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VALPROIC ACID AND PROLONGED QT: HIGHLIGHTS FROM THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) DATABASE

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SUMMARY

Several drugs can induce QT prolongation; however, the role of valproic acid played on the onset of this side effect has not been elucidated yet. Moreover, epilepsy itself represents a risk factor for the development of cardiovascular diseases; therefore, it is crucial to characterize the potential correlation between valproic acid and the occurrence of this cardiovascular complication.

We performed a descriptive analysis on the U.S. Food and Drug Administration Adverse Event Reporting System database, retrieving all adverse event reports involving valproic acid as suspect drug. After deduplication and data cleaning, we selected all cases reporting valproic acid as unique suspect and we analyzed those reporting the adverse event of interest, identified through the Standardized MedDRA Query "Torsade de pointes/QT prolongation". Finally, we evaluated each case presenting other concomitant medications to explore potential drug-drug-interactions.

Of 52,080 reports included in the analysis, 540 cases were referred to "Torsade de pointes/QT prolongation". Loss of consciousness and syncope were the most reported events, included, respectively, in 241 (44.63%) and in 118 (21.85%) Individual Case Safety Reports. QT elongation and abnormal electrocardiogram QT interval are reported only in 26 (0.1%) cases, ventricular arrhythmia only in 2 cases and the development of torsade de pointes has been recorded just in 1 case. Sudden death has been reported in 20 (0.1%) cases.

Our analysis revealed a very low number of cases reporting the adverse event of interest. The adverse event seems to be the consequence of multifactorial coexisting causes rather than imputable to the valproate alone.

Key words

QT prolongation; valproic acid; pharmacovigilance; FAERS; epilepsy.

Impact statement

Our analysis evidences that valproic acid does not significantly influence QT elongation, which is the result of several coexisting factors.

INTRODUCTION

The QT Interval indicates the period of ventricular depolarization and repolarization, defined as the time from the onset of ventricular depolarization to the end of repolarization.

A prolonged QT interval is suggestive of repolarization abnormalities; it can be associated with an increased risk of torsade de pointes (TdP), that can lead to ventricular fibrillation and sudden cardiac death (SCD) and it is considered a marker of arrhythmia (1-3).

The principal risk factors for QT prolongation are electrolyte imbalances, such as hypokalaemia, hypocalcaemia and hypomagnesemia, or medical conditions that can lead to electrolyte abnormalities, as renal dysfunction, diabetes, hypothyroidism, excess weight loss, malnutrition and obesity. Other risk factors are female gender, a positive family history for long QT syndrome, cardiovascular disorders and concomitant use of drugs that might inhibit the metabolism of another drug which causes QT elongation (4). Underlying QT prolongation is often a functional impairment of ion channels within the cardiac muscle. Mutations of ionic channels or their dysregulation can affect both heart and brain functions, leading to a susceptibility to epilepsy and cardiac arrhythmias (5, 6), such that long QT syndrome can also be congenital.

Several drugs can induce QT prolongation, including antiarrhythmic, antihistaminic, decongestant, diuretic, antibiotic and several psychotropic medications (4, 7). Indeed, some antipsychotics and antidepressants show a certain degree of blockade of potassium channels that could cause QT elongation (8). The lengthening of the QT interval seems to be related to the inhibition of repolarizing potassium channels, which leads to an early after depolarization (9, 10). Epileptic seizures themselves could commonly lead to abnormalities of cardiac repolarization, largely found in people with chronic epilepsy (11). Given that channelopathies play a role in the pathogenesis of cardiac disorders, caused by alterations in transmembrane potassium and sodium current, also major antiepileptic drugs, acting as sodium channels blockers, could be involved in this condition (7). It is controversial if antiepileptic drugs are linked to QT prolongation syndrome, which may be underlying several cases of SUDEP (sudden unexpected death in epilepsy). Epileptic patients have an increased risk of premature death compared to the general population affecting about 1 in 1000 people with epilepsy and represents the most important directly epilepsy-related cause of death (12). Since frequent seizures could constitute a major risk factor for SUDEP, the question arises on the role that treatment with antiepileptic drugs plays in it, especially of those drugs that are associated with occurrence of long QT syndromes (5, 13). Valproic acid is widely used in epilepsy, bipolar disorders and other pathologies due to its diverse pharmacologic polymodal action. It exerts antiepileptic effects by suppressing the high-frequency neuronal firing by voltage-sensitive sodium, potassium and calcium channel blockade (14). The association between valproate and prolonged QT interval is still not clear (1, 6, 7, 15), so that in clinical practice pharmacological counselling is often requested on a possible involvement of valproic acid in the onset of this side effect.

In order to try to clarify the association between valproic acid and the occurrence of QT elongation, we conducted a descriptive analysis on the Food and Drug Administration Adverse Event Reporting System database (FAERS). Data mining of large pharmacovigilance databases is of great importance in the detection of the earliest possible signals: spontaneous reporting systems, such as the FAERS, represent a valuable source to obtain real-world data about the safety/efficacy profile of specific drugs, to compare therapeutic options, and gain insight on potential mechanisms of adverse drug reaction (ADR) (16-19).

MATERIALS AND METHODS

We conducted a descriptive analysis on the FAERS database, the largest spontaneous pharmacovigilance system, that contains information related to post-marketing safety surveillance reports in the form of adverse events (AEs) submitted by healthcare professionals and consumers themselves. Adverse events were collected as Individual Case Safety Reports (ICSRs). ICSRs provide administrative information (country, type of report, qualification of the reporter), patient demographics (sex, age, weight), AEs character-

istics (seriousness, date of onset, outcome), details about suspect drug therapy (drug name, exposure start and stop dates, time to onset, dose, route, indication, de-challenge and re-challenge) and information concerning any drug administered at the time of AE but not held responsible for its occurrence by the reporter, referred to as concomitant medication (20).

