjective precursory symptoms of seizures and migraine headaches; however,  
159 it refers to different phenomena in the context of migraine or epilepsy. The ICHD-3<sup>5</sup> defines aura as “recurrent  
160 attacks, lasting (5–60) minutes, of unilateral fully reversible visual, sensory, motor or other central nervous system  
161 symptoms that usually develop gradually and are usually followed by headache and associated migraine  
162 symptoms.” (Box 2). In contrast, a report by the ILAE Task Force on Classification and Terminology describes  
163 aura as “A subjective ictal phenomenon that, in a given individual, may precede an observable seizure; if alone,  
164 constitutes a sensory seizure.”<sup>36</sup> An epileptic aura is confirmed by epileptic discharges on EEG and is part of the  
165 seizure<sup>36</sup>. Some epileptic auras do not have a visible EEG correlate as they can be very focal, occupying such a  
166 small cortical area that the spatial resolution of surface EEG is insufficient to detect them<sup>37</sup>.

167 In migraine, no consistent EEG abnormalities are observed during the aura and headache phase<sup>38,39</sup>. Studies have  
168 found either slow waves, attenuation of background activity amplitude or the presence of normal EEG patterns  
169 during migraine aura<sup>38,40</sup>. During attacks of hemiplegic migraine and migraine with disturbed consciousness,  
170 abnormal EEG patterns with unilateral or bilateral delta activity have been recorded<sup>40</sup>. The EEG has no diagnostic  
171 value in migraine (or headaches)<sup>38</sup>, but is mandatory for diagnosis of epilepsy, which also applies to individuals  
172 with epilepsy and comorbid headache<sup>41</sup>.

173 In rare cases, a migraine-like aura can occur immediately before a seizure<sup>5</sup>. The ICHD-3 refers to seizures that  
174 occur during or < 1 hour after the end of a migraine with aura attack as “A seizure triggered by an attack of  
175 migraine with aura”<sup>5</sup>. These seizures are sometimes referred to as migralepsy<sup>5</sup>. Visual symptoms and  
176 hallucinations are hallmarks of migraine aura and occipital epilepsy, making it difficult to distinguish between  
177 the two conditions. In a meta-analysis published in 2019, the most common visual symptoms of migraine aura  
178 reported were foggy and/or blurred vision, zigzag or jagged lines, scotoma, phosphenes and flickering light<sup>42</sup>.  
179 (Table 2) The symptoms of occipital epilepsy are elementary and visual hallucinations or illusions; blindness;  
180 palinopsia and sensory hallucinations of ocular movements; ocular pain and oculomotor symptoms, including  
181 deviation of the eyes; and nystagmus and repetitive eyelid closure or fluttering<sup>43</sup>. The duration of symptoms is  
182 the most helpful feature for differentiating between migraine-related aura and occipital epilepsy<sup>44</sup>: the median  
183 duration of migraine aura is ~25 minutes, whereas epileptic visual hallucinations last < 1 minute<sup>45</sup>. The hallmark  
184 of migraine aura is a slowly progressive centrifugal or centripetal scotoma that expands over 10–60 minutes<sup>5,42</sup>;



185 a feature not described by people with occipital epilepsy<sup>43,45</sup>. In migraine, visual symptoms are almost always  
186 lateralised<sup>5</sup>. Similarly, event-associated nausea, vomiting, photophobia and phonophobia occur more often in  
187 migraine with aura than in occipital epilepsy<sup>45</sup>. Clinically, the simultaneous occurrence of positive and negative  
188 phenomena is more suggestive of a migraine aura than of epilepsy<sup>5,43,45</sup>.

189 The overlapping features of migraine aura and occipital seizures means that diagnosis requires a detailed  
190 description of the subjective symptoms, and pre-ictal and ictal EEG recordings. The absence of epileptiform  
191 abnormalities when the symptoms are present is the gold standard for ruling out an epileptic origin. The lack of  
192 epileptic EEG abnormalities during the migraine aura phase is essential for diagnosing migraine aura-triggered  
193 seizure. Experts doubt the existence of migraine aura-triggered seizures<sup>46–48</sup> as pre-ictal and ictal EEG recordings  
194 often confirm an epileptic rather than a migraineous origin of the symptoms. For example, in one EEG study, 16  
195 out of a cohort of 4,600 children diagnosed with epilepsy had an epileptic seizure < 1 hour after a presumed  
196 migraine attack. These children had focal or generalized ictal EEG abnormalities during the migraine phase,  
197 indicating an epileptic origin of the migraine-like symptoms<sup>46</sup>. In a more recent study involving a large cohort of  
198 individuals with epilepsy, three participants (<1%) reported epileptic seizures within an hour of an attack of  
199 migraine with aura. Two of these individuals were diagnosed with occipital epilepsy — the migraine-like aura  
200 was interpreted as an occipital seizure — and the third was diagnosed with epilepsy secondary to systematic lupus  
201 erythematosus<sup>49</sup>. In a case report, two individuals presented with visual auras lasting 13–17 minutes, followed by  
202 a forceful turning of the head and, in one individual, a generalised tonic–clonic seizure<sup>48</sup>. EEG recordings showed  
203 a left occipital seizure in the first individual and a right parietal–occipital seizure in the other individual. We  
204 observed a similar presentation in one of our patients, who presented with headache accompanied by epileptic  
205 discharges on the EEG (Supplementary video 1). These individuals, in whom epileptic discharges accompany the  
206 visual symptoms and headaches on the EEG, should receive a diagnosis of ictal epileptic headache (see below),  
207 not migraine aura-triggered seizures, highlighting the challenges involved in diagnosing these conditions.

## 208 ***[H2] Ictal epileptic headache***

209 A headache accompanied by epileptic abnormalities on the EEG is classified as an “ictal epileptic headache” by  
210 the ICHD-3<sup>5</sup>. The headache should develop simultaneously with the seizure, and either be ipsilateral to the ictal  
211 discharge and/or show a substantial reduction in severity immediately after the seizure has terminated. Ictal

212 epileptic headache can be accompanied or followed by other epileptic manifestations, such as motor, sensory or  
213 autonomic signs<sup>50</sup>. If ‘pure’ or ‘isolated’ ictal epileptic headache is the only manifestation of a seizure, it requires  
214 a differential diagnosis from other types of headache. In the ICHD-3 ‘hemicrania epileptica’ signifies a rare  
215 variant of ictal epileptic headache, characterised by headache that is ipsilateral to ictal EEG paroxysms<sup>5</sup>. The  
216 precise definitions of the terms ‘hemicrania epileptica’ and ‘ictal epileptic headache’ have, however, been  
217 extensively debated<sup>27,29,51–53</sup>. Indeed, the ICHD-3 begins the definition of hemicrania epileptica with “if confirmed  
218 to exist”, indicating the difficulties involved in confirming this diagnosis — EEG recordings are rarely performed  
219 in individuals with isolated headache. However, a video-EEG study did identify two instances of hemicrania  
220 epileptica<sup>17</sup>

221 People with ictal epileptic headache can have interictal abnormalities on the EEG<sup>53</sup>. The diagnosis is confirmed  
222 by the presence of epileptiform patterns on the ictal EEG; however, as these abnormalities can occur with different  
223 types of lesional and non-lesional epilepsy, there is no unique EEG pattern linked to ictal epileptic headache<sup>27,53</sup>.  
224 Persistent ictal epileptic headache can occur in non-convulsive status epilepticus and in some individuals the  
225 headache only resolves after intravenous administration of anti-seizure medication<sup>27</sup>. Some researchers have  
226 suggested that an ability of anti-seizure medication to resolve the headache and the epileptic discharges on the  
227 EEG should be added as a diagnostic criterion for ictal epileptic headache<sup>51,54</sup>. Our view is that, owing to potential  
228 pharmacokinetic and pharmacodynamic differences between individuals, a response to treatment should not be  
229 part of a clinical definition.

