Detection of Clinically Significant Drug-Drug Interactions in Fatal Torasdes de Pointes: A Multiple Real-world Data, Retrospective, Pharmacovigilance Study

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Abstract

Background: Torsades de Pointes (TdP) is a rare yet potentially fatal cardiac arrhythmia, and that is often drug-induced. Drug-drug interactions (DDIs) is a major risk factor for TdP development, while the specific drug combinations that increase this risk have not been extensively studied.

Objective: The primary objective of this study was to identify clinically significant DDIs to minimize the risk of TdP, without unnecessary treatment discontinuations or alterations.

Methods: Four frequency statistical models: the ? shrinkage measure, combination risk ratio, chi-square statistics, and additive models were employed to detect DDIs signals using the FDA Adverse Event Reporting System (FAERS) database. The adverse event of interest was TdP, and the drugs targeted were all registered and classified as "suspect", "interacting", or "concomitant drugs" in FAERS. The DDIs signals were identified and evaluated using the Lexicomp® and Drugs.com® databases, supplemented with real-world data from literature evidence.

Results: Of the 4,313 TdP cases, 721 drugs and 4,230 drug combinations reported in at least 3 cases. The ? shrinkage measure model demonstrated the most conservative in signal detection, whereas the chi-square statistic model exhibited the closest similarity in signal detection tendency to the ? shrinkage measure model. 2,158 combinations were detected by the four frequency statistical models, of which 241 combinations were indexed by Drugs.com® or Lexicomp®, and 105 were indexed by both. The most commonly interacting drugs were amiodarone, citalopram, quetiapine, ondansetron, ciprofloxacin, methadone, escitalopram, sotalol, voriconazole, etc. The most common combinations were citalopram & quetiapine, amiodarone & ciprofloxacin, amiodarone & escitalopram, amiodarone & fluoxetine, ciprofloxacin & sotalol, amiodarone & citalopram. While 38 DDIs indexed by Drugs.com® and Lexicomp®, but not detected by any of the four models.

Conclusions: Clinical evidence on DDIs is limited, and not all combinations of QTc-prolonging drugs result in TdP, even when involving high-risk drugs or those with known risk of TdP. This study provides a comprehensive real-world overview of drug-induced TdP, delineateing both clinically significant DDIs and negative DDIs, providing valuable insights into the safety profiles of various drugs and informing the optimization of clinical practice.

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Detection of Clinically Significant Drug-Drug Interactions in Fatal Torasdes de Pointes: A Multiple Real-world Data, Retrospective, Pharmacovigilance Study

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Methods: Four frequency statistical models: the Ω shrinkage measure, combination risk ratio, chi-square statistics, and additive models were employed to detect DDIs signals using the FDA Adverse Event Reporting System (FAERS) database. The adverse event of interest was TdP, and the drugs targeted were all registered and classified as "suspect", "interacting", or "concomitant drugs" in FAERS. The DDIs signals were identified and evaluated using the Lexicomp® and Drugs.com® databases, supplemented with real-world data from literature evidence.
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Keywords: Torsades des Pointes; FAERS database; Drug-drug interactions; QTc-prolonging drugs

Introduction

Torsades des Pointes (TdP) is a rare but life-threatening cardiac arrhythmia, characterized by a prolonged heart rate-corrected QT interval (QTc) noted on the electrocardiogram, and is often drug-induced. Drug-drug interactions (DDIs) is a significant risk factor for TdP development. 268 drugs with cardiac or non-cardiac indications, such as

antibiotics, antipsychotics, antidepressants, antineoplastic drugs, etc., are known to prolong the QTc interval, of which 68 drugs with known risk of TdP, 145 drugs with possible risk of TdP, and 53 drugs with conditional risk of TdP [1]. The resulting exponential increase in potential DDIs is considerable and warrants careful consideration when these medications are used concurrently. The combined use of drugs that prolong the QTc interval may further increase the risk of developing TdP, and the magnitude of such risk depends on the specific drugs included. Unfortunately, the combinations contributing to TdP remain poorly characterized.

In clinical practice, the risks of drug combinations is frequently assessed using one or more sources of DDIs information. However, there is a dearth of trustworthy information on DDIs, with significant variability ($\kappa < 0.20$, $p < 0.05$) in the data provided by different DDIs information resources [2]. In addition to variations in the lists of interacting drug pairs, substantial diaparities are also notable in the severity, mechanism, clinical effects, and management of DDIs among various drug information resources. These inconsistencies contribute to the uncertainty among healthcare professionals regarding interacting drug pairs in clinical practice, thereby increasing the potential for adverse drug outcomes. This is particularly true in the real world, where elderly patients with multiple health conditions often receive many more than the two drugs identified in the DDIs reports, which is entirely different from the ideal world of clinical research. Consequently, physicians and pharmacists face considerable challenges in determining the safety of administering combinations of two or more QTc-prolonging drugs. Therefore, it is imperative to prioritize the identification and management of clinically significant DDIs for TdP.

Literature data serve as valuable real-world evidence, with numerous cases of drug-induced TdP documented. However, there is a notable paucity of evidence concerning DDIs in these reports. Krumpholz et al.[3] conducted a comprehensive review of literature-reported cases of drug-induced TdP from 1980 to 2021, encompassing 424 papers of 634 case reports, which primarily documented suspected and concomitant drugs without adequately considering interacting drugs.

The FDA Adverse Event Reporting System (FAERS) database is a spontaneous reporting system provides information about adverse events (AEs) in clinical settings and is utilized to assess post marketing drug safety. In addition, FAERS has also been applied to detect adverse events associated with DDIs, because two or more suspected, interacting, or concomitant drugs for each event can be given. However, significant uncertainty exists regarding the association between drugs and AEs in a given report, as these reports encompass all potential drugs and AEs for a patient. The quality of the FAERS database may be compromised by inaccurate reports, under-reporting, and missing data. Despite the aforementioned limitations, the FAERS database remains a valuable resource for DDIs research, particularly for identifying DDIs that result in severe or fatal AEs. This study aimed to integrate multiple data sources, including the FAERS database, DDI information resources, and relevant literature, to detect clinically significant DDIs.

2. METHODS

2.1 Data sources

A retrospective, disproportionality, pharmacovigilance study was conducted from 2004 quarter 1 (Q1) to 2023 Q2 using the FAERS database to detect potential DDIs that increase the incidence of TdP in a large-scale population. In the FAERS database, each report is coded using the preferred terms (PTs) provided by the Medical Dictionary for Regulatory Activities (MedDRA), and each drug is assigned a code according to its association with adverse events: suspect drugs, concomitant drugs, or interacting drugs. OpenVigil 2.1-MedDRA-v24, an open tool for data mining and analysis of pharmacovigilance data using cleansed FDA adverse event reporting data, was used to detect DDIs.

2.2 Definition of adverse events

In this study, the targeted AE was torsade de pointe (TdP), which was extracted from FAERS using the PT of torsade de pointes (PT code: 10044066). In these cases, all drugs classified as suspected drugs, interacting drugs, and concomitant drugs were included in the process to investigate DDIs. For signal detection, we focused only on combinations of two drugs with three or more cases.

2.3 Signal detection statistical models and standards

Several statistical algorithms for exploring DDIs signals have been reported, while there is still no de facto standard for DDIs signal detection in spontaneous reporting systems [4][5]. Among them, the Ω shrinkage measure model, proposed by Norén et al. to calculate an observed-to-expected ratio as a statistical model for the disproportionality measurement of potential DDIs [6], which is employed by the World Health Organization Uppsala Monitoring Center, and has been shown in previous studies to exhibt the most conservative signal detection trend among signal

detection methods based on frequentist statistics and has notable benefits in minimizing false positives [7]. The additive model, as proposed by Thakrar et al., demonstrates high sensitivity in detecting DDI signals, which estimates the risk of co-medication in terms of the incidence of target AEs under different drug exposure scenarios for signal detection [8]. Gosho et al. proposed the chi-square statistics model, incorporating Yates' correction, to detect potential DDIs signals [9]. Susuta et al. proposed the combination risk ratio model, as a risk assessment method for the concomitant use of drugs at the frequency of two drugs reported simultaneously, assuming that the possibility of a drug interaction is a combined risk in the occurrence of AEs.

The above-mentioned four frequency statistical models were employed for the detection of DDIs signals, including the Ω shrinkage measure, chi-square statistic, combination risk ratio, and additive model (see Appendix for the calculation methods) [7]. Subsequently, both a four-by-two contingency table (Table 1) and a two-by-two contingency table (Table 2) were constructed. A positive signal was considered when all four models detected a positive signal. The criteria for signal detection for each statistical model are outlined in Table 3.

Table 1. The four-by-two contingency table for signal detection of DDIs

	Target AE	Other AEs	Total
Concomitant use of *drug* D_1 and *drug* D_2	n_{111}	n_{110}	n_{11+}
drug D_1 without *drug* D_2	n_{101}	n_{100}	n_{10+}
drug D_2 without *drug* D_1	n_{011}	n_{010}	n_{01+}
Neither *drug* D_1 Nor *drug* D_2	n_{001}	n_{000}	n_{00+}
Total	n_{++1}	n_{++0}	n_{+++}

AE, adverse event; *n*, the number of reports.

Table 2. The two-by-two contingency table for signal detection of DDIs

	drug D_2	Not *drug D2*
drug D_1	$P_{11} = n_{111} / n_{11+}$	$P_{10} = n_{101} / n_{10+}$
Not *drug* D_1	$P_{01} = n_{011} / n_{01+}$	$P_{00} = n_{001} / n_{00+}$

Table 3. The signal detection criteria for each statistical model

Statistical models	Criteria for positive signals
Ω shrinkage measure model	$\Omega_{025} > 0$, $n_{111} \geq 3$
Chi-square statistic model	$\chi > 2$, $n_{111} \geq 3$
Combination risk ratio model	$PRR_{drug\ D1 \cap drug\ D2} > 2$, $\chi^2_{drug\ D1 \cap drug\ D2} > 4$, $CRR > 2$, $n_{111} \geq 3$
Additive model	$P_{11} - P_{10} - P_{01} + P_{00} > 0$, $n_{111} \geq 3$

PRR, proportional reporting ratio; CRR,Combination risk ratio.

2.4 Evaluation of commonality of signals detected

The commonality of the signals detected by each statistical model was evaluated using Cohen's kappa coefficient (κ), the proportionate agreement for positive rating ($P_{positive}$), and the proportionate agreement for negative rating ($P_{negative}$), as reported in a previous study [7] (see Appendix for the calculation method). Theκprovides a measure that adjusts the observed agreement for the chance agreement, which ranges from -1 to 1, and indicates the level of agreement between observed and expected values [7]. Theκvalue of 0 to 0.20 indicates slight agreement, 0.21 to 0.4 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, 0.81 upward excellent agreement, and the absolute agreement is 1 [10]. Conversely, κless than 0 means that the observed agreement rate is less than the chance agreement rate, which rarely occurs in practical research.