Data, recorded from 1976 to 2021, were obtained from the web-based tool FAERS Public Dashboard, updated to March 31st, 2021.

We included in our analysis all the reports that presented, as a suspect drug, valproic acid or one of its derivatives (*i.e.* valproate, valproate bismuth, valproate calcium, valproate magnesium, valproate magnesium/valproic acid, valproate sodium, valpromide, bismuth/valproate sodium, divalproex sodium, divalproex sodium Dr, divalproex sodium Er, divalproex sodium/valproic acid).

Duplicate records were detected and deleted accordingly, using RStudio: we excluded all the duplicates for gender, age, event date, suspected product active ingredient and report country.

To perform our descriptive analysis, we evaluated the following fields: sex, age, seriousness and type of ADR. Reported events are coded according to the Medical Dictionary for Regulatory Activities, MedDRA, which includes broad System Organ Class, SOC, and specific event categories, *e.g.*, Preferred Term, PT (21); to a single FAERS report is assigned one or more PTs, and each PT is included within a corresponding primary (and secondary, if applicable) SOC. Our analysis was based on MedDRA version 24.0.

We classified ADRs reported using both SOC and SMQ systems. A Standardised MedDRA Query, SMQ, is a group of MedDRA terms, ordinarily at the PT level that relates to a defined medical condition or area of interest. We used the SOC "Cardiac disease" (**supplementary material S1**) and the SMQ "Torsade de pointes/QT prolongation" (**supplementary material S2**).

In order to reduce the risk of bias, we also excluded all reports in which valproate was administered with other drugs referred as suspect. Then we analysed the notoriety of the ADRs reported that were included in the "Torsade de pointes/QT prolongation" SMQ. We also focused on the reason for use of valproic acid; in particular, we evaluated if the drug was administrated for a psychiatric or nervous disease using the respective SOC.

To explore potential drug-drug interactions (DDIs), each case presenting other concomitant medications was evaluated using international databases, *i.e.* Clinical Pharmacology and INTERCheck WEB, with the aim of identifying possible DDI related to adverse events.

RESULTS

To March 31st, 2021, a total of 22,002,078 ICSRs was retrieved from the FAERS database. Of these, 69,642 involved valproic acid as a suspect drug. After data cleaning, 52,080 ICSRs were retained and included in the analysis (**figure 1**).

Among 52,080 ICSRs, the median age was 38.10 ± 22.16 years; of these, 8,848 (17.0%) cases occurred in paediatric patients, 28,561 (54.8%) in adults and 6,121 (11.8%) in patients older than 65 years of age; while in 8,545 (16.4%) age was not available.

Female was the most recorded sex with 24,450 (47.0%) cases; 23,523 (45.2%) cases were male and in 4,107 (7.9%) the gender was not available. Above all cases, 48,200 (92.6%) were serious.

"Cardiac disease" was reported in 6,612 (12.7%) ICSRs and "Torsade de pointes/QT prolongation" events in 2,642 (5.1%) (**table I**).

In 19,025 (36.5%) cases, valproic acid was the only suspect drug. Of these, 1,815 (9.5%) reported the SOC "Cardiac disease" and 540 (2.8%) the SMQ "Torsade de pointes/QT prolongation" (**table II**).

4,751 (25.0%) ICSRs were referred to paediatrics patients, 10,373 (54.6%) ICSRs to adults and 1,948 (10.2%) to over 65 years of age; in 1,953