230 EEG recordings have little diagnostic value in the majority of individuals with isolated headaches, including  
231 migraines, so are rarely performed in this group of people<sup>38</sup>. Therefore, ictal epileptic headache, although rare, is  
232 probably underdiagnosed. For example, one study reported that out of 831 people with epilepsy and peri-ictal  
233 headaches who underwent video-EEG monitoring, six had “headache as an aura of a seizure”, along with epileptic  
234 discharges on the EEG<sup>17</sup>. Therefore, these headaches should be classified as ictal epileptic headache<sup>5</sup>. The  
235 headaches lasted <35s in all cases, which is also suggestive of ictal events<sup>17</sup>. A systematic review published in  
236 2017 analysed 32 cases of reported ictal epileptic headache and found that the headache can be migraine-like or  
237 tension-type, and the location of the pain can vary<sup>53</sup>. The headaches occurred in children and adults and affected

238 the sexes equally. Evidence from this and other studies indicates that the epileptic focus and EEG features of ictal  
239 epileptic headaches are heterogeneous<sup>52,53,55</sup>.

240 As in other focal epilepsies, in some individuals with ictal epileptic headache, epileptic abnormalities can only  
241 be detected with intracranial electrodes, suggesting a deep epileptic focus<sup>56</sup>. Ictal epileptic headache was  
242 identified in just five people in a retrospective review of 8,800 video-EEG recordings of 4,800 individuals with  
243 epilepsy<sup>57</sup>. Three of these five individuals had lesions in the left posterior regions, whereas the other two had  
244 generalised genetic or idiopathic epilepsy. A descriptive study of 47 people with epilepsy or unusual headache  
245 identified 22 individuals reporting headaches during seizures<sup>19</sup>. This high prevalence was attributed to the use of  
246 self-reports, and the absence of an objective tool to evaluate headache characteristics and accurately define the  
247 timing of headache onset relative to the seizure<sup>19</sup>. EEG recordings confirmed ictal headache in two individuals<sup>19</sup>.  
248 These studies and the definitions given in the ICHD-3 highlight the overlap between headaches and epilepsy.  
249 Atypical headaches — especially those with an abrupt onset and ending, or those that do not respond to analgesic  
250 treatment — should suggest to the clinician the possibility of an epileptic origin warranting an ictal EEG  
251 recording, especially if other suggestive features, such as a family history of epilepsy, are present. Paroxysmal  
252 episodes with visual signs can point to migraine with aura or epilepsy, and require detailed history taking. EEG  
253 recordings, ideally with concomitant video and encompassing the pre-ictal and ictal phase, are mandatory to  
254 support these challenging differential diagnoses and should be performed when the clinician has even the slightest  
255 suspicion that the headaches have an epileptic origin<sup>58</sup>.

## 256 **[H2] Post-ictal headaches**

257 Post-ictal headache is defined as a headache caused by an epileptic seizure, occurring < 3 hours after the end of  
258 the seizure event and remitting spontaneously < 72 hours after seizure termination<sup>5</sup>. Evidence indicates that post-  
259 ictal headache occurs in < 45% of individuals with epilepsy (Table 1), making it the most common type of peri-  
260 ictal headache<sup>10-17,19,21</sup>. In ~ 50% of individuals with post-ictal headache, the headache is migraine-like (Table  
261 1)<sup>10-12,14-17</sup>. The results of a meta-analysis published in 2019 indicated that of individuals with epilepsy, one third  
262 experience post-ictal headache and 16% experience post-ictal migraine<sup>59</sup>. Interestingly, in people with focal  
263 epilepsy, post-ictal headache is more common in those with occipital epilepsy than those with epilepsy originating

264 in the frontal or temporal lobes<sup>49</sup>. Post-ictal headache is also more common after convulsive seizures than after  
265 non-convulsive seizures<sup>35</sup>.

266

## 267 **[H1] Pathophysiology of headache disorders in epilepsy**

268 Comparing the pathophysiology of seizures and headache could help uncover the mechanisms underlying the  
269 observed associations between these two disorders. A neuronal excitation/inhibition imbalance is thought to  
270 contribute to attack susceptibility in epilepsy and migraine<sup>60–62</sup>. The link between hyperexcitability, seizures and  
271 cortical spreading depolarisation — the neurobiological correlate of the migraine aura and a putative trigger of  
272 migraine attacks — provides a mechanistic framework for some, but not all, of the clinical observations of  
273 headache in epilepsy (Box 2; Fig. 3).

## 274 ***[H2] Mechanisms underlying seizures and headaches***

275 Epilepsy is characterised by a temporary disruption of neurological function caused by seizures, which spread  
276 across neuronal networks within seconds and are typically associated with hypersynchronous activity on EEG  
277 recordings<sup>63</sup>. This neuronal network synchronisation is thought to be caused by neuronal hyperexcitability<sup>64</sup>,  
278 which is likely to result from multiple factors. These factors include perinatal insults, impaired mitochondrial  
279 function and mutations in genes encoding ion channels or transporters that are involved in glutamatergic or  
280 GABAergic neuronal transmission or glial buffering capacity<sup>65–70</sup>.

281 Unlike seizures, headaches are not associated with hypersynchronous EEG activity, except in the case of  
282 headaches with an epileptic origin<sup>5,71,72</sup>. Headache is thought to result from activation of the trigeminovascular  
283 system, which involves meningeal nociceptive afferents from trigeminal ganglion sensory neurons, the brainstem  
284 trigeminal cervical complex (TCC), and thalamocortical areas contributing to the sensation of pain<sup>73,74</sup>. Several  
285 factors can activate the trigeminovascular system at the meningeal level. These factors include the build-up of  
286 diffusible substances such as extracellular K<sup>+</sup> and H<sup>+</sup> (leading to low pH), release of vasoactive mediators such  
287 as calcitonin gene-related peptide (CGRP) or substance P, as well as inflammatory mechanisms<sup>74–76</sup>. The results  
288 of preclinical studies in rodents indicate that the trigeminovascular system can become activated by cortical  
289 spreading depolarisation<sup>77,78</sup> and that this activation involves inflammatory cascades<sup>79,80</sup>. These observations

290 suggest that cortical spreading depolarisation during migraine aura might initiate headache<sup>81</sup>(Fig.3; but see also  
291 Box 2).

