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Review

Comorbidity between epilepsy and cardiac arrhythmias: Implication for treatment

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ABSTRACT

Epilepsy is often comorbid with either neurological or nonneurological diseases. The association between epilepsy and cardiac arrhythmias is not infrequent, mostly in patients with severe forms of epilepsy or critically ill. Remarkably, these medical conditions share many similarities. Vascular and genetic disorders may predispose to both seizures and abnormalities of cardiac electrophysiology. Repeated and uncontrolled seizures may favor potentially life-threatening arrhythmias. Antiepileptic drugs (AEDs) may facilitate the occurrence of cardiac arrhythmias by acting on ionic channels at heart level. Antiarrhythmic drugs (AADs) can have effects on ionic channels expressed in the brain, as suggested by their efficacy in treating patients with rare forms of epilepsy; AADs may also be proconvulsant, mainly during their overdosage. In clinical practice, the AEDs with the lowest risk to influence cardiac electrophysiology are to be preferred in patients presenting with either seizures or arrhythmias. Traditional AEDs should be avoided because of their arrhythmogenic properties and enzyme-inducing effects, which may make ineffective the concomitant treatment with AADs. Some of the newer AEDs can rarely affect cardiac rhythm, and electrocardiogram (ECG) monitoring should be warranted.

1. Introduction

Comorbidity is a greater than coincidental association of two conditions in the same individual [1]. This scenario is extremely frequent in the case of chronic diseases. A median of two chronic medical conditions is generally observed in young adults, and this figure can rise up to six in patients older than 65 years [1].

Comorbidity between cardiac arrhythmias and epilepsy is intriguing and only marginally taken into account by clinicians. Although these diseases involve different organs, they share similar pathogenesis and electrical background. Indeed, seizures result from an abnormally increased or synchronous neuronal activity in the brain, and cardiac arrhythmias derive from disturbances of electrical activity in the heart [2]. Strong similarities also exist in the mechanisms of action of drugs used in these conditions as most of them affect ionic channels. Despite differences between the heart and brain in the expression of ionic channels, antiepileptic drugs (AEDs) can influence cardiac electrophysiology and antiarrhythmic drugs (AADs) can display antiseizure and proconvulsant properties. A typical example is phenytoin (PHT), which is an AED and AAD with potential arrhythmogenic and proconvulsant effects [3]. Additionally, there is a consistently higher prevalence of unspecified heart diseases in people with than without epilepsy, as shown by several large studies using population-based cohorts and administrative databases [4–9].

The aim of this review was to critically describe practical issues related to the association between epilepsy and cardiac arrhythmias and their treatment. Pathogenic mechanisms underlying these conditions have been previously discussed [10].

1.1. Search methods

We searched MEDLINE up to February 10, 2019 for relevant publications using combinations of the following keywords: epilepsy, arrhythmias, cardiac diseases, AEDs, AADs, any single AED and AAD (all AADs included in a consensus document of the European Society of Cardiology [3] have been considered), sudden unexpected death (SUDEP), sudden cardiac death (SCD), QT interval, and PR interval. Relevant references of the identified articles were also examined.

1.2. Cardiac arrhythmias and epilepsy

Long-standing uncontrolled epilepsy is associated with alterations in cardiac electrophysiology that can lead to the development of cardiac dysfunction [11]. Electroencephalogram (EEG) and electrocardiogram (ECG) monitoring showed that 90–100% of temporal lobe seizures are accompanied by changes in heart rate [12]. The most common and

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benign ictal pattern occurring during seizures is ictal tachycardia [13]. Less frequently, ictal bradycardia, ictal atrioventricular block, or ictal asystole may be observed. Ictal asystole has been defined as the absence of QRS complexes for more than 4 s after EEG seizure onset [10,11]. While the pathogenic mechanism of ictal tachycardia has been attributed to the diffusion of ictal discharges in cortical regions governing sympathetic function (including the anterior cingulate, insular, and prefrontal cortices), ictal bradycardia and asystole are thought to be consequences of the stimulation of cortical areas controlling parasympathetic tone and mediated by the vagus nerve [10,11]. Although ictal bradycardia may have clinical consequences, it has been suggested to be a relatively benign condition [11,12]. A better control of seizures and the withdrawal of drugs with negative ionotropic effects may improve these conditions; pacemaker implantation should be considered in severe cases [11].

Seizure may be also associated with life-threatening abnormalities of cardiac repolarization. Transient prolongation or shortening of QT interval has been observed during the ictal period [10,11], which may increase the risk of SUDEP in subjects with genetic predisposing factors and/or assuming drugs affecting QT interval.

