Personalized Psychiatry and Neurology

Review

Interindividual Variability of Anticonvulsant-Induced QT Prolongation Risk

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Abstract: In connection with the widespread use of anticonvulsants (antiepileptic drugs – AEDs) in psychiatric and neurological practice and the need for their long-term use to treat a wide range of mental disorders and neurological diseases, the question of their safety profile, including the assessment of the risk of developing life-threatening conditions and adverse reactions (ADRs), becomes relevant. In this regard, from the position of personalized medicine, it is critical to develop an interdisciplinary approach with the participation of doctors of various specialties and a new strategy of a personalized approach to predicting AED-induced prolongation of the QT interval as one of the most prognostically unfavorable cardiological ADRs (including sudden death syndrome – SDS). We searched for full-text publications for the period from 2011 to 2021 databases using the following keywords and its combination. We have found and systematized monogenic and multifactorial forms of long QT syndrome (LQTS) and candidate genes that slow down AEDs metabolism in the liver. Identification of risk alleles of single nucleotide variants (SNVs) of the candidate genes predisposing to the development of AED-induced LQTS and SDS will make it possible to adjust the choice and dosage of these drugs and prevent the development of ADRs, which will improve the quality of life of patients and prevent SDS in the patients with psychiatric and neurological disorders.

Keywords: *anticonvulsant; antiepileptic drugs; adverse drug reaction; cardiac repolarization; long QT syndrome; sudden death syndrome; ventricular tachyarrhythmia; candidate genes; biomarkers; predictors.*

Introduction

Anticonvulsants (antiepileptic drugs – AEDs) are used not only in the treatment of epilepsy [1,2], but also in the treatment of other diseases and syndromes, such as neuropathic pain syndrome [3], schizophrenia (as mood stabilizers) [4], olanzapine-induced weight gain [5], dysmorphophobia and behavioral disorders in dementia [6] (**Figure 1**).

In addition to the above, anticonvulsants (AEDs of the benzodiazepine group) are of interest to psychiatrists and toxicologists due to their widespread use by drug addicts [7]. In connection with the widespread use of AEDs in psychiatric and neurological practice and the need for their long-term (often chronic) use to treat a wide range of mental disorders and neurological diseases, the question of their safety profile, including the

assessment of the risk of developing life-threatening conditions and adverse reactions (ADRs), becomes relevant. According to the current Russian Federation classifications and legislative acts [8,9], serious ADRs of psychopharmacotherapy are subject to registration [10]. However, the implementation of the existing regulations is not always implemented in practice. On the one hand, this does not allow us to fully assess the incidence of AED-induced ADRs. On the other hand, against the background of relative well-being a sudden development of heart rate and conduction – associated ADRs is possible. Finally, prediction, risk assessment, correction and registration of AED-induced heart rate and conduction ADRs are determined by the similarity of the mode of action of AEDs (**Table 1**) upon ion channels that are expressed both in the central nervous system (CNS) and in the heart (**Figure 2**).

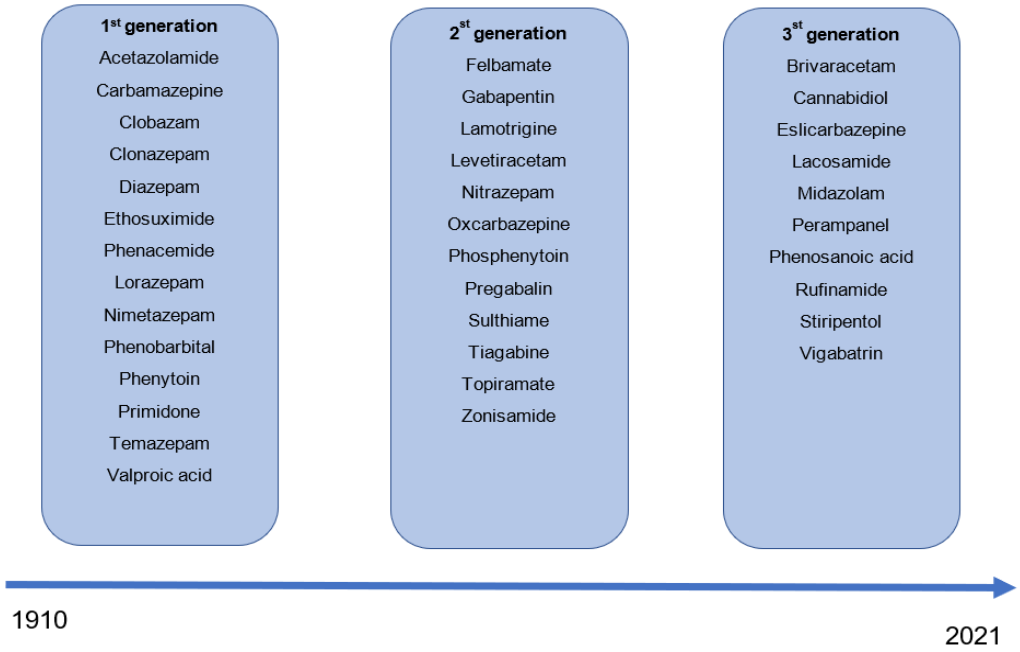

Figure 1. Generations of antiepileptic drugs.

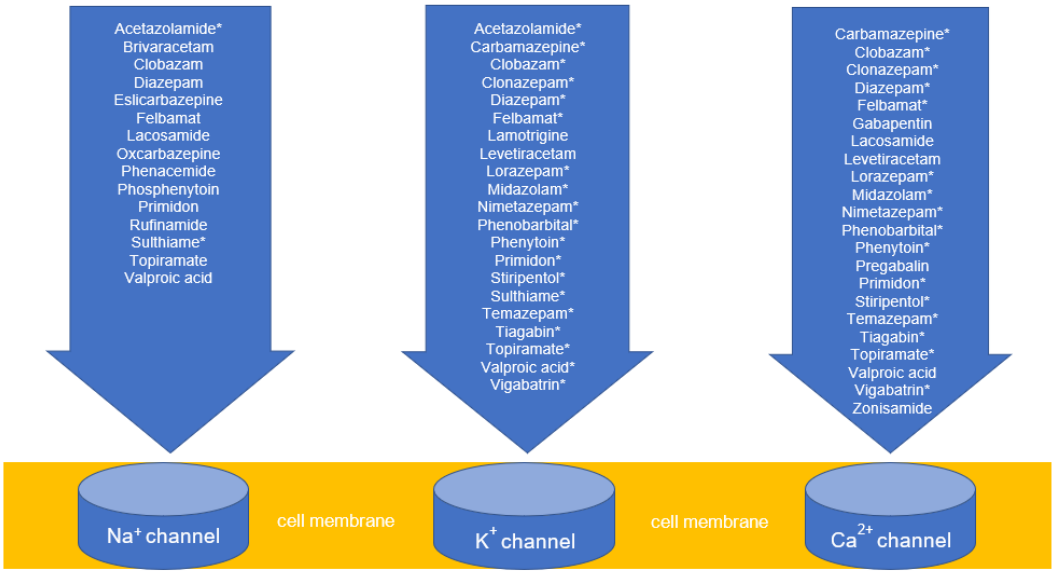

Figure 2. Effect of antiepileptic drugs ion channels. * - indirect influence.

Table 1. The mechanism of action and the effect of antiepileptic drugs on the QT interval, heart rate, and conduction ([2], modification by N.M. Zhuravlev and co-authors).