292 Meningeal vasodilation has been cited as trigger for trigeminovascular system activation, in line with the ancient  
293 ‘vascular theory’ of migraine, but more recent evidence suggests that changes to cerebral blood flow during a  
294 migraine attack are an accompanying phenomenon induced by trigeminal nerve activation<sup>82</sup>. In addition to the  
295 release of vasoactive substances from trigeminal nociceptive afferents, cerebral vasodilation could also result  
296 from activation of cardiovascular nuclei in the brainstem<sup>74</sup>. Neuroimaging studies have identified functional  
297 changes in the thalamic nuclei and brainstem, hypothalamus, frontal cortex, anterior cingulate cortex, basal  
298 ganglia, and insula during headache generation<sup>83,84</sup>. Connectivity changes in some of these regions have also been  
299 observed outside of and during attacks, as have changes affecting other regions such as the pons and  
300 somatosensory cortex<sup>85–89</sup>. Within this larger ‘head pain matrix’, hyperexcitability at any level could contribute  
301 to headache initiation<sup>74,76,90</sup>.

## 302 ***[H2] Interictal headaches***

303 General brain hyperexcitability in people with epilepsy<sup>64</sup> might, even in the absence of seizures, lower the  
304 activation thresholds of brain regions that are part of the trigeminovascular system, resulting in interictal  
305 headaches. This hyperexcitability can be a result of genetic mutations that affect neurotransmission (see section  
306 on overlapping genetics below)<sup>91</sup>. Studies in transgenic mouse models of migraine have identified an association  
307 between migraine-causing mutations and inflammatory changes<sup>92,93</sup>, which might also contribute to  
308 trigeminovascular system activation. In migraine, effects of exogenous triggers such as light or stress, food or  
309 sleep deprivation, and systemic fluctuations in sex hormones are hypothesized to contribute to attack initiation  
310 via the dysregulation of cortical and (hypo)thalamic pathways<sup>74,76,94–101</sup>. For example, in rats, bright-light stress  
311 causes cortical activation<sup>96</sup>, and sleep deprivation is associated with reduced brain glycogen levels and enhanced  
312 susceptibility to cortical spreading depolarization<sup>97,98</sup>. As hyperexcitability seems to contribute to the lowered  
313 threshold to headache triggers in migraine<sup>74,76</sup>, this could be hypothesized to also lead to an increased propensity  
314 for interictal headaches to occur in people with epilepsy.

## 315 ***[H2] Pre-ictal headaches***

316 Brain parenchymal inflammation has been shown to promote seizure initiation in rodent models<sup>102,103</sup>. One  
317 mechanism underlying this inflammatory response involves the neuronal release of brain high mobility group  
318 box 1 (HMBG1) as a result of brain hyperexcitability<sup>104</sup>. In migraine headaches, activation of the  
319 trigeminovascular system by cortical spreading depolarization was shown to activate inflammatory cascades,  
320 including neuronal release of HMBG1, resulting in meningeal nociceptive activation<sup>79</sup>. It could be hypothesized  
321 that cortical network hyperexcitability, if maintained below the thresholds for eliciting epileptiform discharges  
322 and sensorimotor manifestations, could lead to trigeminovascular system activation via neuronal HMBG1 release.  
323 At the subcortical level, pre-ictal hyperexcitability can affect central autonomic circuits, including hypothalamic  
324 and brainstem areas<sup>105</sup>, and projections to the limbic system<sup>106</sup>. Given the involvement of these areas in the  
325 development of head pain<sup>73,74</sup>, pre-ictal hyperexcitability in these regions could be hypothesized to elicit head  
326 pain before the development of widespread seizure activity.

### 327 ***[H2] Migraine-aura triggered seizures***

328 The occurrence of a migraine aura before a seizure suggests an underlying cortical spreading depolarisation,  
329 followed by epileptiform activity. This sequence of events has been observed in preclinical studies, in which  
330 spreading depolarisation increased epileptic activity in rat brain slices<sup>107</sup>, as well as in resected human epileptic  
331 brain tissue<sup>107-110</sup>. Evidence indicates that suppression of inhibitory GABA function can contribute to this increase  
332 in epileptic activity<sup>107,110</sup>. Given the scarcity of clinical evidence for migraine aura-triggered seizures, this  
333 sequence of events is likely to be rare in humans. Indeed, the results of a preclinical study found that spreading  
334 depolarisation protected rat cortical networks from expressing seizure activity<sup>111</sup>.

### 335 ***[H2] Ictal epileptic headache***

336 Multiple mechanisms could be responsible for ictal epileptic headache, including seizure-related changes in the  
337 trigeminovascular system and in pain-causing brain regions. The cortical projections responsible for head pain  
338 are likely to be widespread, involving primary sensory areas and the central autonomic network, that is, the  
339 thalamus, hypothalamus, insula, anterior cingulate cortex, medial prefrontal cortex, precuneus, amygdala,  
340 hippocampus and other parts of the limbic system<sup>54,72,112,113</sup>. A study in people with epilepsy evaluated  
341 participants' responses to direct electrical stimulation of the cortex during pre-surgical evaluation and showed  
342 that pain responses were scarce (observed for 1.4% of the stimulated sites). Pain was only triggered by stimulation

343 of the medial parietal operculum and posterior insula<sup>114</sup>. This deep localisation of several pain areas might explain  
344 why, in some individuals, the electrophysiological correlate of ictal epileptic headache is only recorded using  
345 depth electrodes. However, seizures with a confirmed origin in the parietal operculum and posterior insula lead  
346 to pain sensations in the limbs contralateral to the epileptic focus and do not always lead to head or facial pain<sup>115</sup>.  
347 It is hypothesized that seizure activity in autonomous areas could cause direct neuronal activation of the brainstem  
348 trigeminocervical complex<sup>54</sup> resulting in headache<sup>54,112,113</sup>, but direct evidence for this mechanism occurring in  
349 ictal epileptic headache is lacking.

350 A case series identified a multitude of EEG patterns in ictal epileptic headache<sup>52,53</sup> suggesting that this form of  
351 headache is associated with different seizure types and localisations. As was suggested for pre-ictal headache, the  
352 mechanisms underlying ictal epileptic headache might also involve inflammatory changes caused by enhanced  
353 network excitability during seizures. However, in ictal epileptic headache, the timing of events triggering the  
354 trigeminovascular system occurs in parallel to the expression of symptomatic seizures and epileptiform EEG  
355 bursts. Increased cerebral blood flow during the pre-ictal and ictal period has also been suggested as a possible  
356 trigger of the trigeminovascular system, resulting in headache during seizures<sup>33</sup>. However, we do not consider  
357 this to be plausible as the results of magnetic resonance angiography studies in people with migraine indicate that  
358 arterial dilatation is an effect of headache, as opposed to a cause<sup>116,117</sup>. One such study found no evidence of  
359 arterial dilatation during migraine at all<sup>118</sup>. Indeed, the historical view of vasodilation as a cause of migraine  
360 headaches has now effectively been excluded<sup>74,82</sup>. In addition to the release of vasodilating substances from  
361 trigeminal nerve endings, vasodilation might also result from increased activity of the trigeminovascular system  
362 brainstem nuclei inducing vascular changes such as enhanced cerebral blood flow<sup>74</sup>. These observations suggest  
363 that an ictal epileptic headache is likely to result from direct activation of trigeminovascular system brainstem  
364 regions involved in headache generation, or seizure-related parenchymal changes triggering the activation of the  
365 trigeminovascular system.