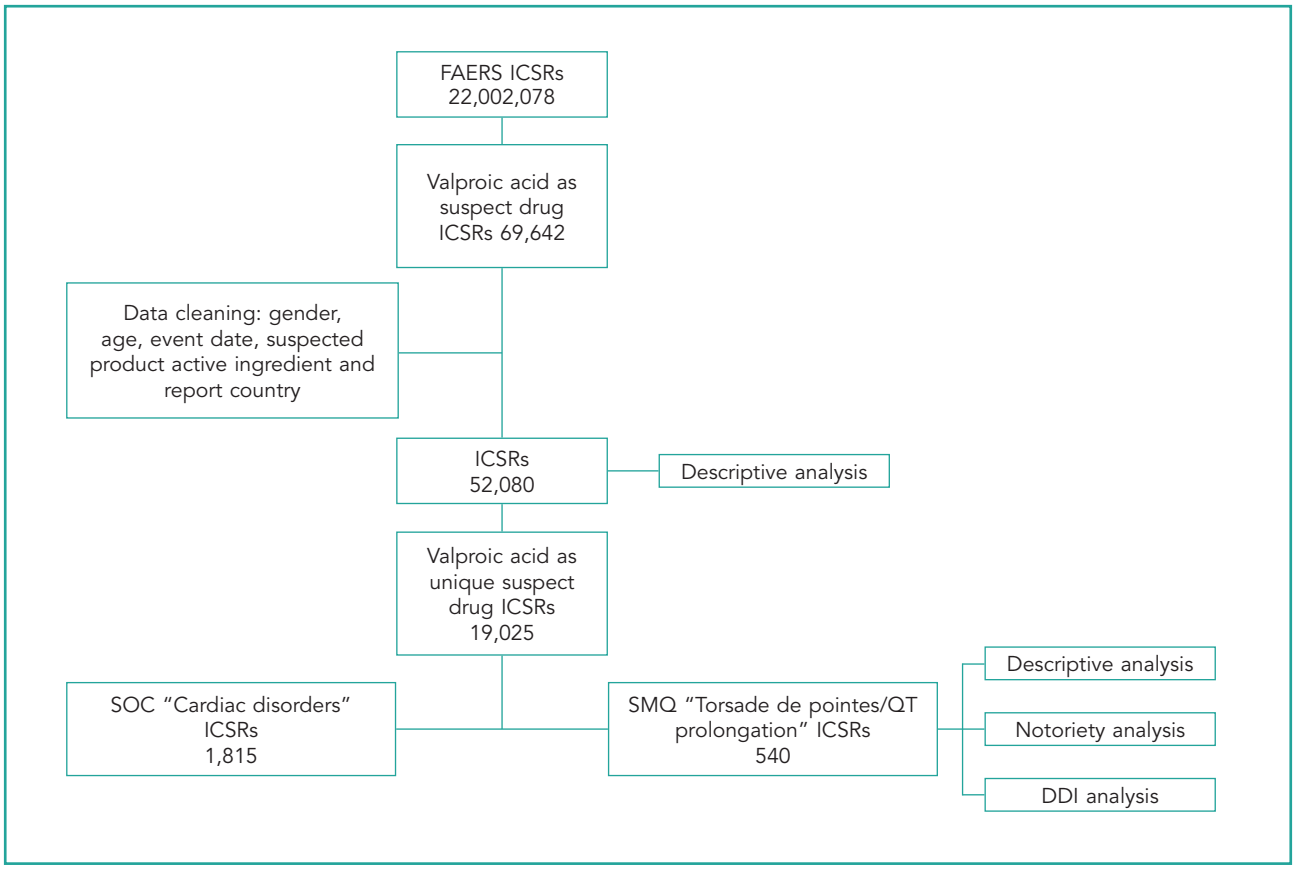

Figura 1. Study flowchart.

Table I. Characteristics of adverse reaction reports (n = 52,080).

Age, yrs.		
	Mean (SD)	38.10 (22.16)
	Paediatrics ≤ 17, n (%)	8,848 (17.0)
	Adults 18-64, n (%)	28,561 (54.8)
	Over 65, n (%)	6,121 (11.8)
	Not Available, n (%)	8,545 (16.4)
	Errors, n (%)	5 (0.0)
Gender, n (%)		
	Female	24,450 (47.0)
	Male	23,523 (45.2)
	Not Available	4,107 (7.9)
Seriousness, n (%)		
	Serious	48,200 (92.6)
	Not Serious	3,880 (7.5)
ADR, n (%)		
	SOC "Cardiac disorders"	6,612 (12.7)
	SMQ "Torsade de pointes/QT prolongation"	2,642 (5.1)

(10.3%) cases, age was not available. Female cases were 9,420 (49.6%) and male 8,749 (46.0%).
About 540 "Torsade de pointes/QT prolongation" cases, 297 ICSRs reported, as reason for use, one of the SOC "nervous system disorders" PTs (**table III**).
The median age was 32.95 ± 22.28 years; of these, 125 (23.2%) were in paediatrics patients,

Table II. Characteristics of adverse reaction reports with valproic acid as the only suspect drug (n = 19,025).

Age, yrs.		
	Mean (SD)	34,76 (22.52)
	Paediatrics ≤ 17, n (%)	4,751 (25.0)
	Adults 18-64, n (%)	10,373 (54.6)
	Over 65, n (%)	1,948 (10.2)
	Not Available, n (%)	1,953 (10.3)
Gender, n (%)		
	Female	9,420 (49.6)
	Male	8,749 (46.0)
	Not Available	856 (4.5)
Seriousness, n (%)		
	Serious	17,112 (90,0)
	Not Serious	1,913 (10,1)
ADR, n (%)		
	SOC "Cardiac disorders"	1,815 (9.5)
	SMQ "Torsade de pointes/QT prolongation"	540 (2.8)

Table III. Characteristics of "Torsade de pointes/QT prolongation" reports (n = 540)

Age, yrs.		
	Mean (SD)	32.95 (22.28)
	Paediatrics ≤ 17, n (%)	125 (23.2)
	Adults 18-64, n (%)	296 (54.8)
	Over 65, n (%)	60 (11.1)
	Not Available, n (%)	59 (10.9)
Gender, n (%)		
	Female	265 (49.1)
	Male	259 (48.0)
	Not Available	16 (3.0)
Seriousness, n (%)		
	Serious	531 (98.3)
	Not Serious	9 (1.7)
Reason for use, n (%)		
	SOC "Nervous system disorders"	297 (55.0)
	SOC "Psychiatric disorders"	101 (18.7)

296 (54.8%) in adults and 60 (11.1%) were in over 65 years old.
The gender distribution was 265 (49.1%) cases for female and 259 (48.0%) cases for male and in 16 (3.0%) the gender was not available. 531 (98.3%) cases were serious.
Loss of consciousness and syncope were the most reported ICSRs, included, respectively, in 241 (44.63%) ICSRs and in 118 (21.85%) (**table IV**).
QT elongation and electrocardiogram QT interval abnormal are reported only in 26 ICSRs (0.1%), ventricular arrhythmia only in 2 cases and the development of TdP has been recorded just in 1 case. Sudden death has been reported in 20 ICSRs (0.1%).
From the notoriety analysis, most of the ADRs resulted unknown; in particular, PTs are reported in order of frequency in **table IV**.
The potential DDIs found were increase serum concentration (92 ICSRs); decrease serum concentration (74 ICSRs); additive sedative, CNS, and/or respiratory-depressant effects (59 ICSRs); unpredictable effect (32 ICSRs); alter pharmacokinetics (21 ICSRs); increase potential side effects (21 ICSRs); reduce effect (5 ICSRs); increase effect (4 ICSRs); additive cardiac conduction effects (1 ICSR).
About the SMQ of interest, the principal DDIs that may alter valproic acid pharmacokinetic and pharmacodynamics were, in order of frequency, decrease serum concentration (59 ICSRs, 10.9%); increase serum concentration (30 ICSRs, 5.6%); alter pharmacokinetics (11 ICSRs, 2.0%); increase potential side effects (10 ICSRs, 1.9%); increase effect (2 ICSRs, 0.4%); additive cardiac conduction effects (1 ICSR, 0.2%).
These DDIs mechanisms and relative drugs involved are reported in **figure 2**.