2.5 Signal Verification

As positive controls, we downloaded a list of 268 drugs with known (68), possible (145), and conditional (53) risk of TdP from CredibleMed®, an online compendium of QTc drugs [1], and 217 drugs with highest (32), moderate (70) and low (115) risk interacting from Uptodate® [11].

In order to ensure the accuracy and reliability of DDIs results, the Lexicomp® point-of-care database, known for its comprehensive scope, was adopted to validate DDIs signals. Additionally, the open-access online drug interaction checker Drugs.com® was employed to the cross-validate the DDIs signals. The severity classifications of DDIs in the two drug databases is presented in Table 4. Subsequently, a search was conducted in the PubMed database for literature pertaining to drug-induced TdP, and an open-access database of literature-derived drug-related TdP cases, containing 624 TdP cases from 424 papers, was used to further evaluate the clinical relevance of the DDIs [3].

Table 4. The severity classification of DDIs in Lexicomp® and Drugs.com®

Lexicomp® [11]	Drugs.com® [12]
X: Avoid combination Clinically significant and generally considered contraindicated; the risk of DDI outweighs the benefit	**Major** Highly clinically significant and avoid combinations; the risk of DDI outweighs the benefit
D: Consider therapy modification Clinically significant and aggressive monitoring, empiric dosage changes, or alternative agents; patient-specific assessment wether benefit outweighs risk	**Moderate** Moderately clinically significant and usually avoid combinations; use only under special circumstances
C: Monitor therapy Clinically significant but benefit usually outweighs risk, dosage adjustment may be needed	**Minor** Minimally clinically significant; minimise risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan
B: No action needed little to No evidence of clinical concern	**Unknown** No DDI information available
A: No known interaction neither PK Nor PD DDI is demonstrated	

3 Results

3.1 Basic information of TdP cases

A total of 4,313 TdP cases from 11,439,756 AE cases were included in the present study. Of the TdP cases, 55.7% were female and 32.4% were male, with an average age of 55.5 years (0-97 years), and 38.3% were over 60 years old. TdP is serious and fatal, with many of the reported cases (30.4%) leading to hospitalization (initial or prolonged), 39.5% to life-threatening and even 8.4% to death. Around 41.4% of these cases were reported from the United States (Table 5).

Table 5. Characteristics of patients with Torsades des pointes in the FAERS database

Category		n	%
Gender	Male	1,398	32.4%
	Female	2,403	55.7%
	Unknown	512	11.9%
Age Category	0-19 yrs	180	4.2%
	20-39 yrs	625	14.5%
	40-59 yrs	1,011	23.4%
	60-79 yrs	1,196	27.7%
	> 80 yrs	457	10.6%
	Unknown	844	19.6%
Serious Category	Died	363	8.4%
	Life Threatening	1,705	39.5%
	Disabled	6	0.1%
	Hospitalized-Initial or Prolonged	1,310	30.4%
	Required Intervention	19	0.4%
	Other Outcomes	882	20.4%
	Unknown	28	0.6%
Reporter country	United States	1,784	41.4%
	Japan	201	4.7%
	China	80	1.9%
	Other countries	1,923	44.6%
	Unknown	325	7.5%

Figure 1. depicts a co-current network of adverse events associated with TdP, providing a comprehensive overview of the patterns of TdP occurrence. Among the 4,313 TdP cases analyzed, the most common presentations were electrocardiogram QT prolonged (1,736), long QT syndrome (298), electrocardiogram QT corrected interval prolonged (61), cardiac arrest (892), ventricular tachycardia (738), ventricular fibrillation (622), syncope (492), ventricular extrasystoles (224), loss of consciousness (214), cardio-respiratory arrest (205), atrial fibrillation (144), arrhythmia (140), ventricular arrhythmia (135), tachycardia (115), palpitations (114), dizziness (109). Patient with risk factors such as hypokaemia, hypomagnesaemia, bradycardia, electrolyte imbalance, blood magnesium decreased, hypocalcaemia were observed in 524, 235, 225, 65, 63 and 50 cases, respectively. Additionally, there were 513, 271, 168, 164, and 162 cases, respectively, with drug-related risk factors such as drug interactions,

overdose, drug abuse, intentional overdose, and toxicity to various agents.

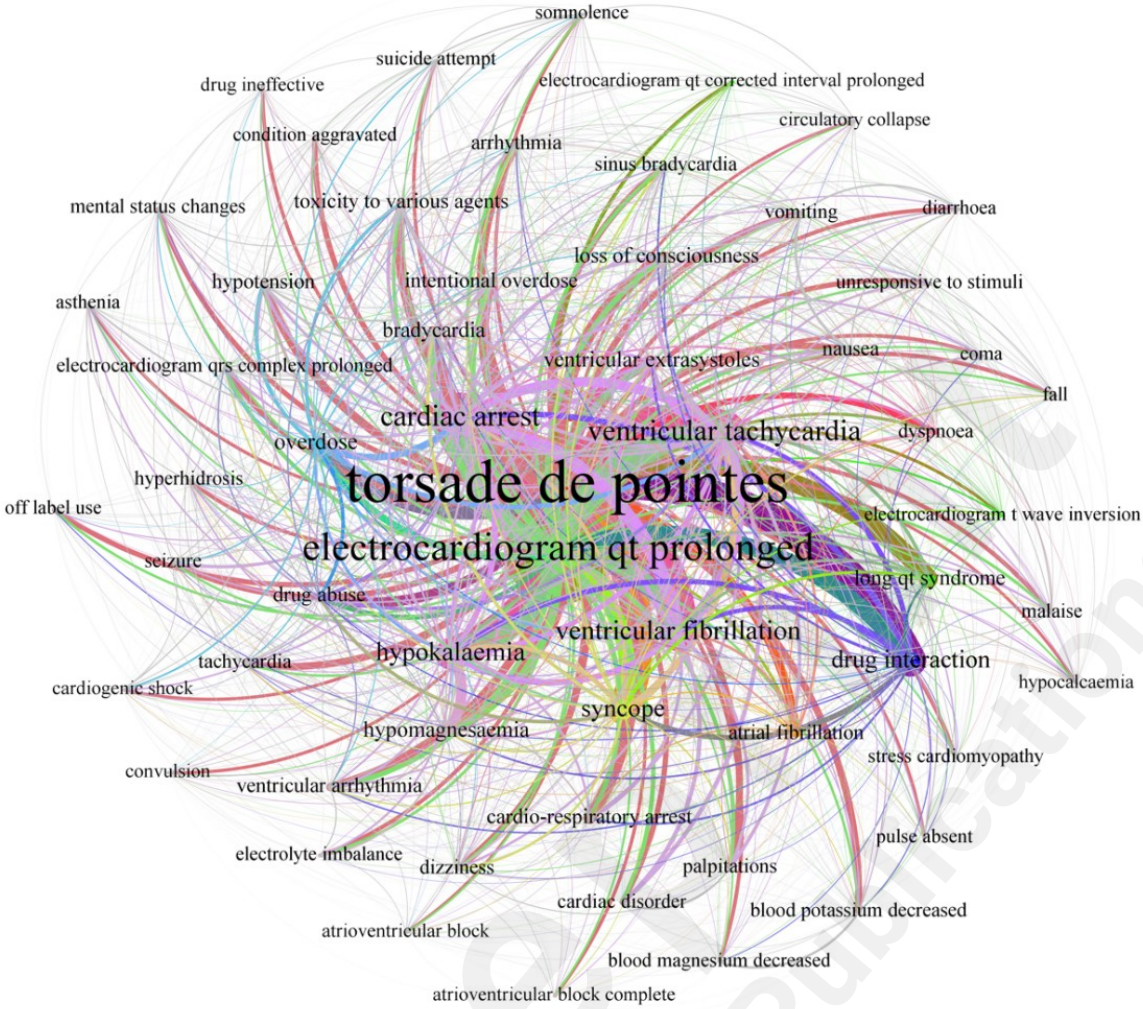

Figure 1. Co-current network diagram of adverse events related to Torsades des Pointes
The size of a node is proportional to the number of neighboring AEs, while the width of an edge is proportional to the number of unique AEs.

3.2 Suspect drugs of TdP cases

721 drugs, including 136 QT-prolonging drugs, reported 3 or more cases were implicated in 4,313 TdP cases analyzed. The most commonly reported drugs were antiarrhythmics, antidepressants, antibacterials, antipsychotics, analgesics, antineoplastics and others (Figure 2). Amiodarone had the most reports (524), followed by furosemide (448), methadone (312), loperamide (301), and citalopram (299). While loperamide [n=260, ROR=53.19, 95%CI (46.87, 60.36)] was the most frequently reported primary suspect drug, followed by amiodarone [n=233, ROR=58.48, 95%CI (51.18, 66.82)], citalopram [n=143, ROR=23.72, 95%CI (20.06, 28.04)], methadone [n=159, ROR=53.91, 95%CI (45.95, 63.26)], furosemide [n=141, ROR=30.93, 95%CI (26.13, 36.62)], and sotalol [n=117, ROR=255.06, 95%CI (210.53, 309.02)]. Ibutilide [n=5, ROR=1206.58, 95%CI (419.04, 3474.16)] had the strongest signal for TdP, followed by halofantrine [n=3, ROR=884.41, 95%CI (239.35, 3267.99)], cisapride [n=69, ROR=325.59, 95%CI (253.16, 418.74)], procainamide [n=5, ROR=270.86, 95%CI (107.87, 680.12)], sotalol [n=117, ROR=255.06, 95%CI (210.53, 309.02)], and these drugs with known TdP risk (Figure 3).