In the postictal period, atrial fibrillation can be observed, which may last several hours [11]. Postictal asystole and ventricular tachycardia/fibrillation are more serious and, fortunately, less common forms of arrhythmia, which may mostly appear after a convulsive rather than focal seizure and may lead to SUDEP [12].

The incidence of definite/probable SUDEP in unselected populations of patients with epilepsy is 1.20/1000 person years; it is higher in men than in women [14], and it is up to 6–9.3/1000 in patients with severe drug-resistant epilepsies [15]; SUDEP is, at least in part, a consequence of the autonomic involvement of cardiovascular and respiratory systems leading to pathologic cardiac repolarization after prolonged seizures [14,15]. The main risk factors for SUDEP include higher frequency of generalized tonic–clonic seizures, longer seizure duration, and AED polytherapy [15,16].

In patients with epilepsy, there are also nonseizure related arrhythmias that can be life-threatening. Sudden cardiac death (SCD) is an unexpected death of someone in a stable medical condition with no evidence of a noncardiac cause [17] and is a consequence of a lethal cardiac arrhythmia. Established risk factors, such as heart failure and ischemic heart disease, are detected in 60–80% of all cases of SCD [18,19]. It has been shown that SCD due to ventricular tachycardia/fibrillation demonstrated by ECG is threefold more common and occurs at younger age in people with epilepsy in comparison with that in control population [20], and the incidence is higher among patients with uncontrolled epilepsies [15]. In patients with drug-resistant epilepsy, the main determinant of ventricular tachycardia/fibrillation leading to SCD is a previous congenital or inherited cardiovascular disease, and not epilepsy characteristics [21]. Atherosclerosis and ischemic cardiac diseases are more frequently observed in patients with epilepsy, and they have been attributed to the direct effect of the disease and of many AEDs [22]. It has been also hypothesized that SCD and SUDEP may be partially overlapping entities [21].

In patients with long-standing uncontrolled epilepsy, several interictal electrophysiological abnormalities predisposing to serious arrhythmias have been reported. The most frequent alteration is the decrease in heart rate variability, which is suggestive of autonomic dysfunction [10,23]. Indeed, aberrant central autonomic output, generated by ictal and interictal epileptic discharges, may potentially involve any organ innervated by the autonomic nervous system. [24].

Alterations in cardiac electrophysiology may be caused by seizures or by the condition underlying epilepsy. Susceptibility to SCD in epilepsy might be the consequence of a shared genetic cause [25]. A number of genes encoding ion channels are expressed both in the brain and heart, and mutations of such genes may lead to pathological electrical activity manifesting as seizures and arrhythmias [10]. Longer QT corrected (QTc) intervals, which are often genetically determined, have been more often observed in patients with long-standing epilepsy in comparison to age-matched controls [26] (see Fig. 1).

In addition to long QT interval, QT dispersion (QTd) and elevated values of T-wave alternans (TWA) have been recently recognized as ECG markers that may predict arrhythmias and increased risk of SUDEP [27,28]; QTd is the difference between the longest and shortest QT intervals, and is a consequence of regional differences in repolarization. Abnormal QTd values (>50 ms) are associated with high risk of arrhythmias [27,28,29]. The TWA, which is a periodic beat-to-beat variation in the amplitude or shape of the ST segment or T-wave (see Fig. 2), represents a biomarker of cardiac electrical instability, and it is associated with a more than 50% increased risk of SCD in patients with cardiovascular disease [28,29]. In patients with focal epilepsies, TWA levels have been shown to double in the postictal phase of secondarily generalized seizures [30,31].

The relationship between epilepsy and arrhythmias emerges also from epidemiological evaluations. A cross-sectional study using data from 67,786 patients collected by a general practitioner register in the Netherlands have assessed all comorbidities between different cardiovascular diseases: 26.5% of the patients had diagnosis of at least one and 10.5% of two or more cardiovascular diseases. The most robust association within cardiovascular diseases was between heart failure and arrhythmias, and the strongest association for cardiovascular and noncardiovascular diseases was between arrhythmias and epilepsy [32].

Frequency and subtypes of arrhythmias in hospitalized patients with epilepsy have been recently assessed in a study performed on administrative data. In about one million and a half of patients from more than 1000 hospitals in USA, around 24% had cardiac arrhythmias, and the most frequent were atrial fibrillation (9.7%), unspecified arrhythmias (7.3%), sudden cardiac arrest (1.4%), bundle branch block (1.2%), and ventricular tachycardia (1%). Furthermore, hospitalized patients with epilepsy with arrhythmia presented a significantly higher mortality and were more frequently males [33].