DISCUSSION

This is, to our knowledge, the first study exploring the potential association between valproic acid and the occurrence of QT elongation syndrome using data extracted from FAERS, one of the largest spontaneous pharmacovigilance surveillance system.
Some studies reported that ADRs of the SMQ "Torsade de pointes/QT prolongation" are more present when valproate is administered together with others drugs, confirming the

Table IV. SMQ PT events.

PT SMQ, n (%)		Notoriety
Loss of consciousness	241 (1.3)	Known
Syncope	118 (0.6)	Unknown
Cardiac arrest	58 (0.3)	Unknown
Multiple organ dysfunction syndrome	57 (0.3)	Unknown
Cardio-respiratory arrest	31 (0.2)	Unknown
Electrocardiogram QT prolonged	25 (0.1)	Unknown
Sudden death	20 (0.1)	Unknown
Ventricular tachycardia	9 (0.1)	Unknown
Ventricular fibrillation	6 (0.0)	Unknown
Electrocardiogram repolarization abnormality	2 (0.0)	Unknown
Ventricular arrhythmia	2 (0.0)	Unknown
Electrocardiogram QT interval abnormal	1 (0.0)	Unknown
Torsade de pointes	1 (0.0)	Unknown
Cardiac death	1 (0.0)	Unknown

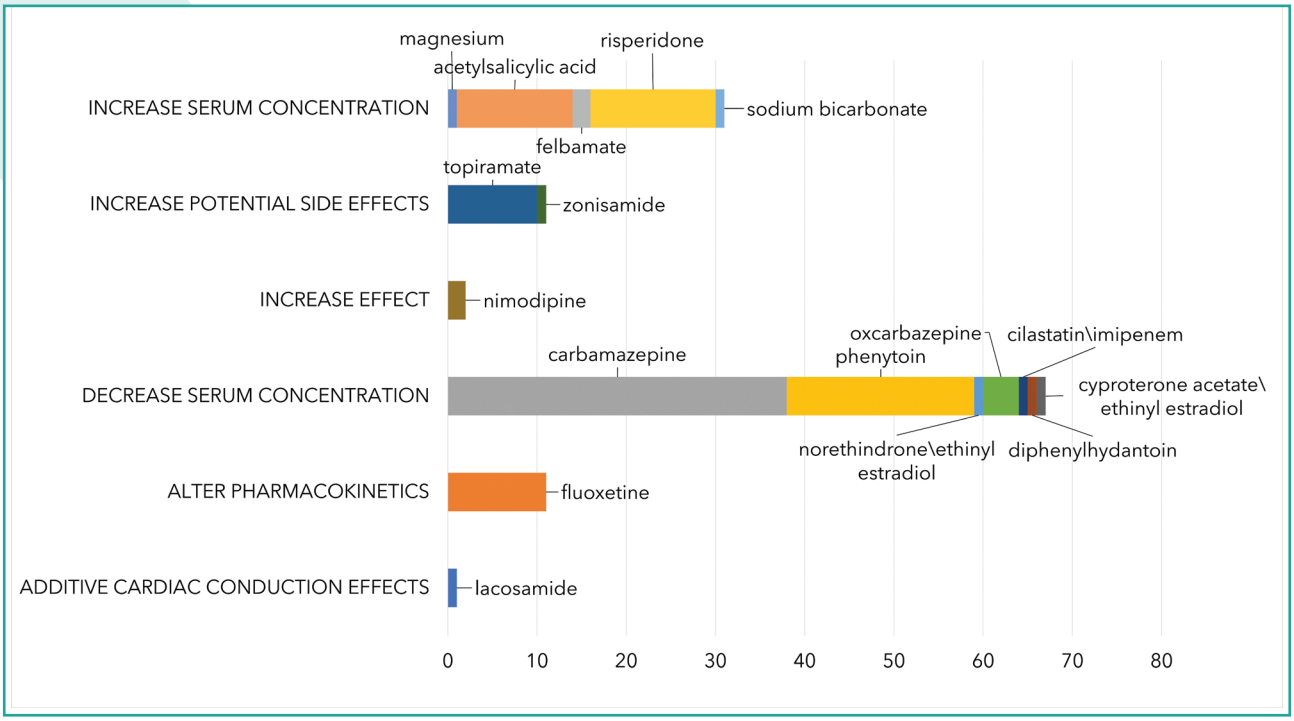

Figure 2. Principal DDIs of interest.

evidence that other co-administered drugs are involved in the onset of QT elongation than valproic acid (4, 8, 22). Consistently with this, the analysis we conducted on reports with valproic acid as unique suspect drug revealed that only 3% of cases involves ADRs of the SMQ of interest; of these, loss of consciousness and syncope are the most reported events, even if sometimes they could be caused by seizure itself (5).

Another study underlines that there is no correlation between seizures frequency and electrocardiogram alterations, except for a slight increase in QTcd (QT interval corrected for heart rate dispersion) in patients taking valproate (15).

On the contrary, Kwon *et al.* suggest that antiepileptic drugs, or even polytherapy of antiepileptic drugs, may not lengthen the QT interval. They also suggest that some traditional antiepileptic drugs are known to shorten the QT interval with an unclear mechanism, so sodium channel blockers may be used in an attempt to normalize the QT interval (7).

This is in contrast with other studies that support the increased risk of QT elongation in patients treated with antiepileptic drugs and, in particular, with valproic acid. Asoğlu *et al.* demonstrate that QT dispersion, QTcd and Pd (atrial depolarization dispersion) values are significantly higher in epileptic patients using carbamazepine and valproic acid than in the healthy control group. They also report that female patients using carbamazepine and male patients using valproic acid have QTcd values significantly higher compared to female population in valproic acid or male patients on carbamazepine (1).