## 366 ***[H2] Post-ictal headaches***

367 Evidence from preclinical studies in rats indicates that seizures can be followed by spreading depolarisation<sup>119–</sup>  
368 <sup>122</sup>; however, post-ictal spreading depolarisation has not been observed in humans (except for studies in  
369 individuals with brain damage<sup>123,124</sup>) suggesting that this mechanism is not responsible for post-ictal headache.

370 Experimental evidence also indicates that neurons do not remain depolarised after the termination of tonic–clonic  
371 seizures, but instead become hyperpolarized<sup>125</sup>(Box 2). This post-ictal neuronal silencing is sudden and  
372 widespread, instead of spreading<sup>126</sup>. Preclinical studies indicate that the mechanisms underlying post-ictal  
373 silencing are multifactorial<sup>126,127</sup>, including astrocytic adenosine release<sup>128</sup>, acidosis and hypoxia-related vesicular  
374 transmitter depletion<sup>128,129</sup>, none of which have been implicated in the initiation of spreading depolarization. There  
375 is no clinical evidence that post-ictal spreading depolarization contributes to post-ictal neuronal silencing (Box  
376 2). In people with epilepsy, levels of adenosine were found to be enhanced post-ictally up to 18 minutes after  
377 seizures<sup>130</sup>, and post-ictal acidosis is evidenced from postictal hypercapnia<sup>131</sup> and enhanced plasma levels of  
378 lactate<sup>132</sup>. Clinical evidence for post-ictal neurotransmitter depletion is lacking<sup>133</sup>. Analysis of neocortical tissue  
379 from individuals with chronic epilepsy and a rat model of epilepsy suggested that the low likelihood of spreading  
380 depolarisation in epileptic tissue results from intrinsic changes in GABAergic transmission<sup>134</sup>.

381 Evidence from studies in rodent brain slices indicates that, even in the absence of post-ictal spreading  
382 depolarisation, excessive neuronal network activation during seizures can lead to trigeminovascular system  
383 activation via mechanisms such as the build-up of K<sup>+</sup>, acidosis and neuronal release of CGRP during or shortly  
384 after a seizure<sup>135–137</sup>. On the basis of evidence from preclinical studies, activation of meningeal nociceptive fibres  
385 by such compounds would be expected to lead to perception of headache by thalamocortical activation within  
386 10–30 minutes<sup>74</sup>, in line with a post-ictal phenomenon. Inflammatory changes also occur during seizures<sup>102</sup>, for  
387 example, neuronal release of HMBG1 was shown to occur within an hour of seizure initiation in animal models<sup>104</sup>.  
388 It is possible that following seizures, these enhanced HMBG1 levels activate the trigeminovascular system  
389 (similar to the activation after spreading depolarization observed in experimental studies) causing post-ictal  
390 headache, although this hypothesis has not yet been tested in animals or humans. Last, seizures can yield post-  
391 ictal hypoperfusion as shown in rodent<sup>138</sup> and some clinical epilepsy studies<sup>139,140</sup>. The resulting hypoxia<sup>138</sup> might  
392 be sufficient to trigger headache mechanisms as occurs in hypoxia-induced migraine attacks<sup>141</sup>.

393

### 394 **[H1] Overlapping genetics**

395 Variants in > 200 genes have been identified as causing or enhancing the risk of specific types of epilepsy<sup>142</sup>.  
396 Some monogenic forms of epilepsy exist, but for other epilepsies the genetic risk is complex and polygenic<sup>143</sup>.



397 Juvenile myoclonic epilepsy has both a monogenetic and a complex genetic origin. In one study, 70% of people  
398 with this form of epilepsy reported a family history of migraine, almost twice as many as in an age-matched and  
399 sex-matched control group, suggesting an overlap in genetic risk between juvenile myoclonic epilepsy and  
400 migraine<sup>144</sup>.

401 Some specific genes have also been associated with both epilepsy and migraine<sup>66,145</sup>. This commonality is most  
402 evident in familial hemiplegic migraine (FHM), which is an autosomal dominant subtype of migraine with aura,  
403 characterised by a transient hemiparesis during the aura and headache characteristics that are identical to those  
404 observed in common forms of migraine<sup>146,147</sup>. Three genes have been associated with FHM: *CACNA1A*, which is  
405 located on chromosome 19p13 and encodes a subunit of neuronal voltage-gated Ca<sup>2+</sup> channel 2.1 (Ca<sub>v</sub>2.1)<sup>148</sup>;  
406 *ATPIA2*<sup>149</sup>, which is located on chromosome 1q23 and encodes the α2 subunit of the glial Na<sup>+</sup>/K<sup>+</sup>-ATPase; and  
407 *SCN1A*<sup>150</sup>, which is located on chromosome 2q24 and encodes a subunit of neuronal voltage-gated sodium  
408 channel 1.1 (Nav1.1). These three genes form the basis for the definition of three subtypes of FHM: mutations in  
409 *CACNA1A* cause FHM1, mutations in *ATPIA2* cause FHM2 and mutation in *SCN1A* cause FHM3. For all three  
410 forms of FHM, specific mutations have been linked to specific presentations of migraine and epilepsy<sup>147,150–153</sup>.  
411 In FHM1 the ‘mild’ R192Q mutation in *CACNA1A* causes hemiplegic migraine without epileptic features<sup>148</sup>,  
412 whereas the more severe S218L mutation can also cause seizures<sup>152</sup>. In FHM2, novel missense mutations in  
413 *ATPIA2* can result in the co-occurrence of migraine and childhood epilepsy<sup>151</sup>. In FHM3, different mutations in  
414 *SCN1A* have been be associated with either childhood epilepsy<sup>150</sup> or generalised tonic–clonic seizures<sup>154</sup>. One  
415 study found that, in people with epilepsy and FHM3, generalized seizures occurred independently from  
416 hemiplegic migraine attacks<sup>154</sup>, suggesting that FHM and epilepsy share common molecular pathways.

417 Functional studies of FHM-associated mutations in vitro and in transgenic animal models have provided  
418 preclinical evidence that epilepsy and migraine result from partially overlapping genetic mechanisms<sup>155,156</sup>. These  
419 mechanisms involve alterations to neuronal and glial ion transport, resulting in network  
420 hyperexcitability<sup>61,146,155,157,158</sup>. Transgenic knock-in mice carrying the human FHM1-causing S218L mutation  
421 mimic the phenotype observed in humans with the mutation and display spontaneous or cortical spreading  
422 depolarisation-induced generalized seizures<sup>159,160</sup>. Results from in vitro studies suggest that the susceptibility for  
423 generalised seizures in FHM1 S218L mice is related to strongly enhanced excitatory transmission, resulting in

424 excessive recruitment of excitatory and inhibitory neuronal networks<sup>161,162</sup>. In FHM3, the spectrum of Nav1.1  
425 defects seems complex, and both gain-of-function and loss-of-function effects of mutations in *SCN1A* have been  
426 reported<sup>163,164</sup>. The identification of gain-of-function effects of FHM3-associated mutations contrasts with the  
427 loss-of-function mutations in *SCN1A* that are associated with Dravet Syndrome and cause impaired firing of  
428 inhibitory interneurons<sup>165</sup>. Computational work indicates that dynamic changes in the activity of genetically  
429 affected excitatory and inhibitory neuronal networks, and associated changes in ion activity determine whether  
430 neuronal hyperexcitability may result in a seizure, a cortical spreading depolarisation, or both<sup>166</sup>(Box 2). This  
431 observation underscores the complexity of predicting the functional outcome of shared genetic defects between  
432 epilepsy and migraine.