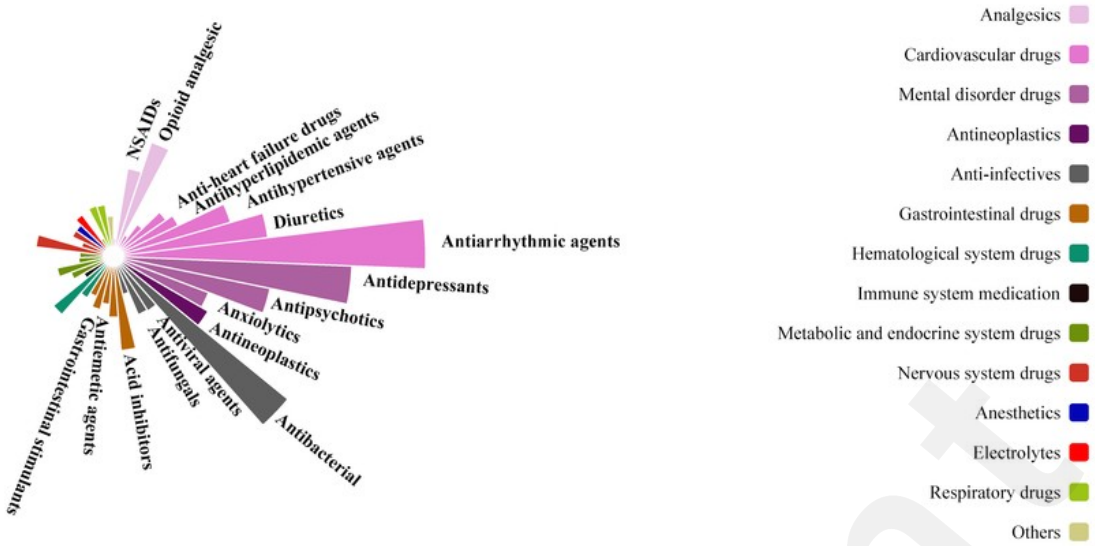

Figure 2. Number of reports of relevant drug classes in Torsades des Pointes

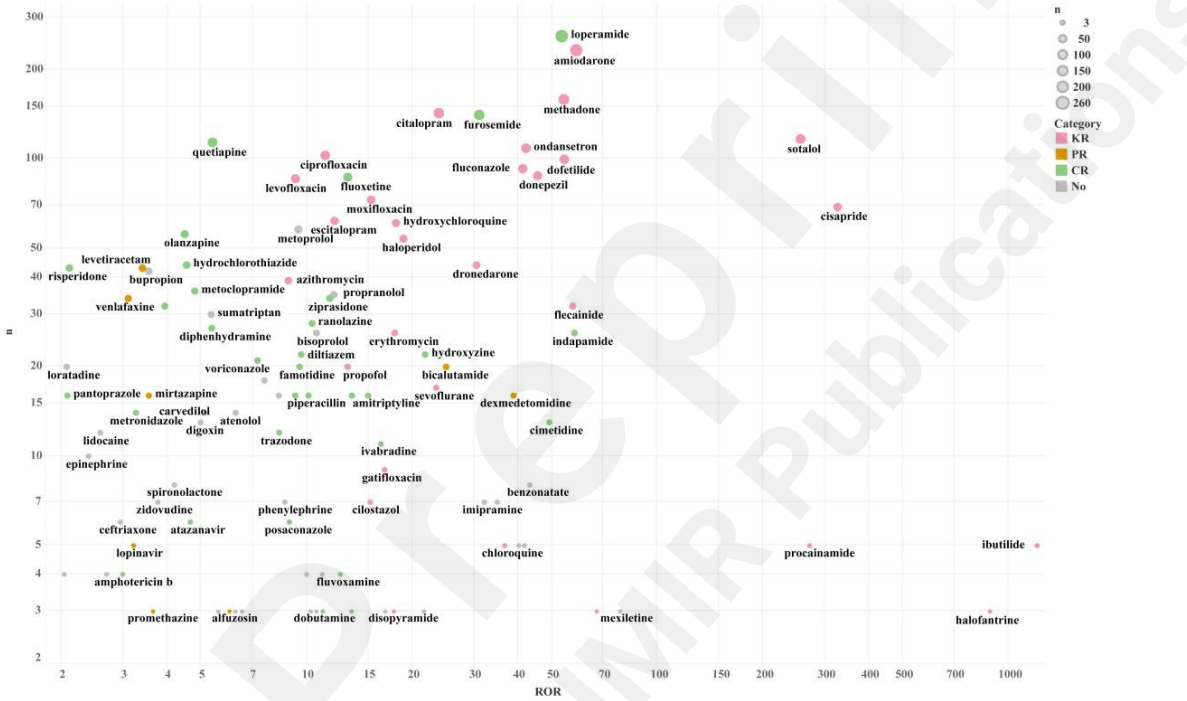

Figure 3. Scatter plot of number of reports and ROR for TdP-related primary suspect drugs

KR, known risk of TdP; PR, possible of TdP; CR, conditional of TdP; No, uncategorized in CredibleMed®; ROR, reporting odds ratio. When ROR≥ 2, 95% CI > 1, $n \geq 3$, it was considered a positive signal.

3.3 DDIs signals of statistical models

We evaluated the reports of TdP for concomitant use of two of the 721 drugs, totaling 8,264 drug combinations, 4,230 combinations were reported in at least 3 cases. The additive model detected the most signals with 3,296 pairs (77.9%), followed by the combination risk ratio model with 2,574 pairs (60.8%), the chi-square statistic model with 2,243 pairs (53.0%), and the Ω shrinkage measure model with 2,236 pairs (52.9%).

3.4 Commonality of DDIs signals detected

Table 6. shows the Cohen's kappa coefficient and proportionate agreement for $P_{positive}$ and that for $P_{negative}$ among four frequency statistical models. The chi-square statistics showed the greatest similarity to the Ω shrinkage measure, with κ, $P_{positive}$, and $P_{negative}$ values of 0.972 (0.942, 1.002), 0.987, and 0.985, respectively. In contrast, the κ, $P_{positive}$, and $P_{negative}$ values for the Ω shrinkage measure and additive models were 0.482 (0.451, 0.513), 0.808, and 0.638, respectively, with moderate similarity.

Table 6. The Cohen's kappa coefficient and proportionate agreement for positive

rating ($P_{postive}$) and that for negative rating ($P_{negtive}$) among four frequency statistical models

	Ω shrinkage measure model	Chi-square statistic model	Combination risk ratio model
Chi-square statistic model	κ:0.972 (0.942, 1.002) $P_{positive}$:0.987 $P_{negative}$:0.985	-	-
Combination risk ratio model	κ:0.780 (0.749, 0.810) $P_{positive}$:0.904 $P_{negative}$:0.874	κ:0.793 (0.762, 0.823) $P_{positive}$:0.910 $P_{negative}$:0.881	-
Additive model	κ:0.482 (0.451, 0.513) $P_{positive}$:0.808 $P_{negative}$:0.638	κ:0.485 (0.454, 0.516) $P_{positive}$:0.810 $P_{negative}$:0.640	κ:0.612 (0.578, 0.646) $P_{positive}$:0.877 $P_{negative}$:0.721

3.5 DDIs signal verification

2,158 combinations (96.2% of the Ωshrinkage measure model) were detected by all four statistical models, with 141 combinations indexed by Lexicomp®, 205 combinations indexed by Drugs.com®, 241 combinations indexed by either, and 1,918 combinations indexed by neither as of October 8, 2023. In addition, 105 combinations were indexed by both, with 52 combinations having 10 or more cases (Figure 4-5).

3.6 DDIs assessment

Out of 2,158 combinations, 409 individual drugs were involved. Categorization in CredibleMeds® showed 35 "known risk", 31 "possible risk", and 45 "conditional risk" drugs. In Lexicomp®, 12 were "high risk", 29 "moderate risk", and 29 "low risk". The drug with the highest number of interactions was amiodarone, which interacted with 68 other drugs, followed by methadone (51), fluoxetine (46), bisoprolol (42), ciprofloxacin (41), citalopram (37) and lorazepam (37).

While the drugs with the most reported interaction cases were amiodarone, citalopram, quetiapine, ondansetron, ciprofloxacin, methadone, escitalopram, sotalol, voriconazole, etc. The drug combinations are shown in Figures 6A-6B, with citalopram & quetiapine (n_{111}=86) having the highest number of cases, followed by amiodarone & ciprofloxacin (n_{111}=49), amiodarone & escitalopram (n_{111}=34), amiodarone & fluoxetine (n_{111}=33), ciprofloxacin & sotalol (n_{111}=31), amiodarone & citalopram (n_{111}=30).

Table 7 presents the characteristics of 105 drug combinations. Lexicomp® classified 18 combinations as "X", 23 as "D", 46 as "C", and 18 as "B". In contrast, Drugs.com® categorized 27 combinations as "Moderate risk" and 78 as "Major risk".

Among the 4,313 cases analyzed, 513 involved drug interaction events, with 460 cases reporting 984 interacting drugs. The most commonly interacting drugs were amiodarone, citalopram, fluoxetine, furosemide, escitalopram, ondansetron, omeprazole, moxifloxacin, and metoprolol. Figure 7 illustrates the drug combinations, with amiodarone & fluoxetine (n_{111}=25), loperamide & cimetidine (n_{111}=23), metoprolol & furosemide (n_{111}=17), venlafaxine & quetiapine (n_{111}=17).

Additionally, 25 combinations were recorded in the literature-derived database of drug-related TdPs with enhanced clinical relevance.

Regrettably, 38 drug combinations, indexed in both databases, but not detected by any of the four models, including 2 "X" class (methadone & quetiapine, quetiapine & ziprasidone), 13 "D" class, 15 "C" class, and 9 "B" class, with amiodarone & sotalol, chlorpromazine & haloperidol, amiodarone & dronedarone being the high-risk QT-prolonging drug combinations (Figure 8).