Anticonvulsant	Mode of action	Effect	Reference
Acetazolamide	Ensures selective inhibition of carbonic anhydrase. Inhibits ion transport in the central nervous system and heart. Causes electrolyte imbalance.	Prolongation of the QT interval.	[13,14]
Brivaracetam	Binds to SV2A glycoprotein. Causes a blockade of voltage-dependent Na + channels.	Prolongation of the QT interval.	[15,16]
Cannabidiol	Increases activity of A1-adenosine receptors. Inhibits the orphan G-protein-coupled receptor, GPR55. Inhibits the transient receptor potential of the TRPM8 melastatin-type channel. Activates serotonin 5-HT1a receptors. Activates α1- and α3-glycine receptors.	No data were found on prolongation of the QT interval.	[17]
Carbamazepine	Stimulates the GABAergic system. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[18,19]
Clobazam	Potentiates GABAergic inhibition in the central nervous system. In large doses, it prolongs the inactivation of sodium channels.	Prolongation of the QT interval.	[17]
Clonazepam	Causes a blockade of voltage-dependent ion channels. Acts as a serotonin agonist. Potentiates GABAergic inhibition in the central nervous system.	Prolongation of the QT interval.	[20]
Diazepam	Stimulates the GABAergic system. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[21]
Eslicarbazepine	Causes a blockade of VGSC.	Prolongation of the QT interval.	[22,23]
Ethosuximide	Causes a blockade of low-threshold T-type calcium channels in the thalamus.	No data were found on prolongation of the QT interval.	[24]
Felbamate	Inhibits NMDA receptor currents. Potentiates the ergic activity of GABA. Causes a blockade of VGSC.	Prolongation of the QT interval.	[25]
Gabapentin	Inhibits the selective ligand of the α2δ-subunit of the calcium channel.	Prolongation of the QT interval.	[26]
Lacosamide	Enhances inactivation of slow sodium channels.	Prolongation of the QT interval.	[27]
Lamotrigine	Causes a blockade of VGSC. Inhibits veratrin (sodium channel activator). Inhibits N- and P-type calcium channels. Ensures direct inhibition of HERG channels that regulate the flow of potassium ions. Modulates the release of a presynaptic transmitter of excitatory neurotransmitters (aspartate and glutamate).	Prolongation of the QT interval.	[28]
Levetiracetam	Ensures glycoprotein binding of SV2A synaptic vesicles. Acts as a low affinity GABA receptor agonist. Inhibits calcium channels. Decreases levels of the amino acid taurine. Inhibits slow potassium current.	Prolongation of the QT interval.	[29,30]
Lorazepam	Stimulates the GABAergic system. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[31,32]
Midazolam	Stimulates the GABAergic system. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[33]
Nimetazepam	Increases the affinity of the GABAergic system for GABA. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[7]
Nitrazepam	Increases the affinity of the GABAergic system for GABA. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[7]
Oxcarbazepine	Causes a blockade of VGSCs.	Prolongation of the QT interval.	[34]
Perampanel	Selective non-competitive antagonist of ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionate.	No data were found on prolongation of the QT interval.	[35,36]

Phenacemide	Causes a blockade of VGSCs.	Prolongation of the QT interval.	[37]
Phenytoin	Stimulates the GABAergic system. Causes a blockade of VGSCs.	Prolongation of the QT interval.	[19]
Phenobarbital	Stimulates the GABAergic system. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[18]
Phenosanoic acid	Ensures stabilization of neuronal membranes by inhibition of peroxidation processes and changes in the lipid composition of the cell membranes of the brain.	No data were found on prolongation of the QT interval.	[38]
Phosphenytoin	Causes a blockade of VGSCs.	Prolongation of the QT interval.	[39]
Pregabalin	Inhibits the selective ligand of the α2δ-subunit of the calcium channel.	Prolongation of the QT interval.	[40]
Primidon	Causes a blockade of VGSC. Activates GABA-A receptors. Inhibits the TRPM3 receptor.	Prolongation of the QT interval.	[41]
Rufinamide	Causes a blockade of VGSC.	Prolongation of the QT interval.	[42]
Stiripentol	Increases the level of GABA in the brain due to inhibition of synaptic uptake of GABA and inhibition of GABA transaminase. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[43]
Sulthiame	Inhibits carbonic anhydrase. Causes electrolyte imbalance.	Prolongation of t he QT interval.	[44]
Temazepam	Increases the sensitivity of GABA receptors to the mediator.	Prolongation of the QT interval.	[45]
Tiagabin	Inhibits presynaptic and glial uptake of GABA. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[46]
Topiramate	Causes a blockade of glutamate kainate / alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid. Increases affinity of GABA for GABA-A receptors. Causes a blockade of glutamate (AMPA) receptors. Causes a blockade of VGSC.	Prolongation of the QT interval.	[47]
Valproic acid	Inhibits carbonic anhydrase isoenzymes of types II and IV. Causes direct inhibition of hERG channels that regulate the flow of potassium ions. Stimulate of the GABAergic mechanism by inhibiting the GABA transferase enzyme. Block voltage-dependent sodium channels and T-type calcium channels. Inhibit a specific sodium / myo-inositol transporter.	Prolongation of the QT interval.	[48,49]
Vigabatrin	Causes irreversible selective inhibition of GABA aminotransferase. Causes a blockade of voltage-dependent ion channels.	Prolongation of the QT interval.	[50]
Zonisamide	Causes a blockade of VGSC. Causes T-type calcium channel blockade. Inhibits carbonic anhydrase isoenzymes of types II and IV.	Prolongation of the QT interval.	[4,51]

Note: GABA – gamma-aminobutyric acid; CNS – central nervous system; 5-HT1a – a subtype of serotonin receptors of the 5-HT1 receptor subfamily; AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; GPR55 – a cannabinoid receptor that is expressed by cells of the brainstem, frontal cortex, striatum, hypothalamus, cerebellum, and hippocampus; HERG – gene for specific potassium channels of the heart; NMDA – N-methyl-D-aspartate; SV2A – synaptic vesicle glycoprotein encoded by the 2A gene; TRPM3 – one of eight members of the melastatin subfamily of ion channels with transient receptor potential; TRPM8 – one of eight members of the melastatin subfamily of ion channels with transient receptor potential.

The voltage-gated sodium channels (VGSC) that are responsible for action potential generation in central neurons are important targets for the actions of AEDs. These channels consist of a complex of three glycoprotein subunits: a pore-forming alpha subunit of 260 kD associated non-covalently with a beta 1 subunit of 36 kD and disulfide-linked to a beta 2 subunit of 33 kD. The alpha subunit forms a functional VGSC by itself, whereas the beta 1 and beta 2 subunits modulate channel gating. The beta 1 and beta 2 subunits also have immunoglobulin-like folds in their extracellular domains that are predicted to interact with extracellular proteins. The alpha subunit is comprised of four homologous domains containing six transmembrane alpha helices (S1 through S6) and additional membrane-associated segments (SS1/SS2). The S4 segments in each domain function as voltage sensors for voltage-dependent activation of the sodium channel. The S5 and S6 segments