1.3. The role of antiepileptic treatments on cardiac arrhythmias

The role of the AEDs in the pathogenesis of life-threatening arrhythmias is complex and debated. For example, in a meta-analysis of all double-blind studies performed with new AEDs on refractory epilepsies, the risk of definite or probable SUDEP was seven times higher in patients randomized to placebo than to adjunctive AEDs, providing evidence in favor of active treatment [34]. On the contrary, in a community-based study, the risk of SCD in patients with epilepsy was significantly, although mildly, associated with uncontrolled epilepsy and the use of AEDs [20]. It is worth to notice that an increased risk was also found with the use of AEDs in nonepileptic conditions, and the increased risk of SCD was specifically associated with AEDs blocking sodium channels, but not with nonsodium channel blockers [20].

It may be concluded that uncontrolled seizures are a strong risk factor of SUDEP, and this risk is reduced by an effective treatment. However, some AEDs have a weak effect in increasing the risk of life-threatening arrhythmias that may lead to SCD [20].

Prolongation of the QT interval, which is the time required for ventricular depolarization and repolarization to occur, is a reliable ECG marker of fatal arrhythmia [35]. *Long QT syndrome* is a group of genetic or acquired disorders deriving from alterations of sodium or potassium cardiac channels. Although these channelopathies are relatively rare and affect about 1 in 2500 individuals in the general population, several of their genetic variants may have a relatively low penetration. In such cases, ECG would be normal, yet they might be still at risk of developing arrhythmias following the exposure to agents able to prolong the QT interval [36]. In this respect, it is worth noticing that different drugs, including many antipsychotics, antidepressants, antihistamines, and antimicrobials, have the potential to prolong the QT interval [31], and

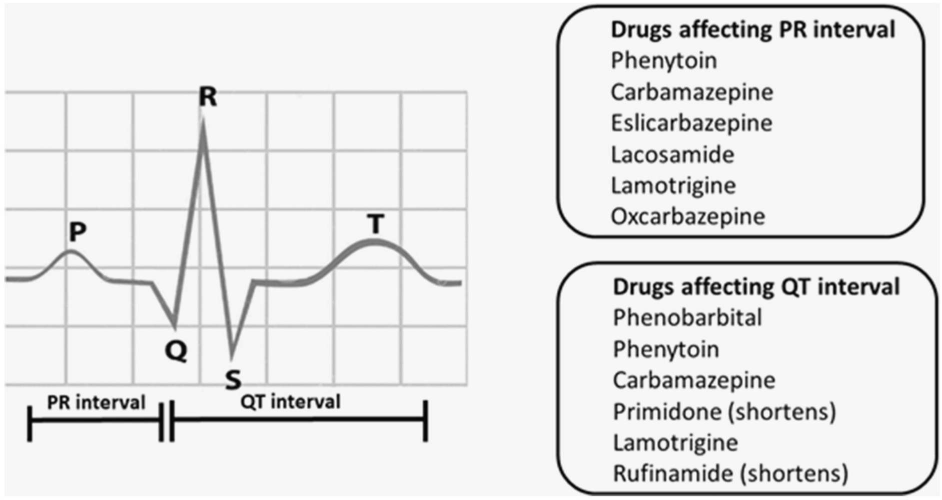

Fig. 1. Antiepileptic drugs found to increase (unless otherwise specified) PR and QT intervals in experimental or clinical studies are reported. See text for references.

there are also AEDs that can have a mild effect on the QT interval and increase the risk of malignant cardiac arrhythmias in vulnerable subjects.

In October 2005, because of the importance of screening drugs about their potential to prolong the QT interval, the International Conference on Harmonization developed a guideline to standardize technical requirements to evaluate QT-interval prolongation and proarrhythmic potential for non-AADs [37]. According to this working group, a parallel or crossover study with a concurrent positive control on healthy volunteers is recommended in the early clinical development of any new drug.