433 Truncating deletions in the *PRRT2* gene, which encodes a proline-rich transmembrane protein, were identified in  
434 a small number of people with (hemiplegic) migraine<sup>167,168</sup>, as a result of which *PRRT2* was put forward as the  
435 fourth FHM-associated gene. However, the same and similar *PRRT2* deletions have been identified in people  
436 with paroxysmal kinesigenic dyskinesia, benign familial infantile convulsions and infantile convulsion  
437 choreoathetosis without signs of migraine<sup>147</sup>. Therefore, the relationship between *PRRT2* and migraine does not  
438 seem to be precise.

439 A missense mutation in the *SLC1A3* gene, which encodes the glutamate transporter EAAT1 that is important in  
440 removing glutamate from the synaptic cleft<sup>169</sup>, has been associated with severe episodes of ataxia, epileptic  
441 seizures and hemiplegic migraine that can be explained by impaired glutamate transport<sup>169</sup>. Other genetic findings  
442 associated with features of epilepsy and migraine include mutations in *POLG* and *C10orf2*, which encode  
443 mitochondrial DNA polymerase<sup>170</sup> and Twinkle helicase<sup>171</sup>, respectively, and are involved in the maintenance of  
444 neuronal and glial energy supply. Some evidence suggests that mutations in mitochondrial genes associated with  
445 MELAS syndrome can predispose individuals to dysfunctional oxidative brain metabolism, explaining the co-  
446 occurrence of migraine-like episodes and epilepsy features in individuals with this syndrome<sup>172,173</sup>.

447 The genetic associations between polygenic forms of epilepsy and migraine remain unclear. However, a greater  
448 prevalence of migraine has been observed among family members of people with non-acquired focal epilepsy or  
449 generalised epilepsy than in the general population<sup>174</sup>, indicating a shared genetic susceptibility to both conditions.  
450 The results of a large-scale genome-wide association study identified a correlation between variants associated

451 with migraine, especially migraine with aura, and variants associated with epilepsy; however, this correlation did  
452 not reach statistical significance<sup>175</sup>.

453

## 454 **[H1] Clinical management**

### 455 ***[H2] Impact and diagnosis***

456 The results of a cross-sectional study indicated that ~50% of individuals with headache and epilepsy report the  
457 headaches as severe<sup>21</sup>. Headaches linked to epilepsy negatively affect quality of life<sup>21</sup>. A study at an epilepsy  
458 clinic found that depression and anxiety were linked to the presence of headache<sup>15</sup>. Postictal headaches, in  
459 particular, were associated with depression and suicidality. The first step for successfully managing any condition  
460 is a correct diagnosis. The results of a Dutch questionnaire-based study found that neurologists underestimate the  
461 occurrence of headache among individuals with epilepsy<sup>28</sup>. This observation suggests that increased awareness  
462 among neurologists of the association between epilepsy and headache is required. Atypical or persistent  
463 headaches not responding to standard treatment should suggest a possible epileptic origin, warranting an EEG-  
464 recording during the symptomatic (headache or possible migraine aura) phase. We are not aware of published  
465 guidelines on managing headaches in people with epilepsy, so we summarize the current practice below,  
466 providing suggestions for managing headaches in people with epilepsy based on the currently available evidence  
467 and our expertise.

### 468 ***[H2] Management of headaches in epilepsy***

469 Physicians managing the care of individuals with epilepsy should actively enquire about ictal, pre-ictal, and post-  
470 ictal headaches. An EEG recording of a headache event is mandatory to ascertain whether or not headaches have  
471 an epileptic origin, especially in the case of atypical, short-lasting and/or peri-ictal headaches<sup>19,45</sup>. Interictal and  
472 peri-ictal headaches that the individual reports as moderate or intense, once correctly diagnosed, should be treated  
473 with analgesics. If migraine is diagnosed concomitantly with epilepsy or vice-versa, an anti-seizure medication  
474 that also has proven efficacy for migraine should be prescribed whenever possible to avoid polypharmacy and  
475 possible drug—drug interactions<sup>176,177</sup>. The anti-seizure medications topiramate and valproate are approved for  
476 treatment of migraine by the FDA and European Medicines Agency<sup>178–180</sup>. However, topiramate and valproate  
477 can be teratogenic, so neither is suitable for treating women of child-bearing age<sup>181–183</sup> unless there is no other

478 effective treatment available<sup>179</sup>. Other anti-seizure medications, such as lamotrigine, can be used off-label,  
479 especially for migraine<sup>184</sup>.

480 Paradoxically, headaches are a common (>10%) adverse-effect of anti-seizure medication, and are most often  
481 associated with carbamazepine, phenytoin, lamotrigine and levetiracetam<sup>185</sup>. When evaluating headache in  
482 epilepsy, the possibility of an adverse effect of medication should be considered. Lower doses of topiramate,  
483 valproate or lamotrigine are used for the treatment of migraine than for the treatment of epilepsy, but people with  
484 migraine still seem to be more prone to the adverse effects of these medications than people with epilepsy<sup>186</sup>.  
485 People with migraine or migraine and epilepsy are also more likely to discontinue medication than those with  
486 epilepsy alone<sup>186</sup>. Medications used for migraine have not been associated with seizures. Individuals with  
487 pharmaco-resistant focal epilepsy can benefit from a resection of the epileptic focus; 34%–74% become seizure-  
488 free following the procedure<sup>187</sup>. However, in one study 12% of participants who underwent the procedure  
489 subsequently developed chronic headaches, which persisted for > 1 year after surgery<sup>188</sup>.

490

## 491 ***[H2] Novel pharmacological therapies***

492 Novel pharmacological therapies for migraine include those that target calcitonin gene-related peptide (CGRP),  
493 a trigeminal sensory neuropeptide that is expressed in neuronal tissue and distributed in discrete areas of the  
494 central and peripheral nervous system<sup>189</sup>. Although the precise mechanisms are unknown, activation of the  
495 trigeminovascular system seems to be associated with the increased release of CGRP from C-fibres in the  
496 trigeminal ganglion. Upon its release, CGRP binds to its receptor on A $\delta$ -fibres, leading to pain perception<sup>190</sup>.  
497 The results of clinical trials of CGRP-inhibiting drugs in migraine have shown an efficacy that is superior to  
498 placebo, and generally good tolerability<sup>191</sup>, making these drugs an attractive new avenue for acute and  
499 prophylactic treatment of migraine. CGRP-inhibiting drugs hold particular promise for individuals with  
500 difficult-to-treat migraine, who have high unmet needs and few treatment options<sup>191–193</sup>. CGRP has vasodilatory  
501 effects and is important for blood pressure regulation<sup>189,194</sup> and the long-term effects of CGRP-inhibition,  
502 especially in individuals with cardiovascular comorbidities, are still unknown<sup>195</sup>. Interestingly, the results of a  
503 study published in 2018 indicate that the new anti-seizure medication perampanel, which acts on glutamatergic

504 AMPA receptors, inhibits CGRP release in rat brainstem<sup>196</sup>. This observation suggests that perampanel could,  
505 in theory, be effective in treating peri-ictal headaches, although this has not been investigated yet.