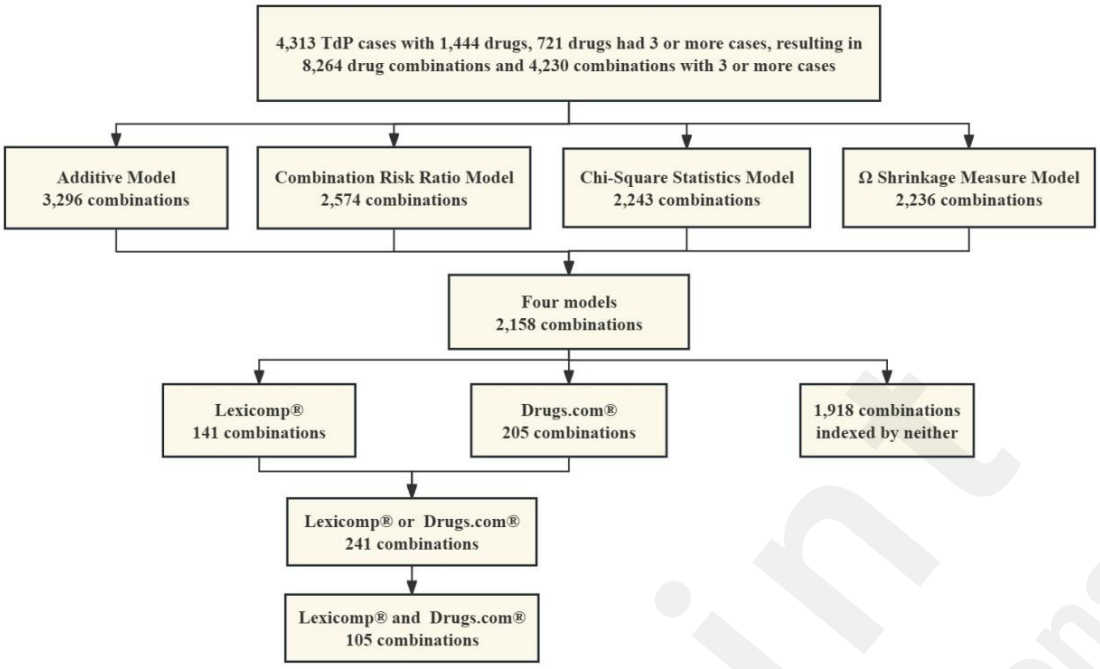

Figure 4. Process of DDIs signal monitoring and verification

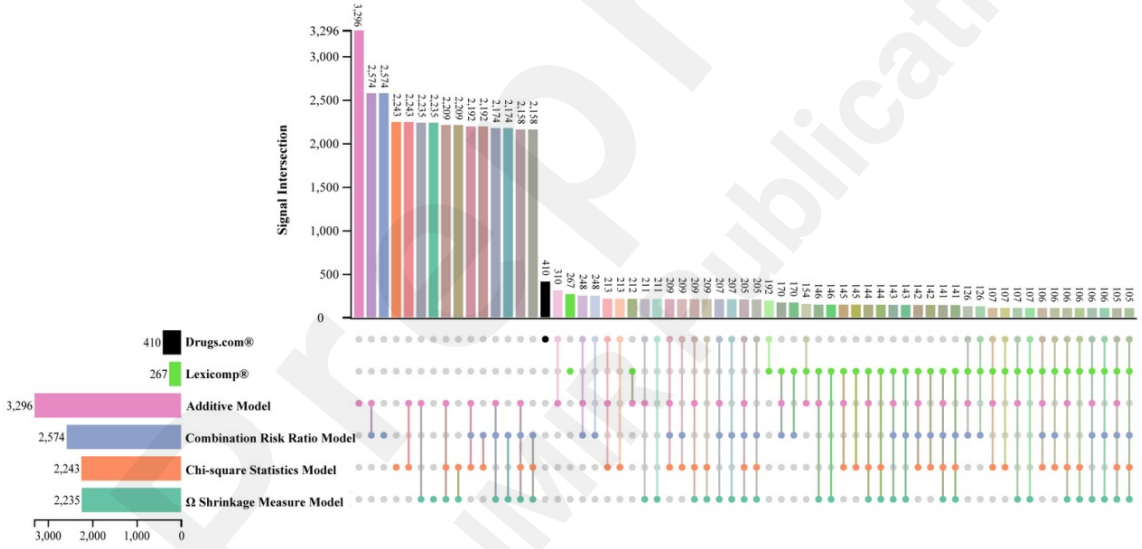

Figure 5. The number of DDIs signals intersection

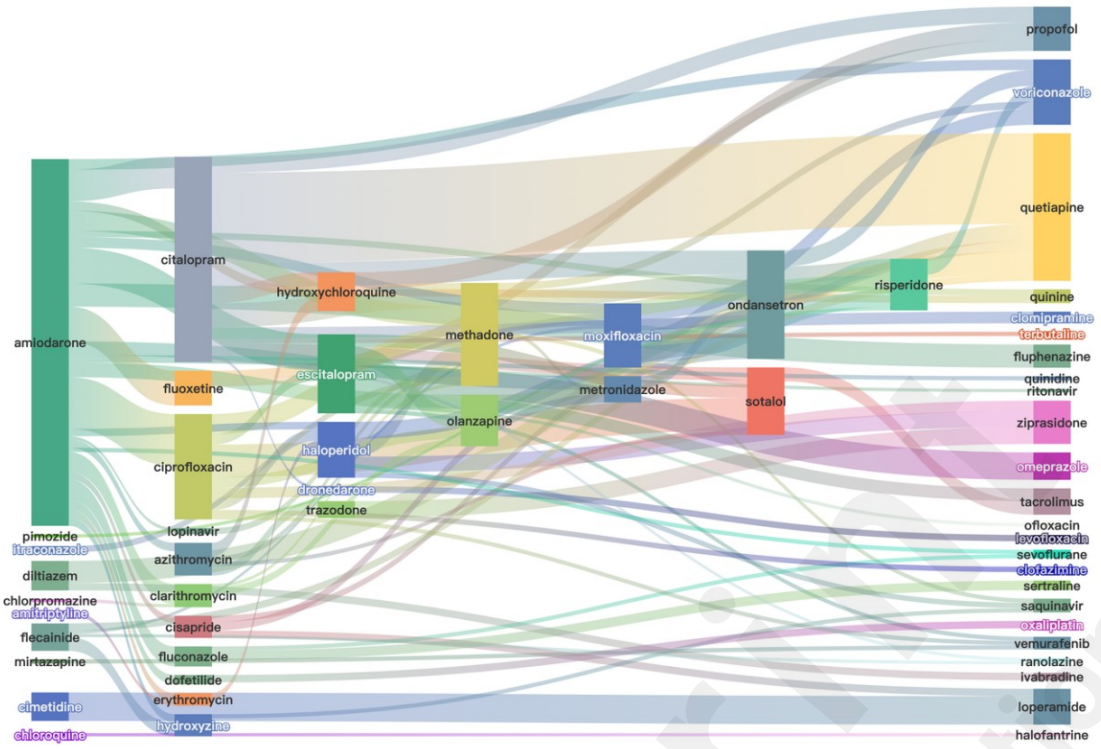

Figure 6A. 105 DDIs for Torsades des Pointes (detected by four models and indexed by Drugs.com® and Lexicomp®, $n_{111} \geq 3$)

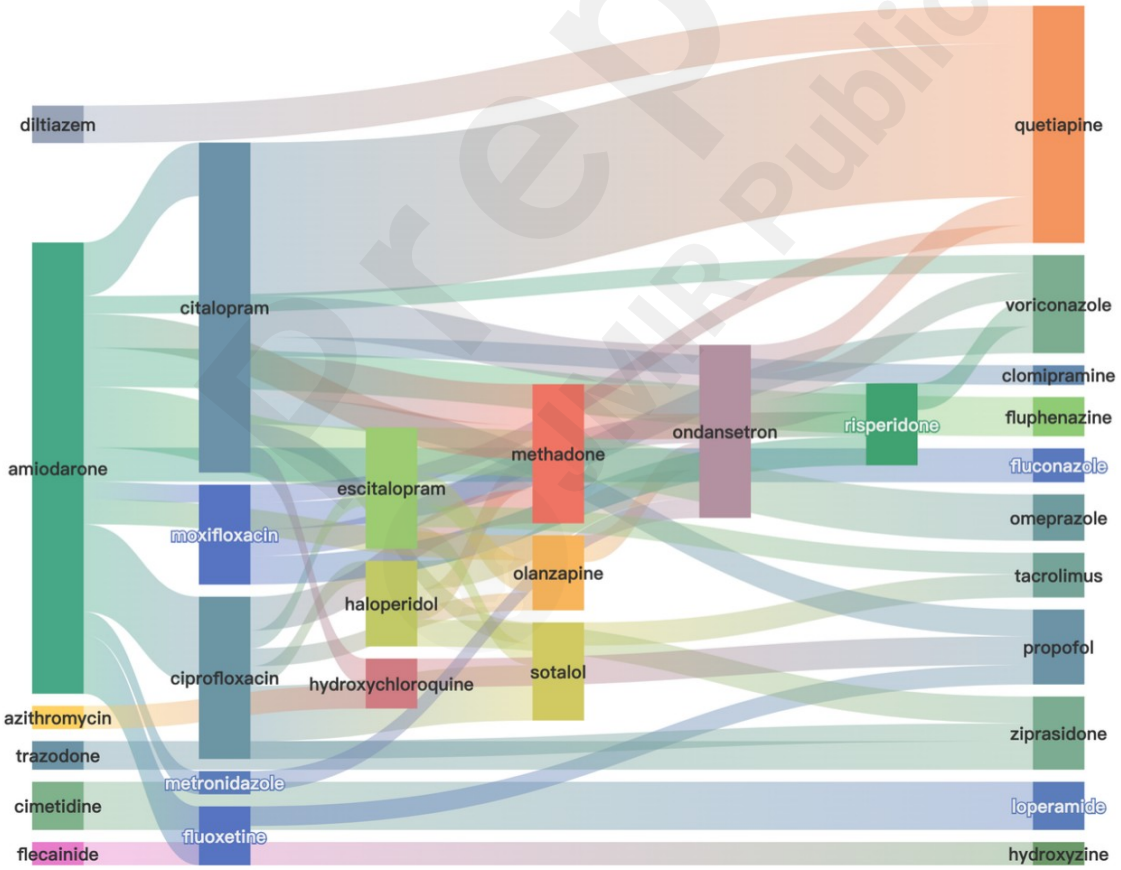

Figure 6B. 52 DDIs for Torsades des Pointes (detected by four models, indexed by Drugs.com® and Lexicomp®, $n_{111} \geq 10$)