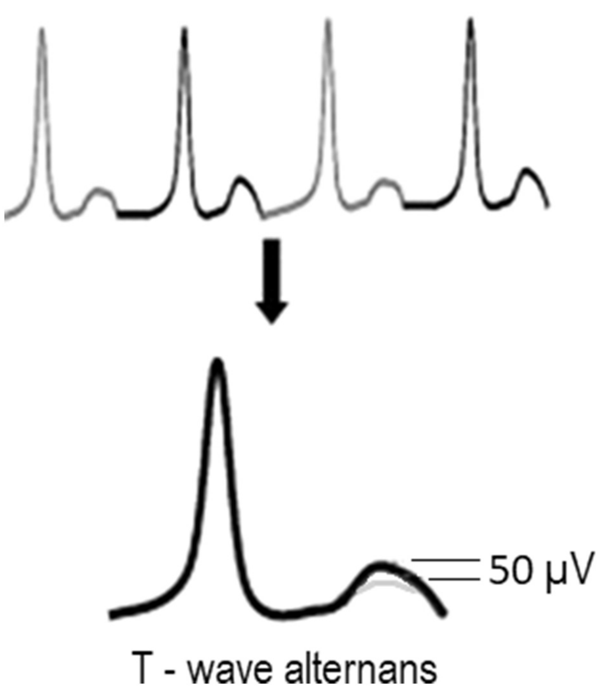

Fig. 2. Assessment of T-wave alternans (TWA) according to the modified moving average method [28]. Above: ECG records showing several QRST complexes. Below: template of QRS-aligned superimposed beats reveal the different morphology of T wave between different beats. Differences in amplitude of ST or T waves between beats ≥47 μV indicates an increased risk of arrhythmic death.

For all traditional and most of the new AEDs, formal studies exploring these aspects have not been done, and limited data are available.

Several drugs may determine alterations of cardiac electrophysiology that, albeit generally not serious, may become life-threatening in rare circumstances. A mildly prolonged PR interval (200 ms is the upper limit of the normal range), also called first degree atrioventricular block (AV block), is a benign disturbance of the electrical conduction system of the heart that may be drug-induced and unfrequently cause dizziness and fainting. This benign dysfunction may progress to type 2 AV block and, in turn, evolve to complete heart block with Stokes–Adam attacks and SCD [38]. Many different traditional and newer AEDs, in particular the sodium channel blockers, have the property to increase the PR interval and, rarely, induce arrhythmias (Fig. 1).

1.3.1. *Effect of traditional antiepileptic drugs on cardiac electrophysiology*

Experimental studies suggest that PHT and phenobarbital (PB) prolong the QT interval, particularly at high plasma concentrations, and might have proarrhythmic potential [39,40]. All available evidence from clinical studies, however, plays against any excess risk with these drugs when used at therapeutic doses. Interestingly, QT shortening rather than prolongation has been reported in some patients after primidone administration, and there are anecdotal reports for the use of this drug in patients with congenital long QT syndrome [41].

In the case of carbamazepine (CBZ), a formal ECG study on healthy volunteers showed a mild prolongation of the PR interval at the dose of 800 mg [42], while no statistically significant change in QTc interval was observed in patients treated with CBZ or lamotrigine (LTG) in a clinical trial conducted in elderly patients with newly diagnosed epilepsy [43].

Carbamazepine can affect sinus node function and delay atrioventricular conduction. Bradyarrhythmia and atrioventricular conduction defects associated with dizziness and syncope have been described [44,45] mostly among elderly women, even at low drug levels. Massive CBZ overdosing has been associated with sinus tachycardia [46]. An increased risk of SUDEP with CBZ administration has been also reported in two case–control studies [47].

No effect on the QT interval and cardiac rhythm has apparently been observed with valproate as intravenous administration in psychiatric inpatients [47–49].

1.3.2. *Effect of new antiepileptic drugs on cardiac electrophysiology*

Gabapentin (GBP) and pregabalin (PGB) have a similar main mechanism of action, i.e., the block of L-type calcium channel. The effect of enacarbil, a prodrug of GBP, on cardiac repolarization has been investigated in a formal QT/QTc study [50]. This was a randomized, double-blind, double-dummy, placebo- and active-controlled, crossover study that enrolled 52 healthy adults. The findings of this study are in keeping with previous experimental studies showing that GBP can only minimally inhibit potassium currents and does not significantly affect the QT interval [47].

Formal QT/QTc studies with PGB have not been published. One experimental study in rabbits showed a statistically significant lengthening of the QTc interval after the administration of a single dose of PGB [51]. A case of an 80-year-old female presenting with syncope attacks and prolonged QT interval that resolved after discontinuation of PGB has been recently signaled [52]. Prolonged PR interval and AV block have been also reported in a young man with tuberculosis and severe pain [53]. An arrhythmogenic potential of this drug is unlikely but cannot be excluded.