506 Cannabidiol has received considerable media attention<sup>197–199</sup> after a case report indicated that it can reduce seizure  
507 frequency in individuals with epilepsy<sup>200</sup>. The results of clinical trials in Dravet syndrome<sup>201–203</sup> and Lennox–  
508 Gastaut syndrome<sup>204,205</sup> suggest that cannabidiol is more effective than placebo in reducing the frequency of  
509 convulsive and drop seizures<sup>206</sup>. Additional open-label studies of cannabidiol in other types of epilepsy are  
510 ongoing<sup>207–209</sup>. An oral cannabidiol solution has been approved by the FDA<sup>210</sup> and the European Medicines  
511 Agency<sup>211</sup> for treatment of seizures in children aged 2 years and older with Dravet syndrome and Lennox–Gastaut  
512 syndrome, two rare forms of severe epilepsy. One trial to assess the effect of cannabis on migraine is ongoing<sup>212</sup>  
513 and another is planned<sup>213</sup>.

## 514 ***[H2] Non-pharmacological approaches***

515 A meta-analysis of studies on transcranial magnetic stimulation (TMS) found that low-frequency TMS was  
516 associated with a reduction in seizure frequency in 30% of participants with treatment-resistant epilepsy<sup>214</sup>. The  
517 studies included in this analysis were, however, relatively small and heterogeneous, so more evidence to support  
518 this approach is needed. A systematic review of TMS for the treatment of headache disorders found that  
519 stimulation was associated with reduced headache frequency, duration, intensity and medication use; however,  
520 few studies reported TMS-associated changes greater than those observed with sham treatment<sup>215</sup>. Several studies  
521 have found an association between treatment with single-pulse TMS and a reduction in headache days and  
522 medication use in individuals with migraine with aura<sup>216–218</sup>. This evidence led the FDA to approve a single-pulse  
523 TMS device for the acute treatment of this type of migraine<sup>219</sup>. Evidence from a study using a rat model of  
524 migraine suggests that the effect of TMS on headache involves the suppression of cortical excitability, including  
525 the cortical spreading depolarisation that underlies the aura phase<sup>220</sup>. Clinical trials have found non-invasive  
526 stimulation of the trigeminal nerve to be moderately effective for acute migraine treatment<sup>221</sup> and prevention<sup>222</sup>.  
527 Non-invasive stimulation of the vagus nerve was highly effective for acute migraine treatment<sup>223</sup> but ineffective  
528 for migraine prevention<sup>224</sup>. In three small randomized controlled trials (n<150 in each study) this form of vagus  
529 nerve stimulation was also shown to be effective in drug-resistant epilepsy<sup>225–227</sup>.

530

531 Evidence is emerging that therapeutic education, including the provision of information on lifestyle factors such  
532 as sleep and alcohol consumption as well as behavioural, self-management and mind-body approaches can have  
533 beneficial effects for individuals with chronic conditions, including headache<sup>228,229</sup>, migraine<sup>230–232</sup> and  
534 epilepsy<sup>233,234</sup>. Although therapeutic education approaches do not cure these conditions, they can help individuals  
535 cope with the associated psychological burden. The ILAE recently recommended the widespread implementation  
536 of such techniques for people with epilepsy<sup>233</sup>.

537

### 538 **[H1] Conclusions and future challenges**

539 Clear evidence exists for an association between headaches and epilepsy. The results of studies published in the  
540 last five years have confirmed that headaches, especially migraines, often co-occur with epilepsy. This  
541 observation is in keeping with the growing body of evidence that comorbidity and multi-morbidity are common  
542 in neurological conditions<sup>235,236</sup>. Highlighting this overlap during neurological and medical training should help  
543 neurologists and general physicians be more attentive to the association between headaches and epilepsy. The  
544 gap between headache and epilepsy classifications highlights the need for closer collaboration between  
545 specialists, within departments and between professional bodies such as the ILAE and IHS. Such partnership  
546 could lead to the development of standardised questionnaires to aid the diagnosis of headache in epilepsy and  
547 guidelines on the management of comorbid headache and epilepsy. These diagnostic tools and guidelines will  
548 help improve the treatment, care, and management of these complex conditions.

549 To improve our understanding of the nature of the association between epilepsy and headache, and to establish  
550 the direction of this association, thorough longitudinal studies in large, multi-centric cohorts will be vital.  
551 Additional research efforts aimed at elucidating the pathophysiological mechanisms underlying headache in  
552 epilepsy and improving the management of these conditions are also needed. Although the pathophysiological  
553 mechanisms underlying epilepsy and migraine are highly complex, animal models of comorbidity<sup>103,237</sup> will help  
554 uncover the mechanistic links between activation of the trigeminovascular system and epilepsy.

555 In conclusion, headaches, and epilepsy are not separate disease entities but seem to be symptoms of altered  
556 neuronal network excitability. Ultimately, it will be important to elucidate the various, likely multifactorial,

557 causes underlying the different epilepsy–headache constellations thus enabling the development of aetiological  
558 diagnostic classifications and corresponding therapies.

559

560

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1119 competing interests.

1120

## 1121 **Review criteria**

1122 We searched PubMed for articles with the MeSH terms and keywords “headache”, “migraine” “epilepsy” and  
1123 “treatment” in the title, abstract or keywords. The search focused on primary studies published in the last 5 years  
1124 (April 2015 – April 2020). Additional articles were identified from the authors’ own files and from chosen  
1125 bibliographies. The articles in this Review were included at the authors’ discretion on the basis of originality and  
1126 relevance of the publication. Selected key works from before 2015 are shown in figure 1.

## 1127 **Informed consent**

1128 The authors affirm that human research participants provided informed consent for publication of the video in Supplementary Video 1.

1129

## 1130 **Key points**

- 1131 • The lifetime prevalence of migraine is 52% greater in individuals with epilepsy than in individuals with  
1132 epilepsy.
- 1133 • The symptoms of epilepsy and headache can present diagnostic challenges; a detailed history and EEG recording  
1134 of the epileptic and/or headache event are important for classification and management.
- 1135 • Enhanced neuronal excitability might be the mechanistic link between headaches and seizures.
- 1136 • Several genetic mutations can cause epilepsy and migraine, but the genetic association between polygenic forms  
1137 of epilepsy and migraine remains unclear.

- 1138
- Novel therapies include calcitonin gene-related peptide-blocking drugs for migraine and
- 1139
- 1140
- 1141
- neuromodulative non-pharmacological approaches for migraine and epilepsy; behavioural and self-management approaches are increasing in popularity.