In the study conducted by Altun *et al.*, valproic acid group shows a significant increase in Tp-e interval, Tp-e/QT and Tp-e/QTc values after three months of treatment, suggesting that valproic acid increases ventricular repolarization (6).

The relationship between valproic acid and the onset of QT prolongation is therefore not completely clarified; the results presented here indicate that valproic acid does not significant-

ly influence QT elongation, which is the result of several coexisting factors.
Multiple mechanisms may be implicated in the QT prolongation and cardiac arrhythmias are more likely to occur if drug-induced QT prolongation coexists with other risk factors, such as inherited long QT syndrome, electrolyte imbalance, cardiac or hepatic diseases (7).
In epileptic patients significantly longer QTmaxc and QTcd intervals are observed than in healthy controls, increased age being associated with longer QTcd intervals but not with the duration of the disease, aetiology of the seizures, mono- or polytherapy treatment regimens (23).
Interactions between antiepileptics and other drugs known to prolong QT may also be clinically important. From our analysis emerged that no less than 17.0% of ICSRs reported valproic acid being co-administered with medications that could alter drugs pharmacokinetic profile. Certain drugs that prolong QT are metabolized by CYP3A4 and, when administrated together with CYP3A4 inhibitors, such as valproic acid, may raise their levels such that the occurrence of ventricular tachyarrhythmia is increased (5, 7).
The use of a spontaneous reporting system database has some important intrinsic limitations because reporting might be influenced by factors including no definitive proof of the causal relationship between exposure to the product and the reported event, notoriety bias, selection bias, under-reporting, stimulated reporting and other confounding factors (24).
Furthermore, neither the incidence of ADRs nor the absolute measures of risk can be computed from the FAERS analysis due to the lack of a denominator (number of patients prescribed the product). Despite these critical aspects, our study highlights the clinical relevance of post-marketing spontaneous reporting, since this kind of analysis are based on real-world data derived from clinical practice and, so, they provide a very large amount of cases about heterogeneous groups of patients that generally are not included in clinical trials. It is worth mentioning that real-world data sources give us a general overview of the drug utilization, letting us better evaluate the safety/effectiveness of drugs in clinical practice, including the long-term impact of therapies.

CONCLUSIONS

In conclusion, the current findings seem to be relatively reassuring. Our analysis revealed a very low number of ICSRs reporting the adverse event of interest and most studies did not report a significant increased risk in QT prolongation associated to valproic acid itself. The adverse event seems to be the consequence of multifactorial coexisting causes rather than imputable to the valproate alone. However, evidence is not conclusive due to the design of the descriptive analysis and the limited number of available studies.
Even if major antiepileptic drugs don't seem to cause QT prolongation themselves, patients remain at risk for cardiac arrhythmia for many possible coexisting factors such as electrolyte imbalance, hepatic or renal impairment and co-medication with other drugs. For this reason, epileptic patients need to be actively screened for QT prolongation due to the increased risk of SUDEP.

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ETHICS

Conflict of interests and fundings

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Availability of data and material

Most of the data generated or analysed during this study are included in this published article (and its supplementary information files). Other datasets associated with the current are available from the corresponding author on reasonable request. The datasets were derived from sources in the public domain: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

Authors' contribution

GG and GC conceptualized and designed the study, interpreted the data drafted the manuscript, revised, and approved the final manuscript as submitted.

VB, GM and CL participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, revised the article, and approved the final article as submitted.

CC and SR participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

MG conceptualized and designed the study, interpreted the data, coordinated, and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

Ethical approval

N/A.

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SUPPLEMENTARY MATERIALS

Supplementary Material S1.

SOC "Cardiac disease" PTs.

- dizziness
- dyspnoea
- oedema peripheral
- tachycardia
- cardiac arrest
- syncope
- cardio-respiratory arrest
- bradycardia
- atrial septal defect
- chest pain
- palpitations
- heart disease congenital
- congenital cardiovascular anomaly
- ventricular septal defect
- sudden death
- pulmonary oedema
- arrhythmia
- atrial fibrillation
- myocarditis
- cyanosis
- myocardial infarction
- cardiac failure
- peripheral swelling
- patent ductus arteriosus
- pericardial effusion
- cardiac disorder
- ascites
- cardiomegaly
- sinus tachycardia
- pericarditis
- sinus bradycardia
- chest discomfort
- cardiomyopathy
- torsade de pointes
- ventricular fibrillation
- ventricular tachycardia
- cardiac failure congestive
- cardiovascular disorder
- supraventricular tachycardia
- atrioventricular block
- ventricular extrasystoles
- angina pectoris
- haemoptysis
- tricuspid valve incompetence
- bundle branch block right
- pulmonary congestion
- mitral valve incompetence
- bradycardia neonatal
- myocardial ischaemia
- propofol infusion syndrome
- presyncope
- coronary artery disease
- bicuspid aortic valve
- arteriosclerosis coronary artery
- acute myocardial infarction
- left ventricular hypertrophy
- pulseless electrical activity
- dyspnoea exertional
- trisomy 21
- ventricular hypertrophy
- bundle branch block left
- cardiogenic shock
- acute pulmonary oedema
- long qt syndrome
- pulmonary valve stenosis
- dilatation ventricular
- ventricular arrhythmia
- brugada syndrome
- hypertrophic cardiomyopathy
- myoglobinuria
- supraventricular extrasystoles
- cardiotoxicity
- congestive cardiomyopathy
- atrioventricular block complete
- extrasystoles
- sudden cardiac death
- cardiopulmonary failure
- dizziness postural
- left ventricular dysfunction
- atrioventricular block first degree
- dextrocardia
- hypoplastic left heart syndrome
- fallot's tetralogy
- coronary artery occlusion
- congenital pulmonary valve atresia
- multiple cardiac defects
- coronary artery stenosis
- cardiac failure acute
- conduction disorder

