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Review

The heart of epilepsy: Current views and future concepts

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ABSTRACT

Cardiovascular (CV) comorbidities are common in people with epilepsy. Several mechanisms explain why these conditions tend to co-exist including causal associations, shared risk factors and those resulting from epilepsy or its treatment.

Various arrhythmias occurring during and after seizures have been described. Ictal asystole is the most common cause. The converse phenomenon, arrhythmias causing seizures, appears extremely rare and has only been reported in children following cardioinhibitory syncope. Arrhythmias in epilepsy may not only result from seizure activity but also from a shared genetic susceptibility. Various cardiac and epilepsy genes could be implicated but firm evidence is still lacking. Several antiepileptic drugs (AEDs) triggering conduction abnormalities can also explain the co-existence of arrhythmias in epilepsy.

Epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease and a poorer CV risk profile than those without epilepsy. Shared CV risk factors, genetics and etiological factors can account for a significant part of the relationship between epilepsy and structural cardiac disease. Seizure activity may cause transient myocardial ischaemia and the Takotsubo syndrome. Additionally, certain AEDs may themselves negatively affect CV risk profile in epilepsy.

Here we discuss the fascinating borderland of epilepsy and cardiovascular conditions. The review focuses on epidemiology, clinical presentations and possible mechanisms for shared pathophysiology. It concludes with a discussion of future developments and a call for validated screening instruments and guidelines aiding the early identification and treatment of CV comorbidity in epilepsy.

1. Introduction

Well over 100 years ago, the occurrence of asystole during the course of an epileptic seizure was described: “He uttered a cry and was seen to be rubbing his hands together. His pulse was immediately examined for but was not palpable” [1]. Since then numerous associations between epilepsy and CV conditions have been identified, including this classical example of ictal asystole.

Co-existing conditions form an important part of the overall burden of epilepsy [2–5]. Several mechanisms of association between epilepsy and comorbid conditions have been described: associations can be explained by cause or effect, a shared risk factor may cause both conditions, or the mechanism of the association is unknown or spurious (i.e. coincidental) (Fig. 1) [3,5].

This review serves to discuss the fascinating borderland between epileptology and cardiology and focuses on the major developments over the last 25 years and on future developments. We use the comorbidity framework (Fig. 1) [3] to review all cardiac conditions known, and alleged, to be linked to epilepsy. Associations with cardiac arrhythmias are discussed first, followed by an overview of all structural cardiac conditions related to epilepsy.

2. Epilepsy and cardiac arrhythmias

Various arrhythmias have been described, occurring during (ictal) or after (postictal) seizures. Sinus tachycardia is the most common ictal pattern, seen in up to 80% of all seizures [6] and in 82% of people with epilepsy [7], but usually without symptoms. The most frequent clinically relevant arrhythmia is ictal asystole, occurring in 0.318% (95% CI 0.316–0.320%) of people with refractory focal epilepsy admitted for video-EEG [8]. Ictal asystole, bradycardia and AV block predominantly occur in people with