in each domain and the short SS1/SS2 segments between them form the pore of VGSC. The intracellular loop between domains III and IV forms the inactivation gate, which folds into the pore and occludes it within 1 msec of channel opening. The activity of brain sodium channels in modulated by protein phosphorylation G proteins. Activation of muscarinic acetylcholine receptors in hippocampal neurons slows the inactivation of VGSCs and reduces peak sodium currents through activation of protein kinase C (PKC) phosphorylation of sites in the inactivation gate and the intracellular loop between domains I and II of the alpha subunit. Other neurotransmitters that activate the PKC pathway are likely to have similar effects. Activation of D1-like dopamine receptors in hippocampal neurons reduces peak sodium currents through activation of cyclic adenosine monophosphate (cAMP)-dependent protein kinase phosphorylation of sites in the intracellular loop between domains I and II. Modulation by PKC and cAMP-dependent protein kinase is convergent-phosphorylation of the inactivation gate by PKC is required before phosphorylation of sites in the intracellular loop between domains I and II can reduce peak sodium currents. Brain sodium channels are also modulated by G proteins. Activation of endogenous G protein-coupled receptors causes negative shifts in the voltage dependence of VGSCs activation and inactivation. Overexpression of G protein beta gamma subunits induces persistent sodium currents. Regulation of VGSCs function by these multiple pathways can produce a flexible tuning of electrical excitability of central neurons in response to neurotransmitters, hormones, and second messengers. The AEDs (phenytoin, carbamazepine, and lamotrigine) inhibit brain VGSCs substantially at clinically relevant concentrations. Their inhibition of VGSCs is increased by depolarization because they bind preferentially to the inactivated state of the channels. This effect increases the inhibition of VGSCs in depolarized tissue at the center of an epileptic focus. Mutations in these amino acid residues prevents preferential binding to the inactivated state and thereby greatly reduces the affinity for inhibition of sodium channels by AEDs [52, 53].

The activity of VGSCs has long been linked to disorders of neuronal excitability such as epilepsy and chronic pain. Recent genetic studies have now expanded the role of VGSCs in health and disease, to include autism, migraine, multiple sclerosis, cancer as well as muscle and immune system disorders [53]. Many epileptogenic and arrythmogenic mutations of the *SNC1A, SCN2A* and *SCN3A* genes exhibit increased persistent currents [54]. Knowledge of the structure-function relationships for drug binding at this receptor site may open the way to prevention of cardiac ADRs of AEDs.

In cardiomyocytes, rapid Na+ influx through VGSCs is responsible for the phase 0 upstroke of the action potential. Alterations in sodium current (INa) lead to action potential prolongation, and can lead to the development of early after depolarizations; these concomitantly lead to triggered automaticity and arrhythmia development [55,56].

All biological cells have K channels; they are crucial for all transmembrane transport mechanisms. In addition, since the evolutionary appearance of VGSCs and calcium channels, K channels are further diversified in relation to their newer function, namely, keeping neuronal excitation within limits. Structurally, K channels consist of transmembrane (TM) protein elements similar to the calcium channels and VGSCs and the cyclic nucleotide-regulated channels, with which the K channels can be grouped into a superfamily of "voltage-gated-like" ion channels. The K-channel family is by far the largest: ,70 human genes encoding for different a subunits have been discovered since the beginning of K-channel cloning. With the formation of heteromers, modulating b subunits, and differential expression, thousands of different K channels are possible. Four a subunits are necessary to build a functional K channel. The a subunits are differentiated according to whether they consist of 2, 4, or 6TM domains. More common are functionally defined names such as "inward rectifier" K (Kir) channels for 2TM channels, "leak two pore domain" K (K2P) channels for 4TM, and "voltage-gated" K (Kv) channels for 6TM [57].

Voltage-gated K+ channels comprise the largest family of voltage-dependent ion channels, displaying a conserved tetrameric structure compromised of an assembly of

four shared pore-forming α-subunits, as well as auxiliary β subunits. The pore-forming α-subunits are composed of six transmembrane segments (S1–6); positively charged residues in the S4 segment form the voltage-sensing domain, while S5, S6 and the intervening P region form the pore domain. In the heart, potassium current is conducted through an array of channels, in which mutations of genes encoding individual α subunits have been linked with five out of the twelve congenital LQTS. [56,58]

In presynaptic nerve terminals, a component of the calcium current was found to be in sensitive to DHP, but was blocked by a peptide, v-conotoxin GV1A, obtained from the bcone shell, Conus geographus. This calcium current was named N-type for "Non-L" and "Neuronal." Another calcium channel subtype was identified in cerebellar purkinje cells and was found to be insensitive to both dihydropyridine channels and v-conotoxin GV1A. These channels were termed P-type after "Purkinje" cells and, subsequently, were found to be sensitive to v-agatoxin IVA, a peptide found in the venom of the American funnel web spider, Agelenopsis aperta. A further component of the v-agatoxin IVA-sensitive calcium current, albeit with lower affinity for the toxin, was identified in cerebellar granule cells and named Q-type. An R-type or "residual" calcium current has also been isolated on the basis of insensitivity to DHPs and the toxins that block N- and P/Q-type currents. Although initially thought to involve distinct channels, the P- and Q-type channels are now often referred to as P/Q-type channels because they are thought to arise from either splice variants or from different accessory subunit interactions with the pore-forming component arising from the same gene [59].

The voltage-gated calcium channels comprise 10 members, all possessing four internally homologous motifs, S1-S6, that forma pseudo-tetramer with a common pore-forming α1-subunit. The T-type calcium channels, Cav3.1, Cav3.2 and Cav3.3 are activated at lower voltage thresholds compared to their L (long)-type counterparts. T-type calcium channels play a pivotal role in the depolarization of both neuronal and cardiac pacemaker cells, with the rapid rate of channel inactivation permitting successive firing in both of these cell populations [56].

Significantly, recent animal studies have reported changes in the transcription and translation of cardiac ion channels secondary to epileptogenesis, accompanied by abnormal cardiac electrophysiology. This has led to the hypothesis that epilepsy secondarily alters cardiac ion channel expression, generating a chronic proarrhythmic state that increases the risk of sudden cardiac death or sudden unexpected death in epilepsy (SUDEP). Although the pathophysiology of an acquired cardiac channelopathy in epilepsy is unclear, candidate mechanisms include autonomic dysfunction and structural remodeling, given their associations with both seizure activity and cardiac ion channel dysregulation. Indeed, the potential relevance of molecular cardiac dysfunction is highlighted by a complex relationship between epilepsy, ion channel mutations, arrhythmogenic disorders, and sudden death [60].

In this regard, from the position of personalized medicine, which is rapidly developing both in the Russian Federation [11] and in the world, it is critical to develop an interdisciplinary approach with the participation of doctors of various specialties (neurologists, psychiatrists, clinical pharmacologists, geneticists, doctors of functional diagnostics, etc.) and a new strategy of a personalized approach to predicting AED-induced prolongation of the QT interval as one of the most prognostically unfavorable cardiological ADRs [12].

Purpose of the narrative review: to analyze the results of studies on AEDs-induced prolongation of the QT interval genetic predictors and gain new knowledge about sudden death syndrome (SDS) in patients with neurological diseases and mental disorders using AEDs.

Results

2.1. Familial Long QT Syndrome

Long QT syndrome (LQTS) is an inherited disorder in which most family members experience repolarization of the ventricles of the heart on an electrocardiogram (ECG) in the form of a prolonged QT interval. This syndrome is associated with an increased tendency to arrhythmogenic syncope, with the development of polymorphic ventricular tachycardia (torsade de pointes - TdP) and SDS [61,62]. A family history of high severity (SDS in a child or young adult), as well as a history of fainting, dizziness, and cardiac arrest, may be characteristic of LQTS. Fainting in LQTS is usually rapid and unexpected, which distinguishes it from the usual vasovagal and orthostatic forms of syncope, in which presyncopal and other warning symptoms occur. Lack of aura, urinary incontinence, and postictal findings help distinguish LQTS-related syncope from epileptic seizures [63]. The disease is relatively rare worldwide, with a prevalence of about 1:3,000 – 1:5,000. The disorder is considered to have variable penetrance. About 85% of reported cases are inherited from one of the parents, while the remaining 15% of cases are associated with de novo mutations [64]. Specifically, the prevalence of LQTS in Italy varies from 1:5,000 to 1:20,000. According to Italian scientists, the prevalence of LQTS in newborns ranged from 23 to 43% [65]. LQTS has been identified in all ethnic groups [63]. In about 10-15% of patients who die from complications of LQTS, death is the first sign of the disorder [63].