- cyanosis central
- right ventricular failure
- right ventricular hypertrophy
- tachyarrhythmia
- atrial tachycardia
- mitral valve disease
- transposition of the great vessels
- congestive hepatopathy
- cardiac aneurysm
- cardiac septal defect
- right ventricular dilatation
- bradyarrhythmia
- nodal rhythm
- pulmonary valve stenosis congenital
- fluid overload
- left ventricular failure
- cardiac septal hypertrophy
- myocardial fibrosis
- bundle branch block
- localised oedema
- ventricular septal defect acquired
- foetal arrhythmia
- pleuropericarditis
- atrial flutter
- sinus arrhythmia
- sinus node dysfunction
- cardiovascular insufficiency
- aortic valve incompetence
- pulmonary valve incompetence
- endocarditis
- subacute endocarditis
- toxic cardiomyopathy
- left atrial dilatation
- cardiac tamponade
- bradycardia foetal
- arrhythmia supraventricular
- cardiac valve disease
- cardiac hypertrophy
- dilatation atrial
- left ventricular dilatation
- eosinophilic myocarditis
- cardiac arrest neonatal
- cardiac death
- hyperdynamic left ventricle
- jugular vein distension
- ebstein's anomaly
- acute coronary syndrome
- foetal heart rate disorder
- foetal cardiac disorder
- hypertensive heart disease
- carditis
- cardiac discomfort
- congenital aortic valve stenosis
- congenital heart valve disorder
- congenital pulmonary valve disorder
- neonatal cardiac failure
- left ventricular enlargement
- right ventricular dysfunction
- cardiac flutter
- cardiac dysfunction
- clubbing
- orthopnoea
- aortic valve sclerosis
- congenital mitral valve incompetence
- mitral valve prolapse
- pulmonary artery atresia
- ventricular hypoplasia
- kleefstra syndrome
- gravitational oedema
- cardiac failure chronic
- cor pulmonale
- atrial enlargement
- atrioventricular septal defect
- diastolic dysfunction
- left-to-right cardiac shunt
- ventricular enlargement
- atrioventricular block second degree
- wolff-parkinson-white syndrome
- foetal heart rate deceleration abnormality
- neonatal tachycardia
- sinus arrest
- rhythm idioventricular
- intracardiac thrombus
- abnormal precordial movement
- cardiac neoplasm unspecified
- aortic valve disease
- aortic valve stenosis
- cardiac valve sclerosis
- heart valve incompetence
- tricuspid valve stenosis
- primary ciliary dyskinesia
- coronary artery dilatation
- arteriospasm coronary
- endocarditis bacterial

- kidney congestion
- pulmonary oedema neonatal
- cardiomyopathy neonatal
- cardiac amyloidosis
- myocardial haemorrhage
- rhabdomyoma
- ventricular hypokinesia
- adams-stokes syndrome
- bundle branch block bilateral
- defect conduction intraventricular
- heart block congenital
- trifascicular block
- arrhythmia neonatal
- cardiac fibrillation
- tachycardia foetal
- tachycardia paroxysmal
- nodal arrhythmia
- cardio-respiratory arrest neonatal
- acute cardiac event
- cardiac ventricular disorder
- cardiovascular deconditioning
- heart injury
- dyspnoea at rest
- dyspnoea paroxysmal nocturnal
- laryngeal dyspnoea
- nocturnal dyspnoea
- cardiac neoplasm malignant
- pericardial cyst
- heart valve calcification
- mitral valve disease mixed
- mitral valve stenosis
- pulmonary valve sclerosis
- congenital tricuspid valve incompetence
- tricuspid valve sclerosis
- cardiac malposition
- ductus arteriosus premature closure
- anomalous pulmonary venous connection
- digeorge's syndrome
- noonan syndrome
- truncus arteriosus persistent
- coronary artery embolism
- angina unstable
- papillary muscle infarction
- endocardial fibrosis
- endocarditis viral
- hepatojugular reflux
- cardiac cirrhosis
- cardio-respiratory distress
- cardiorenal syndrome
- ventricular failure
- hypertensive cardiomyopathy
- stress cardiomyopathy
- myocardiac abscess
- acquired cardiac septal defect
- atrial hypertrophy
- myocardial calcification
- right atrial dilatation
- univentricular heart
- ventricular dysfunction
- ventricular dyskinesia
- viral pericarditis
- pericarditis constrictive
- pericardial disease
- pericardial haemorrhage
- accessory cardiac pathway
- atrial conduction time prolongation
- atrioventricular conduction time shortened
- atrioventricular dissociation
- atrioventricular node dispersion
- atrioventricular node dysfunction
- bifascicular block
- frederick's syndrome
- inherited cardiac conduction disorder
- lenegre's disease
- long qt syndrome congenital
- lown-ganong-levine syndrome
- paroxysmal atrioventricular block
- sinoatrial block
- timothy syndrome
- wolff-parkinson-white syndrome congenital
- agonal rhythm
- anomalous atrioventricular excitation
- baseline foetal heart rate variability disorder
- bezold-jarisch reflex
- brash syndrome
- central bradycardia
- chronotropic incompetence
- foetal heart rate acceleration abnormality
- foetal tachyarrhythmia
- heart alternation
- holiday heart syndrome
- neonatal bradyarrhythmia
- neonatal tachyarrhythmia