Lacosamide (LCM) enhances slow inactivation of voltage-gated sodium channels. The risk of QT-interval prolongation has been evaluated in a formal QTc trial with a parallel design, which randomized 247 healthy individuals to LCM at the daily dose of 400 mg or 800 mg, placebo or active control. No effects of LCM were observed on the QT interval. A small increase in the PR interval of about 7 ms was found at the maximum plasma concentration, but no case progressed to a second-degree or higher AV block [54]. Similarly, no change in the QT interval and small, dose-related increase in the PR interval were found in a population of patients with focal seizures ($n = 944$), pooled from three double-blind, placebo-controlled studies [55]. Single cases of transient second-degree AV block [56], asymptomatic sinus node dysfunction [57], and atrial fibrillation at the dose of 600 mg/day have been however reported [58]. A complete AV block has been signaled in an old patient assuming LCM at low doses [59]. The arrhythmogenic potential of LCM when administered through intravenous infusion for the treatment of status epilepticus (SE) has been analyzed in a retrospective study: cardiac safety was not influenced by the speed of infusion, and one case of PR prolongation was documented [60]. Lacosamide should be used with caution in patients with severe cardiac diseases or when it is administered in combination with agents known to be associated with PR prolongation.

A formal QT/QTc double-blind, placebo- and active-controlled crossover study showed no significant increase in the QT interval with LTG at doses of 100–400 mg [61]. Similar reassuring findings came out from a clinical study comparing LTG to CBZ in elderly patients with newly diagnosed epilepsy [43]. However, some in vitro experiments suggested a significant inhibition of potassium currents by this agent [62], and 4 cases of SUDEP have been reported in women with idiopathic epilepsy treated with LTG monotherapy [63]. Interestingly, postmortem genetic analysis showed a novel mutation in the SCN5A gene (encoding a subunit of the Nav1.5 ion channel protein, which is responsible for the sodium inward current in the heart) in one of these patients. It has been suggested that LTG may have caused QT prolongation and unmasked a Brugada syndrome in this genetically predisposed patient. A prolonged QT interval has also been observed in a case of LTG overdose [64].

The effect of LTG on the PR interval has been studied in healthy volunteers and an increase of about 5 ms has been found after single doses of 150 mg and 200 mg [65]. A prolongation of the PR interval has also been signaled in two clinical studies [43,66]. Also in this case, caution should be exercised in patients with cardiac conduction abnormalities.

As regards levetiracetam (LEV) a formal QT/QTc single-dose, double-blind, placebo- and active-controlled, crossover study was conducted in 52 healthy volunteers and had negative findings [67]. This drug has also no effect on PR interval [68]. Although it has been reported a case of a young female with a previously undiagnosed genetic long QT syndrome whose QT interval increased and developed into *torsades de pointes* after LEV treatment [69], this drug seems devoid of significant cardiac toxicity.

No data on cardiac safety are available for brivaracetam, the latest AED to have obtained marketing authorization as addon treatment for focal-onset seizures, with or without generalization [70].

In a formal crossover, placebo- and active-controlled study performed on 67 healthy volunteers, no effects of eslicarbazepine acetate (ESL) were observed on the QT interval, whereas there was a small increase of the PR interval [71]. Since ESL is the racemic form of the main metabolite of oxcarbazepine (OXC), it can be expected that the two agents have similar effects on the heart. No studies have been however published with OXC, so far. Both compounds should be used with caution in patients with cardiac conduction abnormalities or in those taking concomitant drugs associated with PR prolongation.

Perampanel (PER) has a novel mechanism of action. It is a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. A phase I study evaluating the QT interval in healthy volunteers and pooled clinical data from three phase III studies in patients with drug-resistant epilepsy showed that PER at the doses of 6 and 12 mg did not delay cardiac repolarization [72].

A study of the effect of rufinamide (RFM) on the QT interval has been performed in 19 patients with Lennox–Gastaut syndrome. During the treatment, a significant shortening of the QT interval was observed. Since there is a rare, genetically determined *short QT syndrome* that may lead to lethal ventricular fibrillation [16], ECG monitoring is recommended during treatment with RFM because of its arrhythmogenic potentialities [73].

Topiramate (TPM) does not seem to affect the QT interval, although no formal QT studies have been performed. In a cross-sectional clinical study on 178 children with epilepsy randomized to TPM, CBZ, OXC, and valproate, no differences in the QT interval were observed between the three groups and all drugs were considered safe [74]. A double-blind study of adjunctive TPM for patients with a schizoaffective disorder, and measuring ECG changes among the safety outcomes, reported no changes in any ECG parameter [75].