Studies from the LQTS registry, including patients, individuals with a pathogenic variant (mostly treated), and relatives who died suddenly, show 6-8% cumulative mortality in people under 40 years old in case of LQTS type 1, type 2, and phenotypes type 3 [64,66]. In individuals aged 0 to 18 years with the LQTS phenotype of types 1, 2, or 3, the cumulative mortality is reported to be 2%, 3% and 7%, respectively. At the age of 19 to 40, the mortality rate is 5%, 7% and 5%, respectively. However, syncope is most common in the LQTS1 phenotype (63%), followed by the LQTS2 phenotypes (46%) and the LQTS3 phenotype (18%), the death rate being the same in all three cases [63]. A pedigree study examined mortality in large families with LQTS, when the disease was not known and patients were not receiving therapy, compared with healthy people. According to the results of this study, for the LQTS1 phenotype (one specific pathogenic variant), a sharp increase in mortality in childhood (1-19 years) was shown, for the LQTS2 phenotype, an increased mortality was observed between the ages of 15 and 39, and for LQTS3, an increased mortality was observed in individuals aged 15 to 19 years old [67].

Electrocardiography (ECG) should be done to confirm LQTS. However, this method is not specific in the diagnosis of LQTS, since approximately 25% of patients with LQTS, confirmed by the presence of a single nucleotide variant (SNV) in the LQTS-associated gene, may have a normal QTc range (hidden LQTS) [64]. In healthy individuals, the average QTc duration is approximately 400 ms (**Table 2**). The upper limit of normal is 460 ms for women and 450 ms for men. Patients with QTc intervals greater than 520 ms, autosomal recessive LQT1 inheritance, Jervell and Lange-Nielson syndrome, Timothy syndrome, and those with more than 10 arrhythmia attacks before the age of 18 have an extremely high risk of the cardiovascular ADRs [69].

Table 2. Gender-based interpretation of the QTc interval duration indicators (Bazett's correction) [2,70].

Indicators of the QT interval in adults	Females (ms)	Males (ms)
Normal	< 450	< 430
Shortening	451 – 470	431 – 450
Prolongation	> 470	> 450

For additional diagnosis of patients with "uncertain" QTc values on resting ECG several methods are used. Specifically, they use exercise ECG, which usually reflects the inability of the QTc interval to shorten normally and even prolongation of the QTc interval [71–73]; many people develop characteristic T wave abnormalities on the ECG [74]. Measurement of the QTc interval during the transition from the supine position to the standing position is also used [75] as well as intravenous pharmacological challenge testing (e.g., with epinephrine), which may be helpful by demonstrating inappropriate prolongation of the QTc interval [76]. Given the low risk of arrhythmia induction, a provocative testing is best performed in laboratories with experience in arrhythmia induction and control [77,78]. Also, they use determination of the electromechanical window in echocardiography (this study is the determination of the difference between mechanical and electrical systoles [69]).

Schwartz et al. (1993) proposed a scale for the diagnosis of LQTS on the basis of a clinical picture [79]. In 2011, the scale was revised by Schwartz P.J. and Crotti L. Points are awarded according to various criteria (**Table 3**) [80].

Table 3. Scoring system for the clinical diagnosis of long QT interval syndrome [63].

Parameters			Points[6]
Electrocardiogram [1]	QTc [2]	≥ 480 ms	3
		= 460 - 479 ms	2
		= 450 - 459 ms (for males)	1
	≥ 480 ms at the 4th minute of recovery from exercise		1
	Torsade de pointes [3]		2
	Alternate T wave		1
	Serrated T wave in 3 assignments		1
	Low pulse rate for age-appropriate patient [4]		0.5
Medical history	Fainting [3]	With stress	2
		No stress	1
Family history	LQTS in family members [5]		1
	Sudden death syndrome at age <30 among immediate family members [5]		0.5
Total points			

Notes: [1] in the absence of drug intake or violations that may affect these electrocardiographic characteristics; [2] QTc (corrected QT) = QT interval corrected by Bazett's formula, where QTc = QT / √RR; [3] mutually exclusive; [4] resting heart rate <2% for age; [5] the same family member cannot be counted for both criteria; [6] ≤ 1.0 point = low probability of LQTS; 1.5-3.0 points = intermediate probability of LQTS; ≥ 3.5 points = high probability of LQTS.

The diagnosis of LQTS is established in a proband with one or more of the following signs [81]: 1) risk assessment ≥ 3.5 points (see Table 3) in the absence of a secondary cause of QT interval prolongation; 2) the presence of a QTc interval ≥ 500 ms on repeated ECGs in the absence of a secondary cause of QT prolongation; 3) identification of single nucleotide variants (SNVs) in one of the candidate genes that are associated with LQTS.

2.2. Risk Factors of Anticonvulsant-Induced QT Prolongation

The classical morphology of the resting ECG is represented by three phases: depolarization, propagation of excitation, and repolarization of the atria and ventricles. The P wave and the duration of the PQ interval reflect atrial depolarization and atrioventricular conduction. The QRS complex displays ventricular depolarization. The QT interval shows the duration of the repolarization of the ventricles of the heart. The cellular electrical basis of the ECG is made up of cardiomyocytes and the action potentials arising in them (**Figure 3**). Depolarization (phase 0) occurs due to the rapid influx of positively charged sodium ions (INa) through sodium channels (*SCN5A* / *Nav1.5*). Subsequent repolarization consists

of three phases. In phase 1, after inactivation of sodium channels, a short-term, outwardly directed repolarizing potassium current (IK) occurs. Phase 2 ("plateau phase") is characterized by the presence of balanced, depolarizing inward calcium currents through L-type calcium channels and opposite, repolarized outward potassium currents IKr (*KCNH2* / *HERG*) and IKs (*KCNQ1* / *KvLQT1*). In phase 3, repolarizing external potassium currents (IKs, Ikr, and IK1) prevail. In general, cardiac repolarization of cardiomyocytes (and, consequently, QT duration) is determined by a complex interaction of several depolarizing and repolarizing ion currents [82].

Many AEDs alter the activity of ion channels. For example, phenytoin, carbamazepine, and lamotrigine are INa channel blockers (**Table 1**). Cell expression studies show that several AEDs block the fast potassium channels of internal rectification of IKr, which promotes repolarization of the action potential in the myocardium (**Table 1**) [4].