- nonreassuring foetal heart rate pattern
- ogden syndrome
- pacemaker generated arrhythmia
- pacemaker syndrome
- parasystole
- paroxysmal arrhythmia
- postural orthostatic tachycardia syndrome
- rebound tachycardia
- reperfusion arrhythmia
- sinusoidal foetal heart rate pattern
- withdrawal arrhythmia
- atrial parasystole
- congenital supraventricular tachycardia
- junctional ectopic tachycardia
- neonatal sinus bradycardia
- neonatal sinus tachycardia
- supraventricular tachyarrhythmia
- wandering pacemaker
- accelerated idioventricular rhythm
- foetal cardiac arrest
- ventricular asystole
- ventricular flutter
- ventricular parasystole
- ventricular pre-excitation
- ventricular tachyarrhythmia
- acquired left ventricle outflow tract obstruction
- anaesthetic complication cardiac
- atrial thrombosis
- cardiac autonomic neuropathy
- cardiac complication associated with device
- cardiac contusion
- cardiac function disturbance postoperative
- cardiac herniation
- cardiac perforation
- cardiac procedure complication
- cardiac vein dissection
- cardiac vein perforation
- cardiac ventricular thrombosis
- cardiovascular somatic symptom disorder
- complications of transplanted heart
- congenital rubella syndrome
- coronary sinus injury
- coronary vein stenosis
- dilatation of sinotubular junction
- heart transplant rejection
- heart-lung transplant rejection
- hyperkinetic heart syndrome
- intracardiac mass
- larsen syndrome
- myocardial hypoperfusion
- oedema due to cardiac disease
- orthostatic intolerance
- hypertensive cardiomegaly
- malignant hypertensive heart disease
- cardiac granuloma
- cardiac infection
- cardiovascular syphilis
- gonococcal heart disease
- lyme carditis
- meningococcal carditis
- athletic heart syndrome
- cardiovascular symptom
- dizziness exertional
- gastrocardiac syndrome
- hypoxia intolerance
- left ventricular heave
- mahler sign
- negative cardiac inotropic effect
- oculocardiac reflex
- ortner's syndrome
- positive cardiac inotropic effect
- right ventricular heave
- right ventricular hypertension
- agonal respiration
- bendopnoea
- fat embolism syndrome
- neonatal dyspnoea
- platypnoea
- transfusion-associated dyspnoea
- trepopnoea
- benign cardiac neoplasm
- cardiac fibroma
- cardiac haemangioma benign
- cardiac lymphangioma
- cardiac myxoma
- cardiac neurofibroma
- cardiac polyp
- cardiac teratoma
- cardiac valve fibroelastoma
- carney complex
- leukaemic cardiac infiltration
- metastases to heart

- pericardial mesothelioma malignant
- pericardial mesothelioma malignant recurrent
- primary cardiac lymphoma
- aortic annulus rupture
- aortic valve atresia
- aortic valve calcification
- aortic valve disease mixed
- aortic valve prolapse
- aortic valve thickening
- congenital aortic valve incompetence
- degenerative aortic valve disease
- heyde's syndrome
- subvalvular aortic stenosis
- supravalvular aortic stenosis
- unicuspid aortic valve
- williams syndrome
- carcinoid heart disease
- cardiac valve abscess
- cardiac valve discolouration
- cardiac valve replacement complication
- cardiac valve rupture
- cardiac valve thickening
- cardiac valve vegetation
- congenital heart valve incompetence
- degenerative multivalvular disease
- heart valve stenosis
- lambl's excrescences
- shone complex
- congenital mitral valve stenosis
- degenerative mitral valve disease
- ischaemic mitral regurgitation
- mitral face
- mitral perforation
- mitral valve atresia
- mitral valve calcification
- mitral valve hypoplasia
- mitral valve sclerosis
- mitral valve thickening
- myxomatous mitral valve degeneration
- parachute mitral valve
- systolic anterior motion of mitral valve
- bicuspid pulmonary valve
- pulmonary valve calcification
- pulmonary valve disease
- pulmonary valve thickening
- congenital tricuspid valve atresia
- congenital tricuspid valve stenosis
- degenerative tricuspid valve disease
- straddling tricuspid valve
- tricuspid valve calcification
- tricuspid valve disease
- tricuspid valve prolapse
- tricuspid valve thickening
- congenital great vessel anomaly
- corrected transposition of great vessels
- double outlet left ventricle
- double outlet right ventricle
- ectopia cordis
- laevocardia
- alagille syndrome
- cayler cardiofacial syndrome
- charge syndrome
- chiari network
- cor biloculare
- cor triatriatum
- double inlet left ventricle
- fallot's pentalogy
- fallot's trilogy
- hypoplastic right heart syndrome
- left ventricle outflow tract obstruction
- right ventricle outflow tract obstruction
- trisomy 14
- trisomy 17
- trisomy 18
- trisomy 9
- uhl's anomaly
- velo-cardio-facial syndrome
- emanuel syndrome
- kabuki make-up syndrome
- multiple lentigines syndrome
- myocardial bridging
- persistent foetal circulation
- rubinstein-taybi syndrome
- trisomy 11
- trisomy 13
- trisomy 22
- twin reversed arterial perfusion sequence malformation
- vacterl syndrome
- arteritis coronary
- congenital coronary artery malformation
- coronary artery aneurysm
- coronary artery compression