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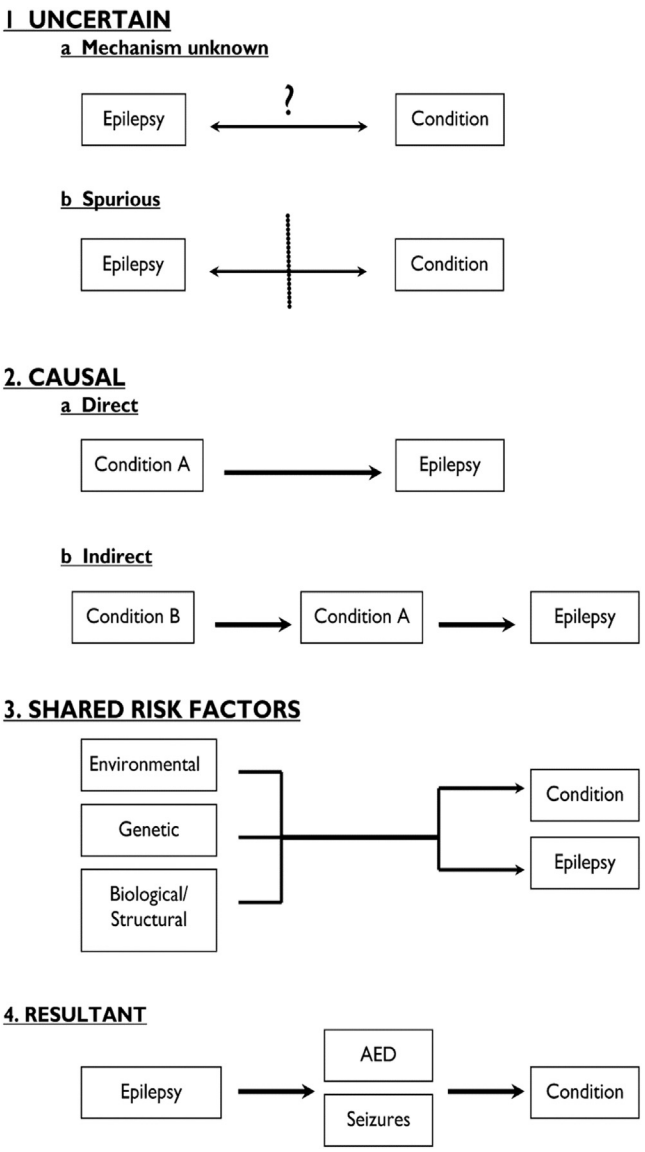


Fig. 1. Mechanisms of association between epilepsy and comorbid conditions. The dotted line indicates that an association does not really exist. Figure originates from Gaitatzis et al. [3], permission to reproduce copyrighted material granted by John Wiley & Sons.

temporal lobe epilepsy (Table 1) [8]. Clinically, ictal asystole is characterised by sudden loss of tone during a dyscognitive seizure [9]. The circulatory pattern resembles vasovagal syncope with a transient, progressive and self-limiting slowing of the heart rate and decrease of blood pressure [9–11]. For many years, ictal asystole was thought to be a possible mechanism underlying sudden unexpected death in epilepsy (SUDEP). This appears to be unlikely: all but one reported case so far of ictal asystole were self-limiting [8]. In this one case successful resuscitation was started after 44 s of asystole and the event was classified as near-SUDEP [12]. The longest ictal asystole reported so far, however, lasted 96 s and appeared self-limiting [13]. Whether an event is classified as near-SUDEP or not will depend on interventions of medical personnel: prompt resuscitation in response to ictal asystole will likely lead to more classified as near-SUDEP cases. While there are no reports of fatal ictal asystole, it remains debatable whether ictal asystole can cause SUDEP.

The precise mechanism of ictal asystole is unknown. It may result from epileptic activity directly stimulating the central autonomic networks [6,14]. For example, focal stimulation of parts of the limbic system (i.e. amygdala, cingulate gyrus) may provoke asystole [6,15–17]. Alternatively, seizure-induced fear and catecholamine release [18] may evoke a vasovagal response causing cardioinhibition and vasodilation [19].

Ictal asystole is assumed to be self-limiting, but may cause falls and injuries due to seizure-induced syncope [20]. Proper trials are lacking but retrospective studies suggest that improving seizure control may prevent ictal asystole [21–23]. It also seems advisable to withdraw negative inotropic drugs and to consider the implantation of a loop recorder to monitor possible future events in individuals in whom ictal asystole has been noted. If the asystolic episodes persist, cardiac pacemaker implantation should be considered to reduce the risk of trauma [20,21,23,24].

In contrast to ictal asystole, postictal asystole is less common, associated with convulsive rather than focal (temporal lobe) seizures and has a higher fatality rate: 7 of 13 reported postictal asystole cases died from SUDEP [8]. All fatal cases had a convulsive seizure with immediate postictal generalised EEG suppression and a stuttering course of transient apnoea and asystole resulting in a terminal apnoea followed by a terminal asystole [25].