Table 1 | Studies of epilepsy and headache comorbidity published 2014–2019

Study	Cohort size and type	Case ascertainment	Number reporting headache								
			Total	Pre-ictal	Ictal	Post-ictal	Inter-ictal	Inter-ictal and pre-ictal	Pre-ictal and post-ictal	Post-ictal and inter-ictal	Pre-ictal, post-ictal and inter-ictal
Begasse de Dhaem 2019 <sup>18</sup>	349 (209 female); new-onset focal epilepsy	Validated headache questionnaire (ICHD)	74 (21.2%) migraine	NA	NA	NA	NA	NA	NA	NA	NA
Çililer 2017 <sup>10</sup>	349 (190 female); consecutive epilepsy cases (69 partial seizures; 209 generalised seizures; 71 secondary generalised seizures)	Interview with questionnaire (ICHD-2)	152 (94 MI; 60 TTH; 43 U)	19 (12 MI; 4 TTH; 3 U)	NA	82 (30 MI; 25 TTH, 27 U)	17 (8 MI; 7TTH, 2 U)	NA	33	26	16
Hofstra 2015 <sup>13</sup>	255 (126 female); cross-sectional	Questionnaire, ICHD-2 criteria	186 (65 MI; 97 TTH; 15 U)	3	NA	28	92	NA	NA	NA	NA
Kim 2016 <sup>17</sup>	831 (391 female); consecutive video EEG cases (775 partial seizures; 55 generalised seizures)	Epileptic aura description, follow-up by phone interview (457 no aura; 374 with aura)	NA	25 (all partial seizures)	6 (2 hemispheric epileptic a, 4 R-TLE, 1 L-TLE, 1 Central seizure)	257 (238 partial <sup>b</sup> ; 18 generalised)	NA	NA	NA	NA	NA
Mainieri 2015 <sup>12</sup>	388 (209 female); consecutive cases with epilepsy (101 generalised epilepsy; 280 focal epilepsy; 7 U)	Self-report and structured interview	209	26 (16 MI; 5 TTH; 5 other)	3	74 (37 MI; 30 TTH)	188 (102 MI <sup>d</sup> ; 74 TTH; 2 cluster; 9 U)	NA	NA	NA	NA
Mameniški enė 2016 <sup>21</sup>	289 (172 female); adults with epilepsy treated in epilepsy center	Self-report and structured interview	233 (69 MI, 85TTH, 79 other)	23	1	46	218 (69 MI, 85 TTH, 52 other)	NA	NA	NA	NA

Mutlu 2018 <sup>14</sup>	420 <sup>c</sup> ; consecutive outpatient cases	Interview (ICHD)	111 (63 MI)	29 (9 MI)	NA	32 (5 MI)	83 (58 MI)	15 (5 MI)	17 (3 MI)	NA	NA
Salma 2019 <sup>19</sup>	47 (28 female); cases with epilepsy or unusual headache (33 focal epilepsy; 6 generalised epilepsy; 8 U)	Interview (ICHD)	37	2	22 (5 isolated IEH <sup>a</sup> )	10 (focal seizures)	15	NA	NA	NA	NA
Seo 2016 <sup>15</sup>	177 (85 female); consecutive individuals with epilepsy diagnosis	Interview	73	3 (1 MI)	NA	48 (17 MI; 24 TTH; 7 U)	34	NA	NA	NA	NA
Wang 2014 <sup>11</sup>	1109 (502 female) (856 partial seizures; 195 generalised seizures; 58 unclassified seizures)	Questionnaire, then interview (ICHD)	667	59 (38 MI)	NA	469 (314 MI)	231 (139 MI)	NA	9	45 (interictal migraine)	9
Whealy 2019 <sup>16</sup>	120 (67 female); epilepsy monitoring unit	Questionnaire (ICHD 3)	NA	NA	NA	75 (15 definite MI; 23 probable MI; 10 definite TTH; 3 probable TTH; 24 U)	97 (22 definite MI; 26 probable MI; 14 definite TTH; 13 probable TTH; 22 U)	NA	NA	NA	NA

1143 Table includes only studies published between 2014 and 2019 that were not included in the two meta-analyses<sup>8,9</sup>, except for the studies  
1144 highlighted in grey. <sup>a</sup> associated with focal onset, most often temporal lobe, <sup>b</sup> discrepancy in the original study, <sup>c</sup> Sex of participants not  
1145 reported. <sup>d</sup> of which, 6 with aura. ICHD=International Classification of Headache Disorders. TTH=tension type headache, U=  
1146 unclassified, TLE=temporal lobe epilepsy, FLE=frontal lobe epilepsy, OLE=occipital lobe epilepsy; MI, migraine.

1147

**Table 2 | Features of migraine aura and occipital seizures**

Feature	Migraine	Occipital lobe seizure <span style="float: right;">1149</span>
Main symptoms	Foggy or blurred vision Zigzag or jagged lines Scotoma Phosphenes Flickering light	Visual hallucinations Visual illusions Blindness Palinopsia Sensory hallucinations of ocular movement Ocular pain Nystagmus, eyelid closure and/or fluttering
Duration	10–60 minutes	<1 minute
Progression	Centrifugal or centripetal progression of visual symptoms	No centrifugal or centripetal progression of visual symptoms
Accompanying symptoms (e.g. nausea, vomiting, photophobia)	Common	Rare

1150 **Figure 1 | A selection of key publications on headache in epilepsy from before 2015.**

1151 This timeline shows milestone publications in the field of headache in epilepsy. We selected publications that  
1152 were particularly notable, for example, the first publication to report a specific finding, or a publication that had  
1153 a large influence on subsequent research. The first reports of an overlap between epilepsy and headache were  
1154 published at the end of the 19<sup>th</sup> century. From the 1960's onward, epilepsy was increasingly seen as a systemic  
1155 disorder with many comorbidities. Technical advances in the 1980's spurred on research in this area, including  
1156 studies that used animal models, in vitro approaches and depth electrodes in patients. From the early 2000's,  
1157 there was an increased interest in the molecular mechanisms of anti-seizure medication and their effect on  
1158 associated conditions such as migraine, and in the molecular genetics of epilepsy and migraine.

1159

1160 **Figure 2 | A timeline showing the different types of peri-ictal headaches.**

1161 The timing of pre-ictal, ictal and post-ictal headaches is shown in relation to the seizure. Pre-ictal  
1162 headaches occur < 24 hours before a seizure and last until seizure onset. Ictal headaches develop  
1163 simultaneously with the seizure. Post-ictal headaches occur < 3 hours after the end of the seizure event  
1164 and remit spontaneously < 72 hours after seizure termination. Specific types of seizure-related headaches  
1165 are also illustrated, including migraine as seizure trigger, hemicrania epileptica and headache as seizure  
1166 aura.