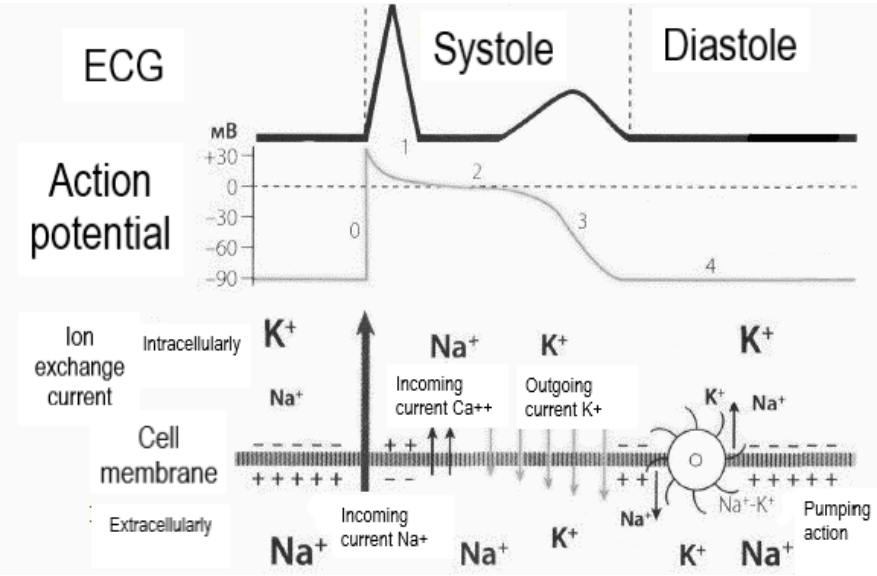

Figure 3. Electrocardiography and membrane action potential. Above is a classic surface ECG in lead II, below is a typical ventricular action potential. Depolarization of cardiomyocytes (phase 0) corresponds in time to the onset of the QRS complex. The end of repolarization (end of phase 3) corresponds approximately in time to the end of the T wave. Ion currents are given for different phases (↓ incoming current; ↑ outgoing current).

Physiological prolongation of the QT interval was recorded during sleep (in the initial phase of sleep apnea [83]) as well as within 60 minutes after meals, when the QT interval increased from 16 to 23 ms [84].

It is possible to assume the development of AEDs-induced LQTS during drug selection in patients from several risk groups. These risk groups can be identified based on the following factors:

- early and young age (cardiac events can occur from infancy to middle age, but are most common in the period from adolescence to 20 years) [63];
- advanced age (patients over 65 years old) [85];
- female sex (the QT interval in females is two times longer than in males and the risk of AEDs-induced ventricular tachyarrhythmia (TdP) is twice as high [85];
- history of cardiovascular complications (myocardial hypertrophy, bradycardia) [85];
- burdened family history, congenital LQTS [63,85];
- electrolyte disturbances (hypokalemia, hypomagnesemia) [85];
- history of subarachnoid hemorrhage [63];
- history of diabetes mellitus [86];
- increased concentration of thyroid hormones [86,87];

- obesity that contributes to the prolongation of the QT interval (in this case, with weight gain 10 kg above normal, the interval increased by > 5 ms) [88,89];
- increased serum cholesterol levels [86,87];
- simultaneous use of drugs participating in one metabolic pathway with anticonvulsants through the cytochrome P450 (CYP) 2D6, 1A2 and 3A4 enzyme system [90];
- taking AEDs that prolong the QT interval [63];
- high concentrations of the AED in the serum [85];
- simultaneous use of two or more IKr potassium channel blockers (e.g., erythromycin and pimozide) [90];
- smoking (the effects of smoking may be mediated by an increase in platelet adhesion and release of catecholamines) [91];
- consumption of caffeine [92];
- dependence on psychoactive substances [93];
- genetic predisposition [94];
- history of new coronavirus infection COVID-19 [95].

There is a hypothesis of multiple hits, which states that in rare cases only one risk factor is needed for the development of the ADR, while most often a combination of the above factors is required [90].

2.3. Genetic Predictors of Long QT Syndrome in Patients Receiving Anticonvulsants

2.3.1. Genes Responsible for Familial Long QT Syndrome

Although it is the responsibility of cardiologists to diagnose and manage patients with familial LQTS, there is a possibility that a patient with neurological diseases and mental disorders may carry the causative gene mutations responsible for familial LQTS. For example, despite the low frequency of a patient having a clinical phenotype "epilepsy + familial LQTS" "schizophrenia + familial LQTS", it is necessary for a neurologist and psychiatrist to keep in mind this possibility. However, at present, no algorithms for an interdisciplinary approach to the management of such an unfavorable phenotype in relation to SDS have been developed. At the same time, with the improvement of molecular genetic diagnostics, panels of DNA profiling of patients with a burdened family history of LQTS or cases of SDS are being actively developed and introduced into clinical practice. Therefore, neurologists and psychiatrists, before prescribing long-term anticonvulsant therapy, need to clarify these issues when collecting the family history and the patient's life history. The most common forms of LQTS are shown in **Table 4.**

It is important to be aware of the pathogenic mutations in the *KCNH2, KCNQ1* and *SCN5A* genes responsible for the vast majority of LQTS cases. In patients with mutations and SNVs of these genes, three clinical phenotypes are distinguished: LQTS1, LQTS2, and LQTS3 [63].

Table 4. Candidate genes responsible for familial long QT interval syndrome

Gene, OMIM	Protein	Chromosome Location	Inheritance	Syndrome	OMIM	Prevalence
KCNQ1 607542	Voltage-gated potassium channel of the KQT subfamily 1 type	11p15.5-p15.4	AR	Familial long QT syndrome - Jervell and Lange-Nielsen syndrome type 1 (LQTS1 or JLNS1)	220400	30% - 35%
			AD	Familial long QT syndrome - Roman-Ward syndrome (LQTS1)	192500	
KCNH2 / *HERG*	Potential-gated	7q36.1	AD	Long QT syndrome type 2 (LQTS2)	613688	25% - 30%

152427	potassium channel H2 type					
*ALG10 B*603313	Asparagine-related glycosylation of the 10 homologue B type	12q12	AD	Long QT syndrome type 2 (LQTS2)	613688	
SCN5A 600163	Alpha subunit of voltage-gated sodium channel 5 type	3p22.2	AD	Long QT syndrome type 3 (LQTS3)	603830	5% - 10%
ANK2 106410	Ancrinin 2 type	4q25-q26	AD	Long QT syndrome type 4 (LQTS4).	600919	< 1%
KCNE1 / MIRP1 176261	Potential-gated potassium channel E1 type	21q22.12	AR	Familial long QT syndrome - Jervell and Lange-Nielsen syndrome type 1 (LQTS5 or JLNS2)	613695	< 1%
KCNE2 603796	Potential-gated potassium channel E2 type	21q22.11	AD	Long QT syndrome type 6 (LQTS6)	613693	< 1%
KCNJ2 600681	Voltage-gated potassium channel J2 type	17q24.3	AD	Andersen-Taville syndrome or long QT syndrome type 7 (LQTS7)	170390	< 1%
CACNA1C 114205	Voltage-gated potassium channel alpha 1C subunit	12p13.33	I / D	Brugada syndrome or long QT syndrome type 8 (LQTS8)	618447	< 1%
CAV3 601253	Caveolin 3 type	3p25.3	AD	Long QT syndrome type 9 (LQTS9)	611818	< 1%
SCN4B 608256	Voltage-gated sodium channel beta 4 subunits	11q23.3	AD	Long QT syndrome type 10 (LQTS10)	611819	N/A
AKAP9 / KCNQ1 604001	Anchor protein A-kinase 9 type	7q21.2	AD	Long QT syndrome type 11 (LQTS11)	611820	N/A
SNTA1 601017	Syntrophin alpha 1 type	20q11.21	AD	Long QT syndrome type 12 (LQTS12)	612955	< 1%
KCNJ5 600734	Voltage-gated potassium channel J5 type	11q24.3	AD	Long QT syndrome type 13 (LQTS13)	613485	N/A
CALM1 114180	Calmodulin 1 type	14q32.11	AD	Long QT syndrome type 14 (LQTS14)	616247	N/A
CALM2 114182	Calmodulin 2 type	2p21	AD	Long QT syndrome type 15 (LQTS15)	616249	N/A
CALM3 114183	Calmodulin 3 type	19q13.32	AD	Long QT syndrome type 16 (LQTS16)	618782	N/A

Note: AD - autosomal dominant; AR - autosomal recessive; I / D - insufficient data; LQTS - prolonged QT interval; N/A – not available.