To date, negative findings from clinical studies or no data have been reported about the cardiac safety of zonisamide, clobazam [76], or less commonly used AEDs such as felbamate, stiripentol, tiagabine, or vigabatrin [77].

In summary, alterations of cardiac electrophysiology constitute a rare complication of AED treatment. While there is little or no risk in healthy individuals, patients with underlying cardiac dysfunction, patients with electrolyte imbalances (such as hypokalemia or hypomagnesemia), elderly patients, or patients with comorbidities requiring drugs affecting cardiac function may be at risk. In such cases, AEDs with little or no effects on cardiac function should be preferred and, if this cannot be assured, monitoring of ECG changes and serum electrolytes are recommended.

1.3.3. Effect of vagal nerve stimulation on cardiac electrophysiology

Vagal nerve stimulation (VNS) is an accepted therapeutic strategy for patients with drug-resistant epilepsy. In 2000, it has been observed that in patients treated with this procedure, after 2 years of follow-up, there was a lower than expected SUDEP rate [78]. More recently, VNS has been also shown to determine a significant reduction in interictal TWA levels [28,29,31,79]. This finding has been explained either as a consequence of seizure suppression or pleiotropic protective effects via peripheral influences. In alternative, VNS may have this protective effect through the reduction of seizure-induced excessive sympathetic nerve activity [29].

1.3.4. Effect of antiarrhythmic drugs on seizures

It is not infrequent that a patient with epilepsy has also a disturbance of cardiac electrophysiology [33] requiring treatment with AADs. Accordingly, it is important to know the effect of these agents on seizures.

Several AADs share their molecular targets with AEDs. According to Vaughan Williams classification system, class 1 AADs are Na+ channel blockers (subclass IC do also exert a moderate block of K+ channels); class II includes strong beta-adrenergic blockers; class III gathers blockers of K+ channels; class IV includes L-type Ca++ channel blockers, and class V drugs working with other or unknown mechanisms [3]. Some AADs have more than one mechanism of action.

Although AADs are specific for heart receptors, those agents able to cross the blood–brain barrier might also have activity on brain receptors [80] and determine anticonvulsant and proconvulsant effects. A short description of the AADs showing antiepileptic activity in experimental and/or clinical studies is reported below.

Intravenous lidocaine (a class I AAD) is often used to treat SE, and there is enough evidence to consider lidocaine for the treatment of resistant forms of SE in pediatric patients [81]. Lidocaine is used also for neonatal seizures [82] and clinical improvement with chronic subcutaneous administration has been observed in a young girl with intractable frontal lobe epilepsy [83].

Quinidine, a KCNT1 blocker, has been suggested as a rational therapeutic approach in patients with migrating focal seizures, which may be caused by a gain-of-function mutation in the KCNT1 potassium channel gene. Notably, a 90% seizure reduction was observed in two patients with this disease [84]. Quinidine has also been investigated in 6 patients with a severe autosomal dominant nocturnal frontal lobe epilepsy due to KCNT1 mutation, but without response [85].

Mexiletine belongs to the Class IB of the AADs and is also a local anesthetic. Experimental studies have shown that this agent has antiseizure effects per se and synergistic pharmacodynamic interactions with some AEDs, namely PGB and TPM [86]. Mexiletine was efficacious in early infantile epileptic encephalopathy related to SCN2A mutation [87] and in medically refractory epilepsies [88].

Propafenone is a Class 1C Na+ channel blocker, and experimental studies showed that it can be efficacious in animal models of epilepsy and enhance the efficacy of several AEDs [89]. No clinical data are available, yet.

Propanolol (a Class II beta blocking agent) has been demonstrated to be effective in several animal models of chemically-induced seizures [80]. Similar findings have been observed with timolol and nevibolol [80]. These drugs can also increase the anticonvulsant effect of several AEDs [80]. In a small double-blind crossover study, propanolol was effective in patients with chronically unstable generalized epilepsies [90].

Verapamil, a class IV AAD, displayed anticonvulsant properties in several experimental epilepsy models [91]. It can also inhibit a glycoprotein that extrudes xenobiotics and several drugs from the brain with the consequence of reducing their availability and efficacy. In patients with drug-resistant forms of epilepsy, verapamil has been coadministrated with other AEDs with the aim to increase their brain concentrations and, hence, the effect against seizure, but results were mostly negative [91].