- coronary artery dissection
- coronary artery insufficiency
- coronary artery perforation
- coronary artery reocclusion
- coronary artery restenosis
- coronary artery thrombosis
- coronary bypass stenosis
- coronary bypass thrombosis
- coronary ostial stenosis
- coronary sinus dilatation
- coronary vascular graft occlusion
- coronary vascular graft stenosis
- diabetic coronary microangiopathy
- haemorrhage coronary artery
- anginal equivalent
- cardiac perfusion defect
- chronic coronary syndrome
- coronary no-reflow phenomenon
- coronary steal syndrome
- kounis syndrome
- microvascular coronary artery disease
- myocardial reperfusion injury
- myocardial stunning
- periprocedural myocardial infarction
- post procedural myocardial infarction
- postinfarction angina
- prinzmetal angina
- silent myocardial infarction
- subclavian coronary steal syndrome
- subendocardial ischaemia
- wellens' syndrome
- acute endocarditis
- endocarditis enterococcal
- endocarditis gonococcal
- endocarditis haemophilus
- endocarditis meningococcal
- endocarditis pseudomonal
- endocarditis q fever
- endocarditis rheumatic
- endocarditis staphylococcal
- endocarditis syphilitic
- janeway lesion
- osler's nodes
- rheumatic fever
- rheumatic heart disease
- streptococcal endocarditis
- syphilitic endocarditis of heart valve
- endocardial disease
- endocardial fibroelastosis
- endocardial varices
- eustachian valve hypertrophy
- subendocardial haemorrhage
- endocarditis candida
- fungal endocarditis
- coxsackie endocarditis
- endocarditis fibroplastica
- endocarditis helminthic
- endocarditis histoplasma
- endocarditis noninfective
- lupus endocarditis
- cardiac asthma
- peripheral oedema neonatal
- pulmonary venous hypertension
- transfusion-related circulatory overload
- cardiac failure high output
- cardiohepatic syndrome
- grey syndrome neonatal
- low cardiac output syndrome
- obstructive shock
- radiation associated cardiac failure
- acute left ventricular failure
- chronic left ventricular failure
- acute right ventricular failure
- chronic right ventricular failure
- cor pulmonale acute
- cor pulmonale chronic
- kyphoscoliotic heart disease
- pulmonary artery wall hypertrophy
- shoshin beriberi
- arrhythmogenic right ventricular dysplasia
- cardiac iron overload
- cardiac steatosis
- cardiomyopathy acute
- cardiomyopathy alcoholic
- chagas' cardiomyopathy
- diabetic cardiomyopathy
- glycogen storage disease type ii
- hiv cardiomyopathy
- ischaemic cardiomyopathy
- kearns-sayre syndrome
- metabolic cardiomyopathy
- mitochondrial cardiomyopathy
- non-compaction cardiomyopathy
- non-obstructive cardiomyopathy

- obesity cardiomyopathy
- peripartum cardiomyopathy
- restrictive cardiomyopathy
- tachycardia induced cardiomyopathy
- thyrotoxic cardiomyopathy
- viral cardiomyopathy
- coxsackie carditis
- coxsackie myocarditis
- cytomegalovirus myocarditis
- enterovirus myocarditis
- malarial myocarditis
- myocarditis bacterial
- myocarditis helminthic
- myocarditis infectious
- myocarditis meningococcal
- myocarditis mycotic
- myocarditis septic
- myocarditis syphilitic
- myocarditis toxoplasmal
- viral myocarditis
- aorto-atrial fistula
- atrial rupture
- atrial septal defect acquired
- atrio-oesophageal fistula
- cardiac lipoma
- cardiac pseudoaneurysm
- cardiac sarcoidosis
- cardiac septal defect residual shunt
- cardiac ventricular scarring
- chordae tendinae rupture
- holt-oram syndrome
- interventricular septum rupture
- ischaemic contracture of the left ventricle
- left atrial enlargement
- left atrial hypertrophy
- left ventricular diastolic collapse
- left ventricular false tendon
- myocardial depression
- myocardial hypoxia
- myocardial necrosis
- myocardial oedema
- myocardial rupture
- myoglobinaemia
- papillary muscle disorder
- papillary muscle haemorrhage
- papillary muscle rupture
- post cardiac arrest syndrome
- right atrial enlargement
- right atrial hypertrophy
- right ventricular diastolic collapse
- right ventricular enlargement
- right ventricular false tendon
- sigmoid-shaped ventricular septum
- single atrium
- systemic right ventricle
- systolic dysfunction
- ventricle rupture
- ventricular compliance decreased
- ventricular dyssynchrony
- ventricular hyperkinesia
- ventricular remodelling
- autoimmune myocarditis
- giant cell myocarditis
- hypersensitivity myocarditis
- immune-mediated myocarditis
- lupus myocarditis
- myocarditis post infection
- radiation myocarditis
- atypical mycobacterium pericarditis
- bacterial pericarditis
- coxsackie pericarditis
- cytomegalovirus pericarditis
- infective pericardial effusion
- pericarditis amoebic
- pericarditis fungal
- pericarditis gonococcal
- pericarditis helminthic
- pericarditis histoplasma
- pericarditis infective
- pericarditis meningococcal
- pericarditis mycoplasmal
- pericarditis rheumatic
- pericarditis syphilitic
- pericarditis tuberculous
- purulent pericarditis
- autoimmune pericarditis
- pericarditis adhesive
- pericarditis lupus
- pericarditis malignant
- pericarditis uraemic
- postpericardiotomy syndrome
- benign pericardium neoplasm
- dressler's syndrome
- intrapericardial thrombosis

- malignant pericardial neoplasm
- pericardial calcification
- pericardial effusion malignant
- pericardial fibrosis
- pericardial lipoma
- pericardial mass
- pericardial neoplasm
- pericardial rub
- pneumopericardium
- radiation pericarditis

Supplementary Material S2.
SMQ "Torsade de pointes/QT prolongation" PTs.

- electrocardiogram qt interval abnormal
- electrocardiogram qt prolonged
- long qt syndrome
- long qt syndrome congenital
- torsade de pointes
- ventricular tachycardia
- cardiac arrest
- cardiac death
- cardiac fibrillation
- cardio-respiratory arrest
- electrocardiogram repolarisation abnormality
- electrocardiogram u wave inversion
- electrocardiogram u wave present
- electrocardiogram u-wave abnormality
- loss of consciousness
- multiple organ dysfunction syndrome
- subacute kidney injury
- sudden cardiac death
- sudden death
- syncope
- ventricular arrhythmia
- ventricular fibrillation
- ventricular flutter
- ventricular tachyarrhythmia