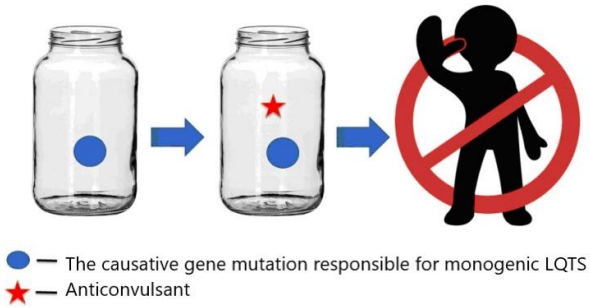

Figure 4. Monogenic forms of LQTS: prescription of anticonvulsants affecting heart rate and conduction is contraindicated due to the high risk of sudden death syndrome even in case of use of anticonvulsants as monotherapy.

From a practical point of view, this is extremely important, since for the development of monogenic forms of LQTS, the additional influence of external environmental factors which, in particular, include the intake of AEDs, is minimal, or their influence is less significant compared to multifactorial forms of the disease. In this regard, the risk of SDS in such patients is high even with monotherapy with AEDs that affect heart rate and conduction (**Table 1**). Therefore, prescribing AEDs that affect the QT interval should be avoided (**Figure 4**) when treating this category of patients. Considering the above, before prescribing AEDs with a high risk of ADRs on heart rate and conduction, it is important to clarify the personal and family history of LQTS, and, according to indications, carry out DNA diagnostics of mutations responsible for family LQTS, since the ECG is not informative in some cases.

2.3.2. Candidate Genes Predisposing to Prolongation of the QT Interval

In the general population and among patients with neurological diseases and mental disorders, the prevalence of multifactorial and polygenic forms of LQTS is higher than that of monogenic ones. Such forms are associated with SNVs of the candidate genes predisposing to prolongation of the QT interval, subject to the additional influence of external environmental factors, which, in particular, include the intake of AEDs. This is due to an increase in the number of associative genetic studies of SNVs of candidate genes encoding ion channels expressed both in the CNS since identifying patients at risk can help prevent the development of SDS with prolonged use of AEDs in patients with neurological and psychiatric profile (**Table 5**).

The *HERG* gene (LQTS2) is located on chromosome 7q35–36 and encodes IKr. Mutations in the *HERG* gene decrease the flow of potassium ions and, thus, lengthen the AP [96]. According to Khera et al. (2019), carriage of SNV rs189014161 (p.Arg744Ter) of the *HERG* gene was associated with the risk of prolongation of the QT interval [97].

The *SCN5A* gene is located on chromosome 3p22.2 and encodes the alpha subunit of the cardiac voltage-gated sodium channel type 5. This ion channel leads to a rapid depolarizing increase in the cardiac action potential. It is known that some SNVs of the *SCN5A* gene increase the risk of developing SDS [98]. Spellmann and co-authors (2018) observed a significant effect of the major (common) SNVs allele rs1805124 (H558R) of the *SCN5A* gene on QTc prolongation. The data presented suggest a general association between H558R and QT interval duration: the homozygous AA genotype was associated with a shorter QT interval [99]. Gouas et al. (2005) found an association between H558R and prolongation of the QT interval in healthy people [100]. Carriers of the G allele showed a long duration of the QT interval. In contrast, Hobday et al. (2006) found no such association in a cohort of SDS patients [101]. Similarly, Lehtinen et al. (2009) did not find a significant effect of H558R on the duration of the QT interval in patients with diabetes mellitus [102].

Pfeufer et al. (2009) did not find the significance of H558R in genome-wide analysis. However, the results suggest at least its small independent effect on QTc duration [103].

The *KCNE1* / *MIRP1* gene is located on chromosome 21q22 and encodes IKs. Mutations in this gene contribute to the slow opening and rapid closing of potassium channels, thereby reducing the flow of potassium into the cell. Some SNVs in the *KCNE1* gene predispose to the development of AEDs-induced LQTS syndrome [104]. Alternative microvoltage T waves (TWA) on the ECG, characterized by fluctuations in the amplitude and morphology of the T wave between heartbeats, is an electrophysiological phenomenon clinically associated with ventricular arrhythmias and is an important marker of arrhythmia risk. Koskela et al. (2008) tested the hypothesis of whether the same SNVs that affect the QT interval affect the TWA variation. The authors studied the association of SNVs rs1805127 and rs727957 of the *KCNE1* gene, and rs1805124 of the *SCN5A* gene with TWA variability during a clinical exercise test. As a result, TWA was the lowest in patients with homozygous TT genotype (rs1805127) of the *KCNE1* gene at all stages of the exercise test. The result remained statistically significant after adjusting for age, history of SDS, and chronic beta-blocker use [105].

The *AKAP9* / *KCNQ1* gene is located on chromosome 7q21.2 and encodes the anchor protein of type 9 alpha kinase. AKAP9 forms a macromolecular complex with the б-subunits of the voltage-gated potassium channel, Kv7.1 (also known as KCNQ1) and its associated в-subunits (KCNE1), which are part of IKs [106]. This AKAP isoform interacts with KCNQ1 and promotes its phosphorylation [107]. However, it not only directly binds and promotes phosphorylation of KCNQ1, but also phosphorylates itself and promotes the transformation of induced phosphorylation of changes in the activity of altered voltage-gated potassium channels. Carin (2015) considered the association of four SNVs (rs11772585, rs7808587, rs2282972, and rs2961024) of the *AKAP9* gene with the risk of prolongation the QT interval. It was revealed that the carriage of the homozygous GG genotype (rs2961024), which is more often represented by homozygotes for the CGCG haplotype, leads to an extension of the QT interval depending on the patient's age (plus 1% for every 10 years) ($p = 0.006$). The T allele (rs11772585), uniquely found in the TACT haplotype, was reported to more than double (218%) the risk of HP from the cardiovascular system ($p = 0.002$) in carriers of the A341V SNV risk genotypes. In addition, it was shown to aggravate the severity of the disease ($p = 0.025$). The GG genotype (rs7808587) was associated with 74% increased risk of cardiac arrhythmias ($p = 0.046$), while the carriage of the T allele (rs2282972), mainly represented by the CATT haplotype, reduced the risk of LQTS by 53% ($p = 0.001$) [108].

Thus, DNA profiling of patients with neurological and psychiatric profiles in order to identify SNVs of the candidate genes predisposing to multifactorial forms of LQTS can help in identifying patients at risk who, while taking AEDs in monotherapy and, especially, in the polytherapy regimen, require ECG monitoring, and consultation of a cardiologist (according to indications) in dynamics (**Figure 5**).

Table 5. Candidate genes and their single nucleotide variants predisposing to prolongation of the QT interval

Gene, OMIM	Protein	Chromosome Location	Single Nucleotide Variant	Effect	Reference
HERG (KCNH2) 152427	Potential-gated potassium channel H2.	7q36.1	rs189014161	Associated with the risk of a prolonged QT interval	[93]
SCN5A 600163	Alpha subunit of voltage-gated sodium channel type 5	3p22.2	rs 1805124	Associated with the risk of a prolonged QT interval	[95]

KCNE1 / *MIRP1* 176261	Potential-gated potassium channel E1 type	21q22.12	rs1805127	Associated with the risk of a prolonged QT interval	[105]
			rs11772585	The T allele is associated with the risk of a prolonged QT interval	[104]
AKAP9 / *KCNQ1* 604001	Type 9 alpha kinase anchor protein	7q21.2	rs7808587	The GG genotype is associated with the risk of a prolonged QT interval	[104]
			rs2282972	The T allele reduces the risk of a prolonged QT interval	[104]
			rs2961024	The GG genotype is associated with the risk of a prolonged QT interval	[104]

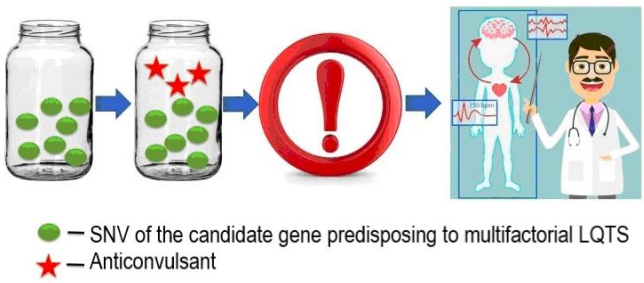

Figure 5. Multifactorial (polygenic) forms of LQTS: prescribing anticonvulsants that affect heart rate and conduction, possibly with caution, preferably in monotherapy, Holter monitoring of the ECG is required in dynamics.