The Class 3 AAD amiodarone is a multichannel blocker crossing the blood–brain barrier. It does not affect seizure threshold in animal models of epilepsy, but significantly potentiates the anticonvulsant effect of CBZ [92].

Diltiazem, a Class IV AAD, is a calcium channel antagonist that potentiated the antiseizure effect of TPM in a mouse model of seizures [93]; no clinical data are available.

Ivabradine is a class V AAD with anticonvulsant effects in animal models of epilepsy [94]. Ranolazine, a class V AAD, is of particular interest. This agent has antiarrhythmic actions with respect to both atria and ventricles [95]. An in vitro study showed that ranolazine has almost no effect on the wild type Na(V) 1.1 channel in the brain, while it is effective on a mutant Na(V) 1.1 channel that exhibits increased persistent current because of incomplete inactivation [96]. Mutation of this channel is associated with several genetic epilepsies, ranging from mild generalized epilepsy to severe myoclonic epilepsy of infancy. This might be an example of precision medicine, where a drug can selectively suppress a mutant channel and improve genetic disorders. No clinical data have been however reported, yet.

No evidence is available or negative findings have been reported about the efficacy on seizures for all other AADs. For more details on the effect of AADs on experimental models of seizures, see Borowicz and Banach [80].

Finally, in rare cases, AADs may also cause seizures, mostly in the contest of overdosage. These complications have been observed with dysopiramide [97], lidocaine [98], mexiletine [99], flecainide [100], propafenone [101], atenolol [102], and ranolazine [103].

1.3.5. Drug–drug interactions between antiepileptic and antiarrhythmic drugs

Traditional AEDs interact with a myriad of non-AEDs, most often inducing their metabolism: as such, several AADs may have their metabolism induced and their efficacy reduced. The AADs may also interact with AEDs, mainly by inhibiting their metabolism and increasing the risk of toxicity [104,105].

A recent analysis of administrative data demonstrated that 12% of the patients treated with enzyme inducers AEDs were concomitantly treated with cardiovascular agents whose metabolism was strongly induced, and their effect completely abolished; a further 11% received cardiovascular drugs that were moderately induced [106]. These data suggest that drug–drug interactions are frequent and may influence efficacy or tolerability of treatment in patients with epilepsy and cardiovascular diseases.

Drug–drug interactions between AADs and AEDs identified through literature [103,104] and Medscape interaction checker [107] are summarized in Table 1 (interactions have been searched for any compound included in the recent guideline on use of AADs [3]).

2. Conclusions

There is growing awareness that epilepsy is often comorbid with other neurological and nonneurological diseases. The association between epilepsy and arrhythmias is intriguing because of the complex mechanisms underlying these conditions and the potentially serious clinical implications.

In patients with preexisting heart disease, and especially in those with disturbances of cardiac electrophysiology, the AEDs with the lowest risk of effects on the heart should be selected. Traditional AEDs (PB, PHT, CBZ) should be avoided because of their inducing properties, which may offset the effect of some AADs, and their potential to enhance disturbances of cardiac rhythms. Arrhythmogenic properties have been rarely observed with some of the newer AEDs, mostly blockers of the voltage-dependent sodium channels, like ESL, LTG, LCM, OXC, and RFM. These drugs should be used with caution in patients with conduction abnormalities, and their combination with agents known to alter cardiac electrophysiology should be avoided. In addition, 12-lead ECG monitoring should be performed, and attention should be paid to any factor that may increase the risk of arrhythmia, including electrolyte imbalances as hypokalemia, elderly age, and concomitant medications. Indeed, worsening of cardiac electrophysiology should encourage assessment of arrhythmogenic potential of all drugs assumed by the patient and suggest treatment revision.

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Table 1
Drug–drug interactions between antiarrhythmic and antiepileptic drugs.