The mechanism underlying this sequence of postictal EEG suppression, apnoea, and terminal asystole has not yet been elucidated. Excessive inhibition causing brainstem depression might play a role [26]. Recent work in two animal models (mice carrying mutations in the *KCNA1* gene or the *SCN1A* gene) demonstrated that seizures initiated by direct cortical stimulation may evoke a spreading depression causing brain stem inhibition and cardiorespiratory collapse [27].

Another rare (post)ictal arrhythmia is ventricular tachycardia/ventricular fibrillation (VT/VF). So far three cases of postictal VT/VF leading to (near) SUDEP have been reported [8]. All VT/VF occurred directly following a convulsive seizure. No cardiac lesions were found in the case reports. There may be a publication bias, however, as cases with seizure-triggered VT/VF and cardiac lesions may not qualify as SUDEP and thus may be less likely to be reported. The mechanism of seizure-induced VT/VF is unclear. Convulsive seizures may exert proarrhythmogenic effects by triggering the sympathetic nervous system, as reflected by the peak in catecholamines and electrodermal activity [18,28]. At the same time, convulsive seizures may increase cardiac oxygen deprivation by inducing sinus tachycardia [7] and respiratory impairment causing hypoxemia [29]. It has also been found that ECG-markers of sudden cardiac death such as QTc-lengthening and/or shortening [30,31], and T-wave alternans are more prevalent [23] during and after convulsive seizures. The various factors might interact as seizure-related cardiac repolarization abnormalities appeared more frequent in seizures with ictal hypoxemia compared to those without [32].

Though seizure-induced VT/VF appears to be rare, a prospective community-based study of out-of-hospital cardiac arrests due to ECG-documented VT/VF showed that VT/VF risk in those with epilepsy was three times as high as the general population [33]. A further analysis of those cases with epilepsy and VT/VF showed that most were not seizure-related, but rather occurred in the context of either pre-existing heart disease or as the immediate result of an acute myocardial infarction [34]. Pre-existing heart disease was a stronger predictor for VT/VF in people with epilepsy than markers of epilepsy severity. In a minority of cases, however, VT/VF was unexplained and a diagnosis of (near) SUDEP was established. It thus appears that sudden cardiac arrest and SUDEP are partially overlapping disease entities.

The increased risk of non-seizure related VF/VT episodes in people epilepsy may be explained by high cardiovascular

Table 1
Reported (post)ictal cardiac arrhythmias. FDS—focal dyscognitive seizure; FAS—focal autonomic seizure; fbCS—focal seizure evolving to bilateral convulsive seizure; GTCS—generalised tonic clonic seizure; LT—left temporal; RT—right temporal; BT—bitemporal; Gen—generalised; Non loc—non-localising; PGES—postictal generalized EEG suppression; *in people with refractory focal epilepsy admitted for a vEEG recording. For more details see van der Lende et al. [8].

Seizure related arrhythmia	Reported in n cases	Associated seizure types	Reported in n cases	EEG seizure onset	Reported in n cases	SUDEP association
Ictal asystole	103	99% FDS 1% FAS	97	46% LT 31% RT 13% BT 10% other	80	Unlikely
Postictal asystole	13	85% fbCS 15% FDS	13	20% LT 60% RT 20% other	10	Very likely, accompanied or preceded by PGES/apnea
Ictal bradycardia	25	100% FDS	8	52% LT 38% RT 10% other	21	Unlikely
Ictal AV block	11	90% FDS 10% FAS	10	73% LT 18% BT 10% other	11	Unlikely
Postictal AV block	2	100% fbCS	2	100% RT	1	Unlikely
Atrial fibrillation	13	46% GTCS 46% fbCS 8% FDS	13	33% LT 33% Gen 33% Non loc	3	Unlikely
(Post)ictal ventricular fibrillation	3	100% GTCS	3	Insufficient data	0	Probable, but in a minority of cases

comorbidity [3,35]. People with epilepsy may have a propensity for sudden cardiac death as reduced heart rate variability, a measure of cardiac sympathovagal balance that is also a risk marker of sudden cardiac death, progressively worsens over time in people with refractory, but not in those with well-controlled, epilepsy [36]. In addition, other markers of sudden cardiac death such as early repolarization pattern and QTc-prolongation are more frequently found in the interictal ECGs of people with epilepsy than in those without epilepsy [37].