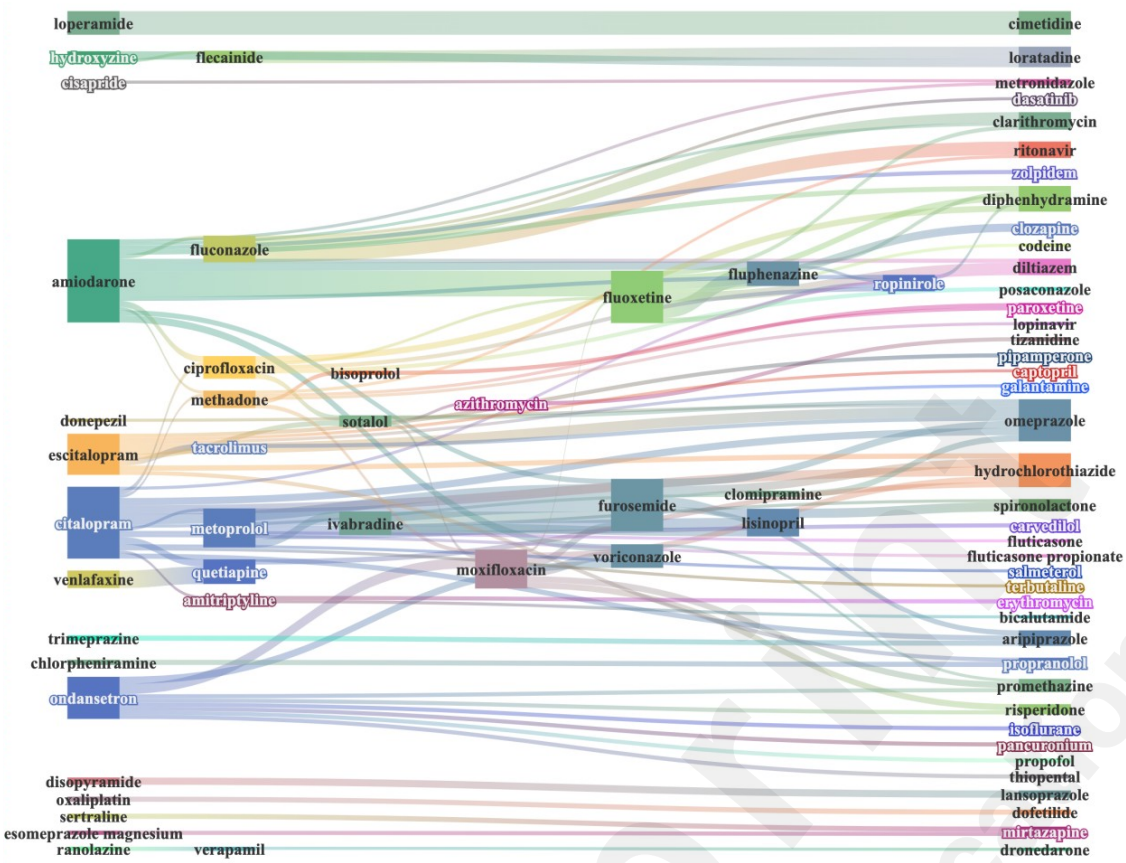

Figure 7. 113 DDIs for Torsades des Pointes (the drugs classified as "interacting drugs" in FAERS)

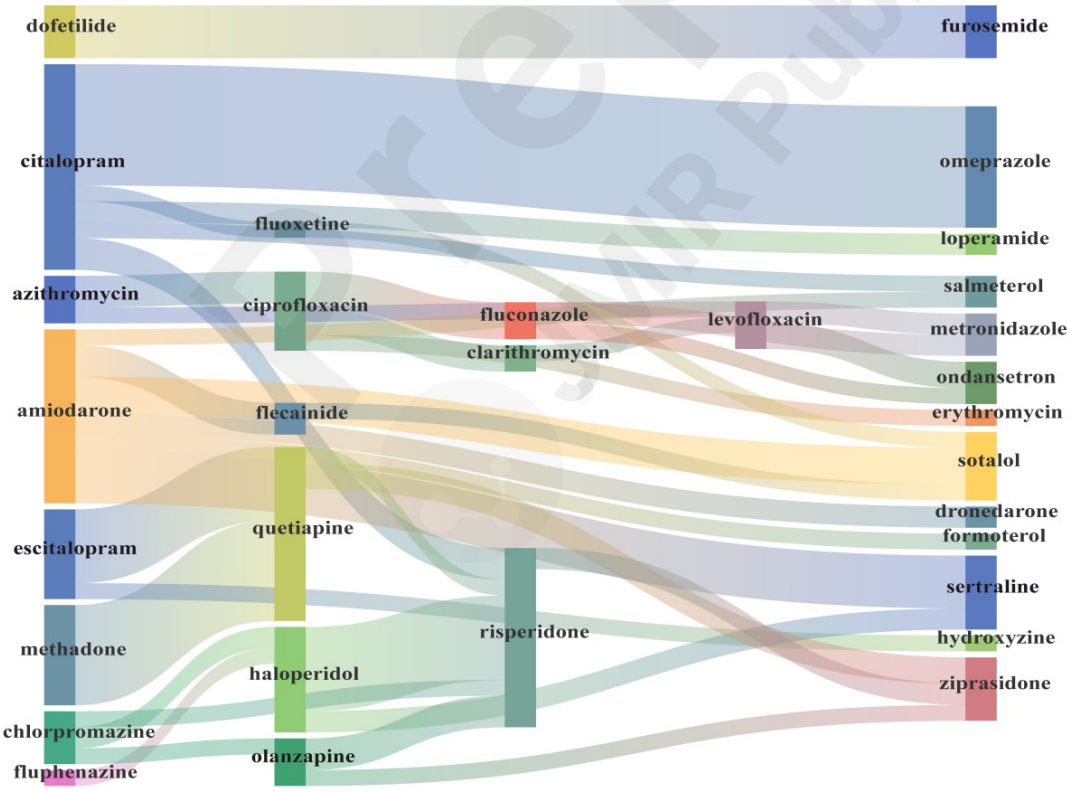

Figure 8. 38 DDIs for Torsades des Pointes (indexed by Drugs.com® and Lexicomp®, $n_{111} \geq 3$, but not detected by any of the four models)

The size of the nodes is proportional to the number of specific drugs with TdP, while the width of the extension branch is proportional to the number of specific combinations with TdP.

4 Discussion

This study presents the initial comparative safety evaluation of the FAERS aimed at assessing the clinically significant DDIs triggering fatal TdP. Matsuo et al. [13] attempted to use the Japanese Adverse Drug Event Report database to identify and summarize potential DDIs associated with an increased risk of drug-induced long QT syndrome. However, their methodology relied on the reporting odds ratio, which retypically employed for assessing safety signals of individual drugs that may not be appropriate for detecting safety signals of DDIs, potentially leading to false positive signals. To address this limitation, four frequency statistical models—namely, the Ω shrinkage measure, combination risk ratio, chi-square statistics, and additive models—were adopted for the detection of DDIs signals in our study, thereby greatly enhancing the validity and comprehensiveness of the identified signals. Furthermore, the verification of these signals was conducted using the Drugs.com®, Lexicomp®, and literature databases, thereby ensuring the credibility and reliability of the DDI data.

Consistent with previous studies, the Ω shrinkage measure model demonstrated the most conservative in signal detection, while the chi-square statistic model exhibited the closest similarity in signal detection tendency to the Ω shrinkage measure model [1]. In contrast, the additive models detected considerably more signals [2], had less similarity in signal detection tendency to the other models, therefore, care must be taken when interpreting the signals. For a specific positive signal result, the more models detected it, the more reliable the result. In this study, 2,158 combinations were detected by the four frequency statistical models, of which 241 combinations were indexed by Drugs.com® or Lexicomp®, and 105 were indexed by both. 171 combinations indexed by only one of the databases, which was related to the poor consistency between the two databases [5], due to employ various rating criteria and procedures, and define different levels of acceptable risk. Drugs.com® validated more interactions than Lexicomp®, which may be related to the fact that Drugs.com® can recognise brand names. Despite utilizing an open-access database of literature-derived drug-related TdP cases, containing 624 TdP cases from 424 papers, to evaluate the clinical relevance of DDIs, only concomitant drugs were documented in all cases except for suspected drugs, with no recorded interacting drugs [3]. Unsurprisingly, only little clinical evidence on DDIs is available, as the inherently difficult of judgement when considering interactions leading to ADEs. However, DDIs do exist which highlights the value of detecting clinically significant DDIs based on real-world data.

In our study, a list containing all potential DDIs of TdP from FAERS was provided. To the best of our knowledge, this list, is the most comprehensive list summarized utilizing a pharmacovigilance database so far. Consistent with the results of existing studies, antiarrhythmics, antidepressants, antipsychotics, antibacterials, analgesics, and antineoplastics drugs, such as amiodarone, citalopram, quetiapine, ondansetron, ciprofloxacin, methadone, escitalopram, sotalol, voriconazole were the most common interacting drugs causing TdP [11]. Additionally, diuretics are also the common interacting drugs cauing TdP, and the potential mechanism underlying it may be related to the electrolyte disorder caused by diuretics. The most common combinations were citalopram & quetiapine, amiodarone & ciprofloxacin, amiodarone & escitalopram, amiodarone & fluoxetine, ciprofloxacin & sotalol, amiodarone & citalopram, and previous studies have proven these DDIs are closely related to TdP [14-17]. Trazodone may lead to QTc prolongation and TdP, potentially fatal even without risk factors for QTc prolongation [18]. And co-interaction with ziprasidone increases the risk of TdP. Therefore, according to this report's proportion result, we can use it to quickly understand the DDIs that commonly result in TdP in the real world. However, it is worth noting that a high reporting ratio does not always represent a high risk because, for different combinations, the frequency of drug use will vary greatly, which will directly affect the proportion of TdP reports.

Amiodarone is the most widely interacting drug, interactions with other 68 drugs, followed by methadone [19-21] fluoxetine, bisoprolol, ciprofloxacin, and citalopram, which interact with 51, 46, 42, 41, and 37 other drugs, respectively. Therefore, additional caution and increased ECG monitoring may be still warranted when these drugs are combined. Especially in patients with risk factors such as increasing age, female sex, bradycardia, heart failure, history of ventricular arrhythmias, use of diuretics, hypothyroidism, hypokalemia, hypomagnesemia, hypocalcaemis, etc.

In addition to offering a complete list of drugs, our study opens up novel perspectives and opportunities for further exploration. As real-world negative reporting is missing, counterexamples that could serve as contradictory evidence may exist. Therefore, identifying negative DDI pairs shall enhance the confidence of healthcare professionals with a level of certainty on DDIs, which in turn will improve medical research and decision-making.

It is widely accepted that co-administration of QTc-prolonging drugs, especially those known risk or high-risk for TdP, heighten the risk of TdP. Our research identified 38 DDIs of QTc prolongation indexed by Drugs.com® and Lexicomp®, but not detected by any of the four models. This finding supports the notion that not all combinations of QTc-prolonging drugs result in TdP, even when involving high-risk drugs or konw risk of TdP. There is only a limited increase in QTc prolongation with concurrent use of QTc-prolonging drugs, and that magnitude of TdP risk

depends on the specific drugs involved and patient risk factors. If clinical decision support systems generate alerts for QTc DDI whenever two QTc-prolonging drugs with a known risk of TdP are combined, irrespective of the clinical relevance of these interactions, a substantial number of false-positive alerts may be produced. The rising incidence of false-positive QTc-DDIs alerts can contribute to alert fatigue among physicians, potentially leading to the disregard of important warnings. Furthermore, these false-positive alerts may prompt unwarranted discontinuation or substitution of medications, therby compromising the efficacy of clinical treatments. Consequently, identifying negative QTc-DDIs is a rational approach to mitigating the challenge of alert fatigue. Nevertheless, caution must be exercised even when a signal is identified as negative, due to the inherent limitations of the FAERS database.