1167

1168 **Figure 3 | Putative pathophysiological mechanisms linking seizures and headache. a |**

1169 Hyperexcitability in epilepsy often involves impaired GABAergic transmission, facilitating  
1170 hypersynchronous seizure bursts. In migraine, hyperexcitability seems to be largely the result of enhanced  
1171 glutamatergic transmission, which could facilitate pain pathway activation via inflammatory changes and  
1172 calcitonin gene-related peptide (CGRP) release in the absence or presence of CSD. In migraine,  
1173 GABAergic transmission seems to be unaltered or could be dynamically enhanced, as indicated by the  
1174 results of preclinical studies on the effects of mutations associated with familial hemiplegic migraine  
1175 (FHM) type 3. Strongly enhanced glutamatergic transmission in migraine resulting from pathogenic  
1176 mutations, as is known to occur in FHM type 1, will increase the likelihood of co-morbid epilepsy. **b |**  
1177 Cortical spreading depolarization (CSD) is likely to be the neurophysiological mechanism underlying



1178 migraine aura. CSD could also trigger migraine headache originating in the trigeminovascular system.  
1179 CSD consists of a slowly propagating wave of network depolarization that is presumably caused by  
1180 cortical hyperexcitability. CSD-associated increases in the concentration of potentially noxious  
1181 molecules, including  $K^+$  and  $H^+$  (i.e. low pH), in the extracellular space could reach pial, arachnoid, and  
1182 dural surfaces and activate perivascular sensory afferents from trigeminal ganglion (TG) neurons.  
1183 Inflammatory changes, involving neuronal release of high mobility group protein 1 (HMBG1) following  
1184 CSD-induced pannexin channel opening, provide a mechanistic link between CSD and pain pathway  
1185 activation. Signals from activated meningeal nociceptors are relayed through TG nerve processes to the  
1186 brainstem trigeminal cervical complex (TCC) and subsequently to thalamic and cortical areas (including  
1187 cingulate cortex, CC) and produce sensations of pain. Adapted from Chen et al, Cephalalgia 2019 and  
1188 Ferrari et al Lancet Neurology 2015.

1189

1190 **Box 1 | ICHD-3 diagnostic criteria relevant to epilepsy**

1191 **Migraine aura-triggered seizure (ICHD-3 code 1.4.4.)**

1192 A. A seizure fulfilling diagnostic criteria for one type of epileptic attack and criterion B below

1193 B. Occurring in a patient with 1.2 Migraine with aura, and during or within one hour after an attack of migraine  
1194 with aura

1195 C. Not better accounted for by another ICHD-3 diagnosis.

1196 While migraine-like headaches are quite frequently seen in the epileptic post-ictal period, sometimes a seizure  
1197 occurs during or following a migraine attack.

1198 This phenomenon, sometimes referred to as migralepsy, is a rare event, originally described in patients with 1.2  
1199 Migraine with aura. Evidence of an association with Migraine without aura is lacking.

1200 **Ictal epileptic headache (ICHD-3 code 7.6.1)**

1201 A. Any headache fulfilling criterion C

1202 B. The patient is having a partial epileptic seizure

1203 C. Evidence of causation demonstrated by both of the following:

1204 1. headache has developed simultaneously with onset of the partial seizure

1205 2. either or both of the following: a) headache is ipsilateral to the ictal discharge. b) headache significantly  
1206 improves or remits immediately after the partial seizure has terminated

1207 D. Not better accounted for by another ICHD-3 diagnosis.

1208 **Hemicrania epileptica (ICHD-3 code 7.6.1.)**

1209 (if confirmed to exist) is a very rare variant of 7.6.1 Ictal epileptic headache characterized by ipsilateral location of headache  
1210 and ictal EEG paroxysms.

1211 **Postictal headache (ICHD-3 code 7.6.2)**

1212 A. Any headache fulfilling criterion C

1213 B. The patient has recently had a partial or generalized epileptic seizure

1214 C. Evidence of causation demonstrated by both of the following:

1215 1. headache has developed within three hours after the epileptic seizure has terminated

1216 2. headache has resolved within 72 hours after the epileptic seizure has terminated

1217 D. Not better accounted for by another ICHD-3 diagnosis.

1218

1219 **Box 2| Spreading depolarization and seizures – a missing link underlying headache in epilepsy?**

1220 Migraine aura<sup>5</sup> is likely to be caused by cortical spreading depolarisation, a slow-spreading (~ 2–6 mm per  
1221 min) wave of neuronal and glial depolarisation followed by neuronal silencing (evident from suppression of local  
1222 field potential (LFP) or EEG activity) lasting a couple of minutes<sup>238–240</sup>. Neuronal hyperexcitability predisposes  
1223 to spreading depolarisation and seizures, and might be a key shared mechanism of epilepsy and migraine<sup>158,241</sup>.  
1224 Changes in ion concentration can shift neurons towards moderate depolarisation leading to synchronous  
1225 epileptiform firing (part a of the figure), or — if extracellular K<sup>+</sup> ([K<sup>+</sup>]<sub>out</sub>) rises above ~12 mM — towards near-  
1226 complete depolarisation, yielding spreading depolarisation<sup>122,166</sup> (part b of the figure shows a hypothetical seizure

1227 followed by spreading depolarisation). Silencing of bioelectrical activity during spreading depolarisation is  
1228 caused by sustained neuronal depolarisation that exceeds the inactivation threshold for ion channels, thus  
1229 preventing action potentials<sup>123</sup>. Conversely, post-ictal suppression in the absence of spreading depolarisation is  
1230 associated with neuronal hyperpolarisation<sup>136</sup>. Spreading depolarisation-related suppression should not be  
1231 confused with post-ictal generalised EEG suppression (PGES)<sup>242</sup>, which is an immediate (within 30 seconds)  
1232 complete suppression of EEG activity following a seizure<sup>243,244</sup>. Clinically, PGES appears non-spreading<sup>245</sup>, lasts  
1233 up to 338 seconds (mean 46 seconds) and is associated with motionlessness<sup>246</sup>, whereas changes in perception  
1234 associated with migraine aura last ~ 20–30 minutes<sup>123</sup>. Preclinical work has indicated that network suppression  
1235 by spreading depolarisation prevents seizures<sup>111</sup>, suggesting that post-ictal spreading depolarisation constitutes  
1236 an intrinsic seizure-termination process. The link between spreading depolarisation and headache remains  
1237 unclear. In rodents, spreading depolarisation activates the trigeminovascular system at the meningeal level<sup>77,247</sup>  
1238 (Fig. 3) and might affect the brainstem via a corticotrigeminal projection<sup>74</sup>. How the trigeminovascular system is  
1239 activated in humans remains unclear, and cortical spreading depolarisation could be one of many triggers<sup>74</sup>. No  
1240 clear evidence exists that spreading depolarisation occurs in association with epileptic discharges in humans  
1241 outside of trauma or stroke<sup>123,124</sup>. When cortical spreading depolarisation was observed in individuals with  
1242 ischemic stroke, headaches were not reported<sup>248</sup>. Research in rodents indicates that the excessive network activity  
1243 during seizures and associated increases in extracellular K<sup>+</sup>, H<sup>+</sup> and inflammatory changes might be sufficient to  
1244 activate the trigeminovascular system without the need of a spreading depolarisation<sup>103</sup>.

1245 Part A adapted from REF<sup>136</sup>. Part B is a stylized representation of the changes that are thought to  
1246 occur during post-ictal spreading depolarization<sup>122,158</sup>.

1247

1248 **Supplementary Video 1 | Video-EEG recording of an individual with ictal epileptic headache**

1249