Another mechanism explaining the association between arrhythmias and epilepsy is a shared genetic risk factor. A rapidly increasing number of genes potentially linking epilepsy to cardiac arrhythmias has been identified. Here we discuss some relevant examples; starting with the genes predominantly known for their cardiac functions and then the 'epilepsy genes'.

Several genetic ion channel mutations are thought to be expressed in the brain as well as in the heart, and might thus cause seizures and cardiac arrhythmias. The first reported genetic link between epilepsy and cardiac arrhythmias was the discovery of cardiac sodium channel gene *SCN5A* in the brain [38]. Subsequently, more pathogenic variants in the long QT (LQT) gene family (i.e. *KCNQ1*,*KCNH2* and *SCN5A*) were associated with a "seizure phenotype" (e.g. self-reported diagnosis of epilepsy and AED use) [39–44]. Mice models indicated that other, non-LQT, cardiac channelopathy genes including *RYR2* (associated with catecholaminergic polymorphic ventricular tachycardia) [45], and *HCN1-4* [46,47] potentially predispose to epilepsy.

Several postmortem studies suggest that the LQT and non-LQT cardiac gene mutations are more common in SUDEP victims [48–50]. As ictal recordings are lacking, it remains questionable whether the fatal events were caused by arrhythmias. The same applies to the identification of 'epilepsy genes' in the post-mortem cohorts [48,49]. These mutations could be markers explaining epilepsy severity or a genetically mediated liability to fatal seizures. In certain epilepsy syndromes, SUDEP risk seems particularly high.

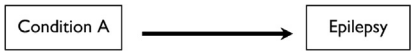
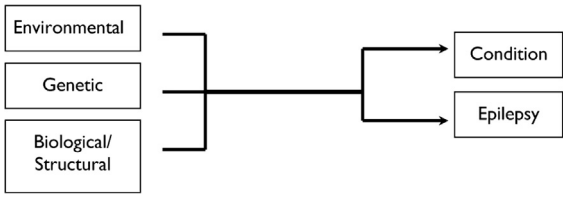
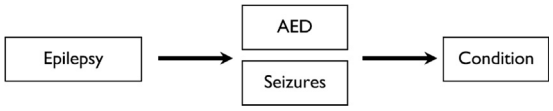
The most recognized example is the Dravet syndrome (DS), a severe epilepsy syndrome with high premature mortality, caused by SCN1A mutation [51]. In mutant *SCN1A* knock-out mice, postictal bradycardia and seizure-triggered ventricular fibrillation were recorded before a death resembling SUDEP [52,53]. In DS subjects, markers associated with the risk of sudden cardiac death (decreased HRV and increased QT-dispersion) have been found [54,55]. Ictal proof is, however, lacking and is the subject of an ongoing study (ClinicalTrials.gov Identifier: NCT02415686).

Other less well studied examples of 'epilepsy genes' possibly mediating SUDEP risk include *KCNA1* and *SCN8A*. *KCNA1* is expressed in the vagal nerve as well as in the brain, and is associated with seizures, cardiac arrhythmias, vagal hyperexcitability and premature death in *KCNA1* null mice [56]. Mutations in this gene were found in a SUDEP case with epileptic encephalopathy and suspected cardiac arrhythmias [57].

A novel pathogenic SCN8A mutation was identified through whole-genome sequencing in a family affected by epileptic encephalopathy and SUDEP [58]. Before then, SCN8A mutations had only been linked to epilepsy in mice [59]. The SCN8A gene encodes a sodium channel that is expressed in heart and brain of mice and rats, and plays a role in excitation-contraction coupling, action potential propagation and pacemaking [60,61].

We previously discussed how seizures may cause arrhythmias. Whether the converse phenomenon exists is a subject of controversy. The major complication is the fact that syncopal events are easily mistaken for epilepsy. Rates of misdiagnosis in epilepsy are high (up to 71%), and syncope is the commonest imitator [62]. This is understandable, as various symptoms and signs are seen in both conditions [11,62–64]. Notably, jerking movements or signs indicative of cerebral standstill (complete flattening of the EEG) such as roving eye movements or stertorous

Table 2
Putative mechanisms of associations between epilepsy and cardiac arrhythmias. HRV—heart rate variability; VT—ventricular tachycardia; VF—ventricular fibrillation; AED—antiepileptic drugs.