We acknowledge the inherent limitations of our study. First, we focused on the analysis of TdP caused by the concomitant use of two drugs. However, in polypharmacy patients, there have been reports of concomitant use of three or more suspect drugs. We cannot exclude the possibility that a third drug may be a confounding factor on the relationship between coadministration and risk of TdP. Second, the spontaneous reporting system, by its nature, introduces various biases into the the signal detection process, thus rendering the obtained signals as hypotheses rather than definitive conclusions. While we have devoted significant attention to the interpretation of results in the context of signal research for DDIs, validation efforts have been conducted using resources such as Lexicomp® and Drugs.com®. Unfortunately, there is a paucity of reliable information on DDIs, and the available data exhibit substantial variability across different drug information resources. Furthermore, there is a scarcity of robust clinical evidence on DDIs. Consequently, it is challenging to utilize "real" true data for signal verification. Third, although two databases were employed for signal validation, there exists a risk of overlooking genuine DDIs due to inconsistencies between the databases when considering only the DDIs present in both as true signals. Fourth, the failure to convert drug trade names to their generic counterparts prior to analysis may have resulted in an elevated number of DDI-positive signals. Nevertheless, this did not substantially affect the outcomes, as the analysis exclusively included DDIs validated by Lexicomp® and Drugs.com® using generic names.

5 Conclusion

This study offers a preliminary overview of potential culprit DDIs for TdP in real-world settings, as well as negative DDIs, providing valuable insights for regulators, healthcare professionals, and stakeholders involved in DDIs management. However, it is important to ackNowledge the limitations inherent of our study stemming from the reliance on a pharmacovigilance database. It is crucial to recognize that DDIs signals only indicate a statistical association between drug combinations and AEs, necessitating further validation through well-designed studies to establish a causal relationship. Although, we used DDIs information resources and literature evidence for signal validation, the available clinical evidence is limited and subject to significant inconsistencies. Therefore, in clinical practice, DDIs signals should be considered as supplementary evidence and not a substitute for the expertise of cardiologists and clinical pharmacists.

ACKNOWLEDGMENTS

We declare no potential conflicts of interests.

All of the authors were involved in the study. Study design: H.H.J., L.S. and Y.T.J. Extraction data: H.H.J., M.L.G., N.Z., R.O.Z., and L.S. Analysis and interpretation of data: H.H.J., L.G., L.S., D.M.D, Y.Y., and Y.T.J. All of the authors took part in the discussions of the results and contributed to the manuscript.

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Landerholm, A., et al. (2023). "C-L Case Conference: Torsades de Pointes in a Patient With Lifelong Medical Trauma, COVID-19, Remdesivir, Citalopram, Quetiapine, and Hemodialysis." J Acad Consult Liaison Psychiatry 64(2): 147-157.

We present a case of Torsades de Pointes (TdP) in a patient with COVID-19 infection and multiple TdP risk factors including QT-interval prolongation, hemodialysis, bradycardia, and treatment with remdesivir, citalopram, and quetiapine. The case was complicated by post-resuscitation anxiety superimposed on a history of medical trauma since childhood. Top experts in the field of consultation-liaison psychiatry, trauma informed care, and cardiac electrophysiology provide perspectives on this case with a review of the literature. Key teaching topics include identification of TdP risk factors in patients with a complex illness; the necessity for prompt electrophysiology consultation in clinical scenarios with high risk for TdP; and the approach to patients with

medical trauma using a trauma-informed lens. We highlight the contributions of COVID-19, the pharmacokinetics of QT-interval-prolonging psychotropic medications, the risks of hemodialysis, and the role of remdesivir-induced bradycardia in this first reported case of TdP in a patient treated with remdesivir.

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Landerholm, A., Fedotova, N. O., Levy-Carrick, N. C., Chung, R., & Funk, M. C. (2023). C-L Case Conference: Torsades de Pointes in a Patient With Lifelong Medical Trauma, COVID-19, Remdesivir, Citalopram, Quetiapine, and Hemodialysis. J Acad Consult Liaison Psychiatry, 64(2), 147-157. doi:10.1016/j.jaclp.2022.11.001

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Table 7. Characteristics of 105 DDIs for Torsades des Pointes (detected by four models and indexed by Drugs.com® and Lexicomp®, $n_{111} \geq 3$)

Drug 1 (ROR, N)	Drug 1 Drugs.com® Risk Category	Drug 2 (ROR, N)	Drug 2 Drugs.com® Risk Category	Combination Risk Category		Literature Database	Cases (n_{111})	Ω_{025}	X^2	CRR (PRR, χ^2)	AM
				Lexicomp®	Drugs.com®						
Citalopram [M] (13.24, 299)	KR	Quetiapine [M] (5.88, 231)	PR	C	Major	Yes	86	1.58	13.01	3.54□46.89, 3741.53)	0.01
Amiodarone [H] (48.53, 524)	KR	Ciprofloxacin [I] (11.45, 200)	KR	C	Major	Yes	49	2.32	15.66	6.78 (324.58, 15314.61)	0.10
Amiodarone [H] (48.53, 524)	KR	Escitalopram [M] (6.36, 146)	KR	D	Major	Yes	34	1.49	8.73	3.78 (180.34, 5841.69)	0.05
Amiodarone [H] (48.53, 524)	KR	Fluoxetine [L] (10.42, 234)	PR	C	Major	Yes	33	1.89	10.88	5.53 (264.87, 8351.69)	0.08
Ciprofloxacin [I] (11.45, 200)	KR	Sotalol [H] (76.65, 221)	KR	C	Major	Yes	31	2.58	15.16	9.02□673.32, 20006.85)	0.23
Amiodarone [H] (48.53, 524)	KR	Citalopram [M] (13.24, 299)	KR	X	Major	Yes	30	1.11	6.52	3.37 (160.89, 4578.14)	0.04
Cimetidine (22.17, 32)	PR	Loperamide [L] (28.66, 301)	PR	B	Major	Yes	27	3.65	25.27	25.14□713.52, 18396.12)	0.26
Escitalopram [M] (6.36, 146)	KR	Omeprazole (2.11, 130)	PR	C	Moderate	No	26	0.88	5.25	2.7□17.1, 376.13)	0.00
Citalopram [M] (13.24, 299)	KR	Methadone [H] (28.34, 312)	KR	X	Major	No	23	0.35	3.09	2.46 (68.91, 1464.73)	0.01
Citalopram [M] (13.24, 299)	KR	Ondansetron (10.40, 211)	PR	C	Major	No	23	0.35	3.11	2.94 (38.71, 803.72)	0.01
Amiodarone [H] (48.53, 524)	KR	Fluphenazine [L] (45.24, 29)	NA	C	Major	No	22	4.03	32.75	55.81□2665.98, 55708.44)	0.98
Diltiazem (8.33, 119)	PR	Quetiapine [M] (5.88, 231)	PR	C	Moderate	No	21	2.21	11.25	10.92□90.71, 1766.58)	0.03
Amiodarone [H] (48.53, 524)	KR	Clarithromycin [M] (12.82, 103)	KR	X	Major	Yes	19	1.64	7.95	5.64 (269.24, 4793.58)	0.08
Ciprofloxacin (11.45, 200)	KR	Methadone [H] (28.34, 312)	KR	C	Major	Yes	19	2.24	11.12	10.55□296.01, 5273.79)	0.10
Amiodarone [H] (48.53, 524)	KR	Fluconazole [M] (16.41, 142)	KR	D	Major	Yes	19	1.15	5.89	4.16 (198.50, 3524.43)	0.05
Amiodarone [H] (48.53, 524)	KR	Methadone [H] (28.34, 312)	KR	D	Major	No	19	3.08	17.64	25.84 (1234.59, 22112.41)	0.44
Escitalopram [M] (6.36, 146)	KR	Olanzapine [M] (4.45, 101)	PR	C	Moderate	No	18	0.57	3.71	3.22 (20.41, 312.02)	0.00
Haloperidol [H] (13.96, 114)	KR	Methadone [H] (28.34, 312)	KR	D	Major	No	17	2.00	9.53	9.60 (269.45, 4267.03)	0.09
Methadone [H] (28.34, 312)	KR	Ondansetron (10.40, 211)	KR	D	Major	No	17	0.57	3.65	2.93 (82.15, 1278.30)	0.02
Trazodone [L] (4.85, 89)	PR	Ziprasidone [H] (9.94, 55)	PR	C	Major	No	16	1.36	6.44	4.83□48.51, 695.43)	0.01
Haloperidol [H] (13.96, 114)	KR	Ondansetron (10.40, 211)	KR	C	Major	No	16	1.68	7.84	8.66□120.32, 1769.96)	0.04
Moxifloxacin [M] (17.34, 128)	KR	Risperidone [M] (3.43, 106)	PR	C	Major	No	16	3.48	23.48	37.44□645.39, 9627.81)	0.24
Hydroxychloroquine [L] (4.30, 101)	KR	Propofol [M] (17.04, 82)	KR	B	Moderate	No	16	2.80	14.78	15.81□267.9, 3978.39)	0.09
Ondansetron (10.40, 211)	KR	Risperidone [M] (3.43, 106)	PR	C	Moderate	No	16	2.45	12.09	12.61□130.66, 1924.62)	0.04
Ondansetron (10.40, 211)	KR	Quetiapine [M] (5.88, 231)	PR	C	Moderate	No	16	0.91	4.76	4.28 (44.37, 633.44)	0.01
Citalopram [M] (13.24, 299)	KR	Propofol [M] (17.04, 82)	KR	C	Moderate	No	15	2.51	12.44	18.85□319.39, 4434.09)	0.11