Antiarrhythmic drug and relative class	Type of interaction	Antiepileptic drugs and level of interaction	Mechanism of interaction
Disopyramide (Class IA)	Concentrations of disopyramide are decreased by	carbamazepine (moderate) phenobarbital (minor) primidone (minor) oxcarbazepine (minor) eslicarbazepine (minor) topiramate (minor)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
	Concentrations of disopyramide are decreased but toxicity increased by	phenytoin (moderate)	Unknown mechanism
Quinidine (Class IA)	Concentrations of quinidine are decreased by	phenytoin (moderate) carbamazepine (major) phenobarbital (moderate) primidone (moderate) oxcarbazepine (moderate) eslicarbazepine (moderate) topiramate (moderate)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
	Concentrations of both drugs are increased by the combination	lacosamide (moderate)	Each drug affects hepatic/intestinal enzyme CYP3A4
Lidocaine (Class IB)	Concentrations of lidocaine are decreased by	carbamazepine (moderate) phenobarbital (moderate)	Inducing AEDs affect hepatic enzyme CYP1A2
	Concentrations of lidocaine are decreased by	phenytoin (major)	Phenytoin affects hepatic enzyme CYP3A4
Mexiletine (Class IB)	Concentrations of mexiletine are decreased by	phenytoin (moderate) carbamazepine (moderate) phenobarbital (moderate)	Inducing AEDs increase metabolism of mexiletine
Propafenone (Class IC)	Concentrations of propafenone are decreased by	carbamazepine (moderate) phenytoin (minor) phenobarbital (minor) oxcarbazepine (minor) eslicarbazepine (minor) topiramate (minor)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
Atenolol (Class II)	Concentrations of atenolol are decreased by	phenobarbital (moderate) primidone (moderate)	Inducing AEDs increase atenolol metabolism
Esmolol (Class II)	Concentrations of esmolol are decreased by	phenobarbital (moderate) primidone (moderate)	Inducing AEDs increase esmolol metabolism
Nadolol (Class II)	Concentrations of nadolol are decreased by	phenobarbital (moderate) primidone (moderate)	Inducing AEDs increase nadolol metabolism
Amiodarone (Class III)	Amiodarone increases the level of	phenytoin (moderate)	Amiodarone inhibits hepatic enzyme CYP2C9
	Concentrations of amiodarone are decreased by by	phenytoin (moderate) phenobarbital (moderate) carbamazepine (major) oxcarbazepine (moderate) topiramate (moderate)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
Dronedarone (Class III)	Dronedarone increases the level of	carbamazepine (moderate) zonisamide (minor)	Dronedarone inhibits hepatic/intestinal enzyme CYP3A4
	Concentrations of dronedarone are reduced by	phenytoin (major) phenobarbital (major) primidone (major) carbamazepine (major) oxcarbazepine (major) topiramate (major)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
Dofetilide (Class III)	Either increases effects of the other	phenytoin (major)	Pharmacodynamic synergism
Sotalol (Class III)	Concentrations of sotalol are decreased by	phenobarbital (moderate) primidone (moderate)	Inducing AEDs affect metabolism of sotalol
Diltiazem (Class IV)	Concentrations of diltiazem are decreased by	phenobarbital (moderate) primidone (major) phenytoin (moderate) oxcarbazepine (moderate) topiramate (moderate)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
Verapamil (Class IV)	Concentrations are decreased by	phenobarbital (moderate) phenytoin (moderate) carbamazepine (moderate) primidone (moderate) oxcarbazepine (moderate) topiramate (moderate)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4
	Verapamil increases concentrations of	carbamazepine (moderate) zonisamide (moderate)	Verapamil inhibits hepatic/intestinal enzyme CYP3A4
Digoxin (Class V)	Concentrations are reduced by	phenobarbital (moderate) phenytoin (moderate)	AEDs affect P-glycoprotein (MDR1) efflux transporter
	Concentrations are reduced by	topiramate (minor)	Unspecified mechanisms
Ivabradine (Class V)	Concentrations are reduced by	phenobarbital (major) phenytoin (major) carbamazepine (major) primidone (major)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4

(continued on next page)

Table 1 (*continued*)

Antiarrhythmic drug and relative class	Type of interaction	Antiepileptic drugs and level of interaction	Mechanism of interaction
Ranolazine (Class V)	Concentrations are reduced by	oxcarbazepine (major) phenobarbital (major) phenytoin (major) carbamazepine (major) primidone (major) oxcarbazepine (major) topiramate (major)	Inducing AEDs affect hepatic/intestinal enzyme CYP3A4

Legend: In the table, only AADs presenting interactions with AEDs have been included.
Level of interaction was classified as major (potentially serious, the combination should be avoided), moderate (clinically significant, caution is needed) or minor (probably not clinically relevant) according to the criteria proposed by Johannessen and Johannessen Landmark [108]. It should be considered that the magnitude of the interaction is influenced by several factors

Declaration of Competing Interest

GZ has received speaker's or consultancy fees from Eisai, Sanofi-Aventis, and UCB Pharma. SL has no conflict of interest.

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