Putative mechanisms of associations between epilepsy and cardiac arrhythmias	
Mechanisms of association	Conditions
Direct causal 	Arrhythmias → seizures
Shared risk factor 	Genetics → epilepsy and arrhythmias - Important 'heart genes': *KCNQ1, KCNH2, SCN5A, RYR2* - Important 'epilepsy genes': *SCN1A, KCNA1, SCN8A*
Resultant 	AED → arrhythmias - Particularly carbamazepine, phenytoin and lacosamide Seizures → arrhythmias - Ictal: tachycardia, asystole, bradycardia and AV block - Postictal: asystole, AV block, atrial flutter or fibrillation and ventricular fibrillation

breathing [11] are often interpreted as signs specific to epilepsy. The true cause of these symptoms can only be determined with help of a detailed history (taking into account the circumstances and other diagnostic clues) or a proper investigation (e.g. ictal recording of video, heart rate, blood pressure and EEG) [65]. Two large scale surveys of up to 2000 tilt-table tests failed to identify any adult case with syncopal-induced seizures [66,67]. In children, however, a few cases have been reported with a cardioinhibitory reflex syncope followed by video-EEG documented clonic seizures [68–70]. The reason why this phenomenon only appears to affect children is unknown. It may be that the seizure threshold is lower in children (paralleling febrile seizures that also peak in childhood). Alternatively, the depth of cerebral anoxia may be more profound in children as reflected by prolonged asystolic spells. For clinical management it is important to stress that syncope-induced seizures are extremely rare and probably only affect children. The diagnosis requires an ictal video-EEG recording.

Several AEDs, particularly those with sodium blocking properties are known to trigger conduction abnormalities or arrhythmias [71]. Atrioventricular (AV) conduction is the most frequent reported complication. ST changes, Brugada-like patterns, atrial fibrillation and QTc prolongation have also been reported but the association with AED treatment is less well established [72–86]. Most clinically relevant arrhythmias were related to AED overdose. Carbamazepine is, however, known to cause AV conduction blocks at low levels; this is almost exclusively reported in elderly women [77,79,87]. Rapid administration of phenytoin may also cause sinus arrest and hypotension; elderly people and those with pre-existing heart disease seem most vulnerable to these adverse effects. IV administration should, therefore, be undertaken slowly, with continuous cardiac monitoring [76,83,86,88]. The above-mentioned AED effects do not seem to play a role in ictal arrhythmias. Nevertheless, it is important to take these effects into consideration in the selection of an AED and to monitor adverse effects closely especially in elderly people and those with cardiovascular comorbidities.

3. Epilepsy and structural cardiac conditions

Epidemiological studies have consistently shown that people with epilepsy have a higher prevalence of structural cardiac disease than those without epilepsy [4,5,89–92]. Cardiovascular disease seems to be a significant contributor to the increased mortality in people with epilepsy, compared with the general population [93–95].

Shared cardiovascular risk factors can account for the relationship between epilepsy and heart disease, in addition to shared genetics and etiological factors. People with a history of epilepsy are more likely to be obese, physically inactive, and current smokers [90] and have a worse cardiovascular risk profile (i.e. hypertension, hypercholesterolemia, diabetes mellitus, stroke/TIA) than the general population [35,90,96,97]. Unsurprisingly, people with epilepsy have higher rates of fatal and nonfatal cardio- and cerebrovascular disease than controls (mortality ratios up to 5.3 and morbidity ratio up to 7) [35,98,99]. The presence of cardiovascular disease (e.g. congestive heart failure and cardiac arrhythmias) was also associated with higher mortality risk in people with epilepsy [100].