Citalopram [M] (13.24, 299)	KR	Hydroxychloroquine [L] (4.30, 101)	KR	C	Major	Yes	15	1.17	5.61	4.48–59.06, 796.55)	0.02
Haloperidol [H] (13.96, 114)	KR	Ziprasidone [H] (9.94, 55)	PR	D	Major	No	15	0.29	2.72	2.85 (39.53, 523.77)	0.01
Olanzapine [M] (4.45, 101)	PR	Ondansetron (10.40, 211)	KR	C	Moderate	No	15	0.70	3.98	3.34 (34.56, 454.48)	0.01
Amiodarone [H] (48.53, 524)	KR	Olanzapine [M] (4.45, 101)	PR	D	Moderate	Yes	14	1.68	7.59	5.84–280.1, 3609.02)	0.09
Methadone [H] (28.34, 312)	KR	Risperidone [M] (3.43, 106)	PR	D	Major	No	14	0.95	4.77	3.42–96.01, 1219.52)	0.03
Sotalol [H] (76.65, 221)	KR	Tacrolimus [L] (1.38, 38)	PR	C	Major	No	13	1.99	9.00	7.85–586.19, 7002.03)	0.20
Amiodarone [H] (48.53, 524)	KR	Metronidazole [L] (3.95, 42)	PR	C	Moderate	Yes	13	1.04	5.00	3.51–167.89, 1987.69)	0.05
Flecainide [M] (28.01, 78)	KR	Hydroxyzine [L] (6.20, 59)	PR	B	Moderate	Yes	13	2.77	14.54	18.9–524.02, 6256.75)	0.19
Azithromycin [M] (7.75, 78)	KR	Hydroxychloroquine [L] (4.30, 101)	KR	C	Major	Yes	13	0.17	2.33	2.47 (19.08, 204.51)	0.00
Escitalopram [M] (6.36, 146)	KR	Tacrolimus [L] (1.38, 38)	PR	B	Major	No	12	2.60	13.08	15.76–100.05, 1077.18)	0.04
Citalopram [M] (13.24, 299)	KR	Sotalol [H] (76.65, 221)	KR	X	Major	No	12	0.66	3.72	3.15 (234.68, 2557.30)	0.06
Escitalopram [M] (6.36, 146)	KR	Sotalol [H] (76.65, 221)	KR	D	Major	No	12	0.79	4.12	3.22 (239.98, 2615.50)	0.06
Fluoxetine [L] (10.42, 234)	PR	Propofol [M] (17.04, 82)	KR	B	Moderate	No	11	2.17	9.94	16.14–273.37, 2713.04)	0.09
Citalopram [M] (13.24, 299)	KR	Clomipramine [M] (9.75, 16)	PR	C	Major	No	11	1.71	7.45	8.1–106.75, 1046.77)	0.03
Ciprofloxacin [I] (11.45, 200)	KR	Haloperidol [H] (13.96, 114)	KR	C	Major	No	11	1.84	8.07	13.25–183.97, 1818.93)	0.06
Metronidazole [L] (3.95, 42)	PR	Ondansetron (10.40, 211)	KR	B	Moderate	No	11	0.32	2.71	2.65 (27.46, 254.10)	0.01
Amiodarone [H] (48.53, 524)	KR	Voriconazole [M] (9.22, 47)	PR	X	Major	No	10	1.51	6.52	6.63 (316.49, 2831.86)	0.10
Ciprofloxacin [I] (11.45, 200)	KR	Olanzapine [M] (4.45, 101)	PR	C	Major	No	10	1.49	6.42	7.66–88.32, 776.7)	0.03
Ciprofloxacin [I] (11.45, 200)	KR	Ziprasidone [H] (9.94, 55)	PR	C	Major	No	10	2.73	15.27	43.15–492.32, 4415.63)	0.18
Moxifloxacin [M] (17.34, 128)	KR	Quetiapine [M] (5.88, 231)	PR	C	Major	No	10	2.06	9.24	13.29–229.18, 2045.44)	0.08
Ciprofloxacin [I] (11.45, 200)	KR	Escitalopram [M] (6.36, 146)	KR	B	Major	No	10	0.39	2.87	3.50 (39.92, 340.83)	0.01
Amiodarone [H] (48.53, 524)	KR	Moxifloxacin [M] (17.34, 128)	KR	X	Major	No	10	1.03	4.73	5.06 (241.68, 2158.04)	0.07
Azithromycin [M] (7.75, 78)	KR	Trazodone [L] (4.85, 89)	PR	B	Moderate	Yes	9	1.24	5.40	7.32–56.55, 436.38)	0.02
Fluconazole [M] (16.41, 142)	KR	Sertraline [L] (2.03, 78)	PR	B	Moderate	Yes	9	0.34	2.72	2.56–42.41, 323.13)	0.01
Amiodarone [H] (48.53, 524)	KR	Dofetilide [H] (53.53, 124)	KR	D	Major	No	9	0.39	2.84	4.51 (236.84, 1881.14)	0.06
Amiodarone [H] (48.53, 524)	KR	Hydroxychloroquine [L] (4.30, 101)	KR	C	Major	No	9	0.18	2.30	2.14 (102.23, 802.36)	0.02
Amiodarone [H] (48.53, 524)	KR	Erythromycin [M] (10.37, 37)	KR	X	Major	No	8	1.41	6.04	7.30 (348.50, 2431.80)	0.11
Cisapride [H] (296.27, 82)	KR	Metronidazole [L] (3.95, 42)	PR	C	Moderate	No	8	0.72	3.69	3.46–924.28, 6474.28)	0.26
Amiodarone [H] (48.53, 524)	KR	Azithromycin [M] (7.75, 78)	KR	D	Major	No	8	0.48	3.05	3.07 (146.61, 1014.39)	0.04

Hydroxychloroquine [L] (4.30, 101)	KR	Quinine [H] (6.31, 9)	PR	C	Major	No	7	2.68	25.43	75.71□476.84, 2861.53)	0.18
Dofetilide [H] (53.53, 124)	KR	Oxaliplatin [L] (1.84, 16)	KR	C	Major	No	7	2.45	15.66	39.34□2066.32, 12443.2)	0.76
Clarithromycin [M] (12.82, 103)	KR	Olanzapine [M] (4.45, 101)	PR	C	Moderate	No	7	1.95	9.14	18.45□235.4, 1406.09)	0.08
Amiodarone [H] (48.53, 524)	KR	Cisapride [H] (296.27, 82)	KR	D	Major	No	7	1.45	6.22	8.70 (2324.61, 14000.22)	0.77
Flecainide [M] (28.01, 78)	KR	Quetiapine [M] (5.88, 231)	PR	C	Moderate	No	7	0.79	3.87	4.69 (130.05, 771.01)	0.04
Methadone [H] (28.34, 312)	KR	Moxifloxacin [M] (17.34, 128)	KR	X	Major	No	7	1.38	5.92	11.23 (315.20, 1887.12)	0.10
Amiodarone [H] (48.53, 524)	KR	Haloperidol [H] (13.96, 114)	KR	D	Major	No	7	0.20	2.36	2.95 (140.88, 836.34)	0.03
Lopinavir [L] (3.42, 17)	PR	Methadone [H] (28.34, 312)	KR	C	Major	No	6	0.77	3.82	4.65□130.63, 646.96)	0.04
Cisapride [H] (296.27, 82)	KR	Ondansetron (10.40, 211)	KR	D	Major	No	6	0.61	3.39	3.98 (1062.43, 5340.01)	0.30
Itraconazole [L] (11.35, 25)	PR	Methadone [H] (28.34, 312)	KR	X	Major	Yes	6	2.31	17.09	70.98□1992.06, 10022.14)	0.74
Erythromycin [M] (10.37, 37)	KR	Haloperidol [H] (13.96, 114)	KR	C	Major	No	6	1.52	6.80	16.63□230.96, 1152.29)	0.08
Dronedarone [H] (23.16, 51)	KR	Levofloxacin (6.63, 116)	KR	X	Major	No	6	1.99	10.57	26.69□612.94, 3076.13)	0.22
Amiodarone [H] (48.53, 524)	KR	Quinine [H] (6.31, 9)	PR	D	Major	No	6	1.64	7.51	11.91□569.16, 2855.62)	0.20
Azithromycin [M] (7.75, 78)	KR	Methadone [H] (28.34, 312)	KR	D	Major	No	5	0.76	3.87	6.48 (181.88, 727.07)	0.06
Moxifloxacin [M] (17.34, 128)	KR	Sotalol [H] (76.65, 221)	KR	X	Major	No	5	0.65	3.55	5.74 (428.30, 1724.28)	0.13
Ciprofloxacin [I] (11.45, 200)	KR	Clofazimine [M] (8.47, 8)	PR	B	Moderate	No	5	1.55	7.78	19.39□221.29, 886.54)	0.08
Haloperidol [H] (13.96, 114)	KR	Saquinavir [M] (8.49, 5)	PR	X	Major	No	5	2.15	28.64	191.17 (2655.47, 10737.23)	1.00
Azithromycin [M] (7.75, 78)	KR	Sotalol [H] (76.65, 221)	KR	D	Major	No	4	0.34	2.85	4.74 (353.98, 1076.48)	0.10
Fluoxetine [L] (10.42, 234)	PR	Moxifloxacin [M] (17.34, 128)	KR	B	Major	No	4	0.12	2.32	5.36 (92.34, 275.69)	0.03
Methadone [H] (28.34, 312)	KR	Metronidazole [L] (3.95, 42)	PR	C	Moderate	Yes	4	0.19	2.48	4.03□112.97, 338.82)	0.03
Mirtazapine [L] (3.68, 59)	PR	Vemurafenib [M] (2.32, 7)	PR	B	Major	No	4	1.70	19.78	120.39□442.47, 1347.34)	0.17
Escitalopram [M] (6.36, 146)	KR	Vemurafenib [M] (2.32, 7)	PR	C	Major	No	4	1.57	12.13	47.8□303.41, 921.7)	0.11
Hydroxyzine [L] (6.20, 59)	PR	Saquinavir [M] (8.46, 5)	PR	B	Major	No	4	1.72	23.58	139.45□1179.93, 3604.56)	0.44
Amiodarone [H] (48.53, 524)	KR	Quinidine [H] (5.35.9)	KR	D	Major	Yes	4	0.13	2.34	3.42□163.37, 493.09)	0.04
Methadone [H] (28.34, 312)	KR	Saquinavir [M] (8.49, 5)	PR	D	Major	No	4	1.57	12.09	47.3□1327.42, 4056.01)	0.49
Citalopram [M] (13.24, 299)	KR	Terbutaline [M] (5.00, 5)	NA	C	Major	No	4	1.10	5.83	12.39□163.37, 493.09)	0.06
Fluconazole [M] (16.41, 142)	KR	Sevoflurane [M] (30.22, 44)	KR	C	Moderate	Yes	4	1.23	6.77	23.68□707.96, 2159.94)	0.25
Ciprofloxacin [I] (11.45, 200)	KR	Vemurafenib [M] (2.32, 7)	PR	B	Major	No	4	1.56	11.70	44.32□505.69, 1540.82)	0.19
Amitriptyline [L] (5.38, 87)	PR	Erythromycin [M] (10.37, 37)	KR	B	Moderate	No	4	0.33	2.83	5.97□61.74, 182.04)	0.02