2.3.3. Candidate Genes Responsible for Slowing the Metabolism of Anticonvulsants

Most AEDs used in real clinical practice by neurologists and psychiatrists are metabolized in the liver with the participation of cytochrome P450 isoenzymes. There are four phenotypes of drug metabolism, depending on the rate of metabolism of drugs, including extensive metabolization (EM), intermediate metabolization (IM), slow (poor) metabolization (PM), and ultrarapid metabolization (UM) [109–113].

From the standpoint of the development of AEDs-induced ADRs, non-functional SNVs / polymorphisms of genes encoding liver cytochrome P450 isozymes are of greatest clinical interest (**Table 5**). Heterozygous and homozygous (to a greater extent) carriers of low functional SNVs have the PM phenotype, a significantly reduced metabolic rate of AEDs with a hepatic (or predominantly hepatic) metabolic pathway, and an increase in the level of the drug and / or its active metabolite (metabolites) in the blood. This explains the high risk of developing ADRs, including those related to the cardiovascular system.

The clinical situation may be aggravated by the fact that a patient requiring long-term use of AEDs in the form of mono- or polytherapy can be both a carrier of SNVs / polymorphisms associated with LQTS (**Tables 4-5**), and with low-functional SNVs / polymorphisms of the genes, encoding isozymes of cytochrome P450 of the liver (**Table 6**). This option is the most difficult clinical situation when a patient with a neurological disease or mental disorder, receiving AEDs, is included in the group of cumulative high risk of developing SDS and needs an interdisciplinary follow-up by a neurologist, psychiatrist, and cardiologist (general practitioner).

Through a personalized medicine prism, it is important to develop pharmacogenetic panels that allow assessing the cumulative risk of developing AED-induced LQTS in the above-mentioned category of neuropsychiatric patients.

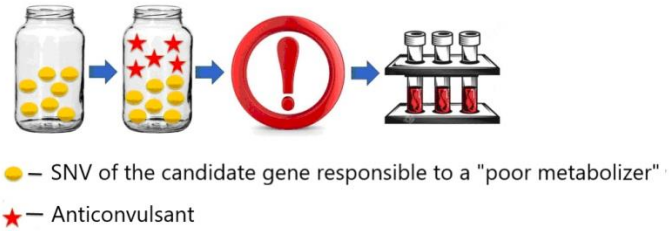

Figure 6. A "poor metabolizer" phenotype predisposing to an increase in the level of anticonvulsants in the blood to toxic and the development of symptomatic prolongationg of the QT interval: prescribing anticonvulsants that affect heart rate and conduction is possible, but with caution, preferably in monotherapy; medication monitoring (over time testing of the level of anticonvulsants taken) is required.

Table 6. Candidate genes predisposing to poor metabolism of anticonvulsants in the liver (by oxidation).

Enzyme	Gene, OMIM	Chromosome Location	Non-functional SNV / polymorphism	Anticonvulsant
CYP1A1	*CYP1A1* 108330	15q24.1	*CYP1A1*2C* *CYP1A1*4* *CYP1A1*9*	Cannabidiol
CYP1A2	*CYP1A2* 124060	15q24.1	*CYP1A2*1C* *CYP1A2*1D* *CYP1A2*1K* *CYP1A2*3* *CYP1A2*4* *CYP1A2*6* *CYP1A2*7* *CYP1A2*8* *CYP1A2*11* *CYP1A2*16* *CYP1A2_1545T > C*	Cannabidiol Carbamazepine Styripentol Phenytoin Phenobarbital
CYP2A6	*CYP2A6* 122720	19q13.2	*CYP2A6*2* *CYP2A6*4* *CYP2A6*5* *CYP2A6*6* *CYP2A6*7* *CYP2A6*9A* *CYP2A6*11* *CYP2A6*12A* *CYP2A6*17* *CYP2A6*18A* *CYP2A6*18B* *CYP2A6*19* *CYP2A6*20* *CYP2A6*23* *CYP2A6*24A* *CYP2A6*26* *CYP2A6*27* *CYP2A6*35A* *CYP2A6*35B* *CYP2A6*41*	Valproic acid Carbamazepine Lamotrigine Phenytoin Phenobarbital
CYP2B6	*CYP2B6* 123930	19q13.2	*CYP2B6*5A* *CYP2B6*8* *CYP2B6*18* *CYP2B6*27*	Valproic acid Diazepam Carbamazepine Clobazam

			*CYP2B6*28*	Ethosuximide Phenytoin Phenobarbital
CYP2C8	*CYP2C8* 601129	10q23.33	*CYP2C8*2* *CYP2C8*5*	Carbamazepine Phenytoin Phenobarbital
CYP2C9	*CYP2C9* 601130	10q23.33	*CYP2C9*2* *CYP2C9*3* *CYP2C9*6* *CYP2C9*15* *CYP2C9*25*	Valproic acid Zonisamide Cannabidiol Carbamazepine Clobazam Lamotrigine Phenytoin Phenobarbital Ethosuximide
CYP2C18	*CYP2C18* 601131	10q23.33	*CYP2C18*	Clobazam
CYP2C19	*CYP2C19* 124020	10q23.33	*CYP2C19*2* *CYP2C19*2B* *CYP2C19*3* *CYP2C19*4* *CYP2C19*5* *CYP2C19*6* *CYP2C19*7* *CYP2C19*8*	Valproic acid Diazepam Zonisamide Cannabidiol Carbamazepine Clobazam Oxacarbazepine Styripentol Topiramate Felbamat Phenytoin Phenobarbital
CYP2D6	*CYP2D6* 124030	22q13.2	*CYP2D6*3A* *CYP2D6*3B* *CYP2D6*4* *CYP2D6*4F* *CYP2D6*4G* *C YP2D6*4H* *CYP2D6*4xN* *CYP2D6*5* *CYP2D6*6* *CYP2D6*7* *CYP2D6*8* *CYP2D6*12* *CYP2D6*15* *CYP2D6*17* *CYP2D6*18* *CYP2D6*19* *CYP2D6*20* *CYP2D6*21* *CYP2D6*38* *CYP2D6*40* *CYP2D6*42* *CYP2D6*44* *CYP2D6*56*	Cannabidiol Carbamazepine Lamotrigine Phenytoin Phenobarbital
CYP2E1	*CYP2E1* 124040	10q26.3	*CYP2E1*1B* *CYP2E1*2* *CYP2E1*3* *CYP2E1*4* *CYP2E1*7*	Valproic acid Zonisamide Felbamat Phenytoin Phenobarbital