Epilepsy treatment can also contribute to a poorer cardiovascular risk profile in epilepsy. Use of the enzyme-inducing AEDs phenytoin or carbamazepine may lead to elevated serological

vascular risk markers (e.g. total cholesterol, LDL, homocysteine), and, thus, result in accelerated atherosclerosis [101–104]. Certain AEDs (e.g. valproic acid, carbamazepine) are also known to cause weight gain and increase the risk of developing non-alcoholic fatty liver disease and metabolic syndrome, leading to further deterioration of the cardiovascular risk profile [102].

The co-occurrence of epilepsy and (congenital) heart disease, often accompanied by intellectual disability, may result from a multiple malformation syndrome: genetic defects may affect the development of both heart and brain, or abnormal cardiovascular function may lead to poor (intrauterine) brain growth [105].

CV disease can sometimes (indirectly) cause epilepsy through a predisposition to stroke [106,107]. Stroke is a common risk factor for epilepsy and accounts for about a third of newly diagnosed seizures in people over the age of 60 years [107–110]. In particular, those with ischemic events with cortical involvement, cerebral hemorrhage (i.e. primary hemorrhage or hemorrhagic transformation of ischemic stroke) and early post-stroke seizures, have an increased risk of post-stroke epilepsy [107].

Seizure activity may not only induce arrhythmias but may also lead to structural cardiac changes [71,111–113]. Epileptic seizures have been reported to provoke cardiac ischaemia via both acute and chronic effects on the heart (e.g. impaired heart rate variability, cardiac fibrosis, ST-segment depression and increased heart rate) [71,114]. Transient myocardial ischaemia as indicated by ST-segment depression, was reported in a small-scale study in 40% of all 15 seizures [114]. Another study, however, failed to demonstrate troponin increases, suggesting that the reported ST changes do not usually cause myocardial damage [115].

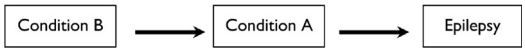
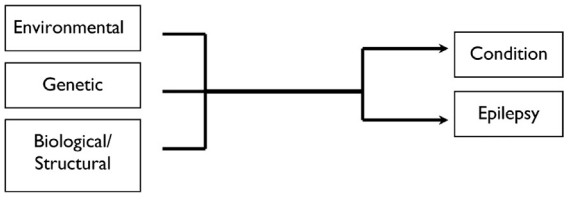
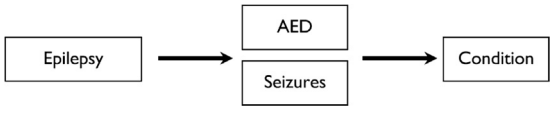
Seizures are the second most frequent CNS condition known to induce the cardiomyopathy known as Takotsubo syndrome (TTS) [116]. TTS mimics myocardial infarction clinically, electrocardiographically and chemically [117]. It is characterized by acute onset of chest pain and dyspnoea, sometimes concomitant with palpitations, tiredness, oedema, fever, syncope, anxiety, nausea or vomiting [116]. The seizure type that most frequently causes TTS is the generalized tonic-clonic seizure [118,119]. Seizures most likely trigger TTS by the stress-induced release of catecholamines [120]. This abundant catecholamine release may be a contributing factor in fatal status epilepticus [121]. A relationship between TTS and SUDEP, however, does not appear likely [116].

4. Future concepts

Significant progress has been made since the publication of Russel's case history: the complex interrelationship between epilepsy and cardiac conditions has been explored widely and this review aimed to capture all major discoveries made in this field (Table 2 and 3). Many discoveries of coexisting conditions were made by serendipity, and underlying mechanisms are yet to be uncovered. Treatment regimens are consequently often speculative and lack a personalized approach involving all comorbid conditions. As comorbidity gains recognition we now need to become better at noticing these symptom patterns. Today a substantial gap still remains between the specialties, but as we are now becoming aware of all overlapping syndromes epileptologists will increasingly need to improve their cardiac skills. Pattern recognition can be fostered by incorporating validated screening instruments and guidelines, aiding the early identification and treatment of cardiovascular comorbidity in epilepsy. Concomitantly, a fundamental change in the way clinicians think of epilepsy is crucial.

Epilepsy will soon be viewed as a collection of individual disorders that share a phenotype of an abnormal tendency for unprovoked epileptic seizures. The number of rare epilepsy syndromes with cardiac phenotypes will increase substantially. Epilepsy will be seen as a symptom-complex, and all comorbidities, even the most inconspicuous, should be considered as part of

Table 3
Putative mechanisms of associations between epilepsy and structural cardiac disease. AED—antiepileptic drugs; TTS—Takotsubo syndrome.

Putative mechanisms of associations between epilepsy and structural cardiac disease	
Mechanisms of association	Conditions
Indirect causal 	Cardiac condition → stroke → epilepsy
Shared risk factor 	Genetic → malformation of cortical and cardiac development → epilepsy and cardiovascular comorbidity Increased prevalence of cardiovascular risk factors in epilepsy → stroke/cardiac disease
Resultant 	AED → poorer cardiovascular risk profile (e.g. arteriosclerosis, weight gain, non alcoholic fatty liver disease and metabolic syndrome) Seizures → transient myocardial ischaemia and seizure-triggered Takotsubo syndrome (TTS)

the stratification and phenotyping in people with epilepsy. Cardiovascular comorbidities will provide insight into common mechanisms for epilepsy and give a window into common genetic predispositions. They may also provide important diagnostic clues. Channelopathies, for example, are increasingly identified in people with epilepsy. Genetic factors may explain both the epilepsy and the comorbid disorder(s), even in people with sporadic epilepsies [122]. Genome wide scanning will be widely available and drive the paradigm shift in epilepsy. Certain genes might be identified as contributing to SUDEP [48,49], potentially allowing the development of individualised risk prevention strategies. Another major contributor to early identification of overlapping syndromes will be the development of new non-invasive tools to record heart function at home. The miniaturisation of sensors will favour long-term home-based recordings thus aiding the early identification of cardiac arrhythmias.

Advances in seizure detection will likely take off. ECG alone will help to detect a wide variety of seizures but lacks specificity. Combining ECG with other modalities including an accelerometry and electrodermal activity will likely improve accuracy and facilitate the widespread use of seizure detection devices in those with refractory epilepsy [123,124].

Another unmet need relates to the treatment of epilepsy: many AEDs have proarrhythmogenic and arteriosclerogenic effects. Though non-pharmacological options exist, drug therapy is still the mainstay of epilepsy treatment and other options are usually only explored after AEDs have failed to successfully control seizures [125]. Many new AEDs have been launched in the last two decades, but have failed to improve the burden of side effects or substantially change prognosis for seizure control [126,127]. With improved understanding of epileptogenesis, epigenetic determinants and pharmacogenomics comes the hope for better, disease-modifying or even curative pharmacological and non-pharmacological treatment strategies. Until then, comorbidity should be considered when prescribing AEDs.

The incorporation of neurocardiology into the paroxysmal spectrum will require a critical review of the epilepsy services. We need to validate new instruments to screen for cardiovascular conditions. Modern non-invasive long-term ECG devices may help screen for cardiac conditions and a cardiologist should review any relevant abnormalities. In cases where there is a relevant family history or abnormal ECG findings, a specialist cardiac assessment should be done. Identification and adequate treatment of cardiovascular disorders in epilepsy should therefore be an important part of epilepsy management.

Particular attention should be given to modifiable risk factors such as smoking, obesity, sedentary lifestyle, high cholesterol and hypertension. Physicians should screen for these risk factors in people with epilepsy, provide general health information and if necessary adjust AED treatment. Further studies are needed to improve risk profiling, thus allowing for screening in high risk individuals (with, for example, implantable loop recorders) and targeted interventions (e.g. defibrillators).

Conflict of interest statement

SS, MvdL and RJL report no conflict of interest. JWS reports personal fees from Lundbeck and Teva, grants and personal fees from UCB, Eisai, grants from GSK, WHO and Dutch National Epilepsy Fund, outside the submitted work; his current position is endowed by the Epilepsy Society, he is a member of the Editorial Board of the Lancet Neurology, and receives research support from the Marvin Weil Epilepsy Research Fund. RDT receives research support from the Dutch National Epilepsy Fund, NUTS Ohra Fund, Medtronic, and AC Thomson Foundation, and has received fees for lectures from Medtronic, UCB and GSK.

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