			CYP2E1_ 10463T> C (F421F) *CYP2E1_ 1055C> T* *CYP2E1_ 1295G> C*	Ethosuximide
CYP3A4	*CYP3A4* 124010	7q22.1	*CYP3A4*1B* *CYP3A4*3* *CYP3A4*17* *CYP3A4*18* *CYP3A4*20*	Diazepam Zonisamide Cannabidiol Carbamazepine Clobazam Clonazepam Lamotrigine Midazolam Tiagabin Styripentol Felbamat Phenytoin Phenobarbital Ethosuximide
CYP3A5	*CYP3A5* 605325	7q22.1	*CYP3A5*2* *CYP3A5*3* *CYP3A5*3D* *CYP3A5*3F* *CYP3A5*6* *CYP3A5*7* *CYP3A5*8* *CYP3A5*9* *CYP3A5*10* *CYP3A5*11* *CYP3A5_3705C > T (H30Y)* *CYP3A5_7298C > A (S100Y)*	Diazepam Cannabidiol Carbamazepine Phenytoin
CYP3A7	*CYP3A7* 605340	7q22.1	*CYP3A7*1B* *CYP3A7*1C* *CYP3A7*1D* *CYP3A7*1E* *CYP3A7*2* *CYP3A7*3*	Phenytoin
CYP3A43	*CYP3A43* 606534	7q22.1	*CYP3A43*1B* *CYP3A43*2A* *CYP3A43*2B* *CYP3A43*3*	Ethosuximide

Discussion

Currently, medical practitioners have a large choice of AEDs. When prescribing these medications, the doctor should be guided by the interests of the patient and the safety of the drug, which makes specialists take into account both the peculiarities of the mechanism of drug action and the presence or absence of genes that increase the risk of developing LQTS.

AEDs cannot be considered as class A drugs according to the classification proposed by Fanoe et al. in 2014 [112] (**Table 6**), since they are reported to cause prolongation of the QT interval, or there is no data on their effect on the QT interval. This makes medical practitioners prescribe anticonvulsants carefully assuming the risk of developing LQTS and, as a consequence, possible SDS (**Table 7**) [2].

Table 7. Classification of psychotropic drugs according to the risk of prolongation of the QT interval and the development of arrhythmias [2,112].

Category	Characteristic
Class A	The drug without the risk of prolongation of the QT interval or TdP.
Class B	A drug that can cause prolongation of the QT interval.
Class C	A drug with marked prolongation of the QT interval, reported cases of TdP, or other serious arrhythmias.

Note: TdP - fr. torsades de pointes (pirouette-type tachycardia, polymorphic ventricular tachycardia in patients with a long QT interval).

The manifestation of AED-induced LQTS is influenced by various genes (**Figure 7**), described above: genes responsible for the familial forms of LQTS (**Table 4**); candidate genes for the risk of developing multifactorial LQTS (**Table 5**); candidate genes for the risk of slowing down the metabolism of anticonvulsants (**Table 6**).

Therefore, it is important to identify these genes before prescribing AEDs in order to prevent the development of LQTS (**Figure 8**).

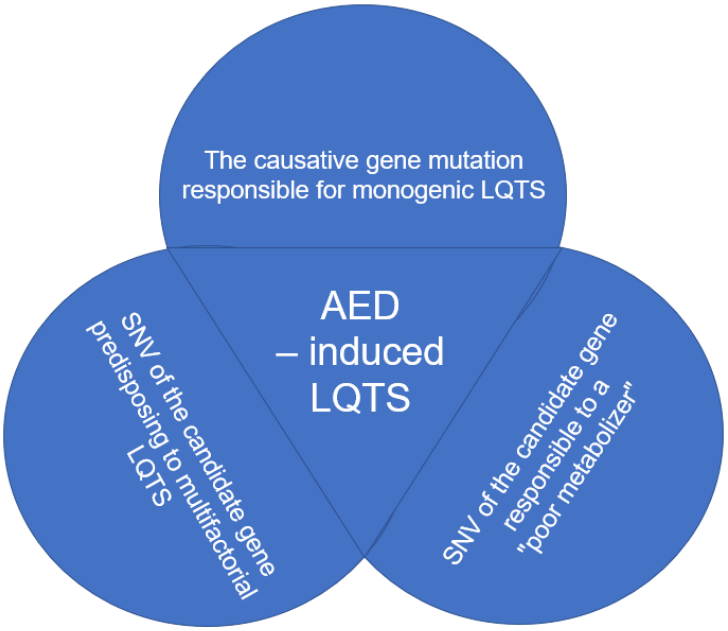

Figure 7. Genetic predictors of the risk of developing a long QT syndrome (LQTS) while taking antiepileptic drugs (AEDs).

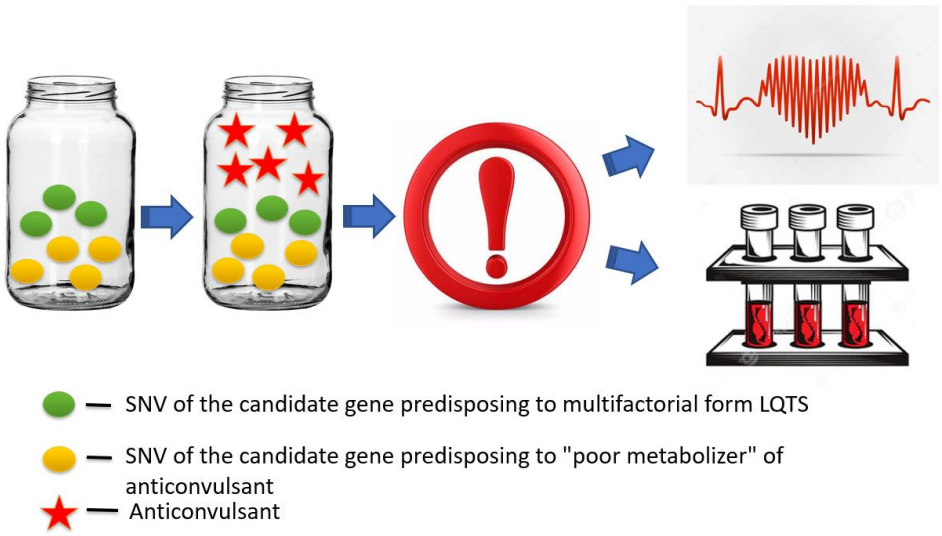

Figure 8. Assessment of the cumulative risk of multifactorial LQTS during the use of anticonvulsants includes a single nucleotide variants of candidate genes predisposition to LQTS and a single nucleotide variants of anticonvulsant metabolism candidate genes.

Materials and Methods

We searched for full-text publications in Russian and English for the period from 2011 to 2021 in the Cochrane, E-Library, PubMed, Web of Science, Springer, Clinial Keys, and Google Schooler databases using the following keywords: anticonvulsant-induced cardiac repolarization disorders, cardiac ventricular repolarization, prolonged QT interval, sudden death syndrome, ventricular tachyarrhythmia, and anticonvulsants. In addition, earlier publications of historical interest were included in this thematic review. Despite a comprehensive search, some publications of recent years may not have been found by us.

Conclusions

Given the widespread use of anticonvulsants (or AEDs) in neurological and psychiatric practice and the high probability of developing cerebrocardiac syndrome and life-threatening ADRs, a personalized approach to prescribing this group of drugs is important. Identification of risk alleles of SNVs of genes predisposing to the development of AEDs-induced LQTS will make it possible to adjust the choice and dosage of drugs and prevent the development of ADRs, which will improve the quality of life of patients and prevent the death of the patient.

In addition to the above, preventing the development of LQTS and, as a consequence, SDS will improve the quality of medical care, preserve the working-age population and, potentially, improve the state's economy.

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