Amiodarone [H] (48.53, 524)	KR	Ritonavir (2.98, 40)	PR	X	Major	No	3	0.03	2.37	4.39□209.54, 431.43)	0.06
Chloroquine [M] (18.14, 13)	KR	Halofantrine [M] (723.61, 3)	KR	C	Major	No	3	1.15	17.15	3.50 (1990.68, 4140.92)	0.75
Citalopram [M] (13.24, 299)	KR	RaNolazine [L] (10.57, 41)	PR	B	Major	No	3	0.02	2.32	7.46 (98.30, 199.77)	0.03
Flecainide [M] (28.01, 78)	KR	Moxifloxacin [M] (17.34, 128)	KR	C	Major	No	3	0.78	5.62	26.1□723.88, 1502.61)	0.26
Amiodarone [H] (48.53, 524)	KR	Lopinavir [L] (3.42, 17)	PR	D	Major	No	3	0.66	4.72	11.91□568.76, 1179.55)	0.20
Chlorpromazine [H] (5.40, 11)	KR	Clarithromycin [M] (12.82, 103)	KR	X	Moderate	No	3	0.98	8.28	41.61□530.85, 1100.58)	0.19
Flecainide [M] (28.01, 78)	KR	RaNolazine [L] (10.57, 41)	PR	B	Moderate	No	3	0.73	5.19	19.14□530.85, 1100.58)	0.19
Escitalopram [M] (6.36, 146)	KR	ofloxacin (2.96, 4)	PR	B	Major	No	3	0.96	7.87	30.6□194.21, 399.5)	0.07
Pimozide [M] (28.80, 5)	KR	Risperidone [M] (3.43, 106)	PR	X	Major	No	3	0.11	2.55	3.04□86.55, 175.29)	0.03

CredibleMeds® risk category: KR, known risk of TdP; PR, possible of TdP; CR, conditional of TdP; No, uncategorized in CredibleMed®. Lexicomp® Risk Category: H, QT-prolonging agents (Highest Risk) interacting drug; M, QT-prolonging agents (Moderate Risk - Avoid) interacting drug; L, QT-prolonging agents (Low Risk - Avoid) interacting drug; I, QT-prolonging Agents (Indeterminate Risk - Avoid) interacting drug. Lexicomp® Risk Rating: X, Avoid combination; D, Consider therapy modification; C, Monitor therapy; B, No action needed. Literature Database: Yes or NO, presence or absence of Drug 1 and Drug 2 combinations in the open database of drug-related TdP case literature. Ω_{025}, the signal value of the Ω Shrinkage measure model. AM, the signal value of the Additive model. CRR, Combination risk ratio. PRR, proportional reporting ratio of drug D1 ∩ drug D2. χ^2, Chi-squared of drug D1 ∩ drug D2. χ, the signal value of the Chi-square statistics model.

Table 8. 38 DDIs for Torsades des Pointes (indexed by Drugs.com® and Lexicomp®, n_{111}≥3, but not detected by any of the four models)

Drug 1 (ROR, N)	Drug 1 Drugs.com® Risk Category	Drug 2 (ROR, N)	Drug 2 Drugs.com® Risk Category	Combination Risk Category		Literature Database	Cases (n_{111})	Ω_{025}	X^2	CRR (PRR, χ^2)	AM
				Lexicomp®	Drugs.com®						
Citalopram [M] (23.72, 143)	KR	Omeprazole (3.92, 32)	CR	D	Major	No	23	-0.90	-1.18	0.81 (10.69, 191.43)	0.00
Methadone [H] (53.91, 159)	KR	Quetiapine [M] (5.37, 114)	CR	X	Major	Yes	19	-0.71	-0.33	1.03 (28.87, 481.76)	0.00
Haloperidol [H] (18.08, 54)	KR	Risperidone [M] (2.10, 43)	CR	C	Major	No	16	-1.34	-1.95	0.75 (10.34, 125.39)	0.00
Escitalopram [M] (11.96, 62)	KR	Quetiapine [M] (5.37, 114)	CR	C	Major	Yes	14	-1.21	-1.38	1.20 (7.59, 73.48)	0.00
Dofetilide [H] (54.10, 100)	KR	Furosemide (30.93, 141)	CR	D	Major	Yes	10	-1.17	-0.81	0.90 (47.22, 406.57)	0.00
Amiodarone [H] (58.48, 233)	KR	Sertraline [L] (2.03, 78)	CR	C	Major	No	10	-0.97	-0.36	0.85 (40.40, 345.19)	0.00
Ciprofloxacin [I] (11.25, 103)	KR	Fluconazole [M] (41.16, 93)	KR	B	Moderate	No	7	-2.30	-2.61	0.65 (10.59, 51.54)	-0.01
Amiodarone [H] (58.48, 233)	KR	Sotalol [H] (255.06, 117)	KR	D	Major	Yes	7	-2.50	-3.02	0.52 (39.23, 223.69)	-0.03
Citalopram [M] (23.72, 143)	KR	Risperidone [M] (2.10, 43)	CR	C	Major	No	6	-2.18	-2.07	0.52 (6.90, 24.62)	0.00
Amiodarone (58.48, 233)	KR	Flecainide [M] (57.13, 32)	KR	D	Major	No	6	-2.04	-1.81	0.73 (34.64, 169.07)	-0.01
Azithromycin [M] (8.84, 39)	KR	Ciprofloxacin [I] (11.25, 103)	KR	B	Moderate	Yes	6	-1.52	-0.88	1.14 (12.97, 54.77)	0.00
Olanzapine [M] (4.47, 56)	CR	Risperidone [M] (2.10, 43)	CR	C	Moderate	No	6	-2.81	-3.28	0.48 (2.13, 2.55)	0.00

Fluconazole [M] (41.16, 93)	KR	Metronidazole [L] (3.25, 14)	CR	B	Moderate	No	4	-2.38	-1.70	0.55 (8.96, 20.88)	0.00
Amiodarone [H] (58.48, 233)	KR	Dronedarone [H] (30.38, 44)	KR	D	Major	No	4	-2.24	-1.50	0.69 (32.88, 93.75)	-0.01
Haloperidol [H] (18.80, 54)	KR	Sertraline [L] (2.03, 78)	CR	C	Major	No	4	-1.88	-0.96	0.73 (10.07, 24.24)	0.00
Levofloxacin [I] (9.25, 86)	KR	Metronidazole [L] (3.25, 14)	CR	B	Moderate	No	4	-2.00	-1.15	0.88 (5.81, 11.48)	0.00
Citalopram [M] (23.72, 143)	KR	Loperamide [L] (53.19, 260)	CR	B	Moderate	No	4	-2.56	-1.97	0.56 (15.78, 41.55)	-0.01
Risperidone [M] (2.10, 43)	CR	Ziprasidone [H] (11.59, 34)	CR	D	Major	No	4	-2.60	-2.05	0.52 (5.16, 9.58)	0.00
Citalopram [M] (23.72, 143)	KR	Fluoxetine [L] (13.05, 87)	CR	D	Major	No	3	-3.52	-2.86	0.39 (5.10, 6.21)	-0.01
Amiodarone [H] (58.48, 233)	KR	Formoterol [L]	NA	C	Moderate	No	3	-2.70	-1.69	0.38 (18.26, 33.20)	-0.01
Azithromycin [M] (8.84, 39)	KR	Levofloxacin [I] (9.25, 86)	KR	C	Moderate	No	3	-2.58	-1.54	0.80 (6.16, 8.32)	0.00
Ciprofloxacin [I] (11.25, 103)	KR	Erythromycin [M] (17.76, 26)	KR	B	Moderate	No	3	-1.90	-0.66	1.37 (15.67, 27.84)	0.00
Escitalopram [M] (11.96, 62)	KR	Hydroxyzine [L] (21.68, 22)	CR	B	Major	No	3	-2.37	-1.26	0.98 (6.22, 8.44)	0.00
Fluphenazine [L] (40.10, 5)	NA	Haloperidol [H] (18.80, 54)	KR	C	Major	No	3	-2.50	-1.44	0.66 (29.27, 56.07)	-0.01
Clarithromycin [M] (15.61, 63)	KR	Levofloxacin [I] (9.25, 86)	KR	C	Moderate	No	3	-2.74	-1.75	0.59 (7.58, 11.17)	0.00
Olanzapine [M] (4.47, 56)	CR	Ziprasidone [H] (11.59, 34)	CR	D	Moderate	No	3	-3.50	-2.83	0.35 (3.48, 3.11)	0.00
Amiodarone [H] (58.48, 233)	KR	Salmeterol [L]	NA	C	Moderate	No	3	-2.67	-1.66	0.39 (18.60, 33.91)	-0.01
Chlorpromazine [H] (5.40, 11)	KR	Olanzapine [M] (4.47, 56)	CR	D	Moderate	No	3	-1.87	-0.63	1.25 (6.72, 9.45)	0.00
Flecainide [M] (57.13, 32)	KR	Sotalol [H] (255.06, 117)	KR	D	Major	Yes	3	-2.94	-2.03	0.46 (34.62, 67.19)	-0.02
Fluoxetine [L] (13.05, 87)	CR	Sotalol [H] (255.06, 117)	KR	C	Major	No	3	-1.61	-0.30	1.06 (78.84, 159.23)	0.00
Citalopram [M] (23.72, 143)	KR	Salmeterol [L]	NA	B	Moderate	No	3	-2.37	-1.26	0.52 (6.86, 9.72)	0.00
Fluconazole [M] (41.16, 93)	KR	Ondansetron (42.06, 109)	KR	C	Moderate	No	3	-3.83	-3.36	0.30 (4.84, 5.70)	-0.01
Quetiapine [M] (5.37, 114)	CR	Risperidone [M] (2.10, 43)	CR	C	Moderate	No	3	-4.75	-5.06	0.15 (0.87, 0.00)	0.00
Chlorpromazine [H] (5.40, 11)	KR	Risperidone [M] (2.10, 43)	CR	D	Moderate	No	3	-1.65	-0.35	1.30 (7.00, 10.01)	0.00

CredibleMeds® risk category: KR, known risk of TdP; PR, possible of TdP; CR, conditional of TdP; No, uncategorized in CredibleMed®. Lexicomp® Risk Category: H, QT-prolonging agents (Highest Risk) interacting drug; M, QT-prolonging agents (Moderate Risk - Avoid) interacting drug; L, QT-prolonging agents (Low Risk - Avoid) interacting drug; I, QT-prolonging Agents (Indeterminate Risk - Avoid) interacting drug. Lexicomp® Risk Rating: X, Avoid combination; D, Consider therapy modification; C, Monitor therapy; B, No action needed. Literature Database: Yes or NO, presence or absence of Drug 1 and Drug 2 combinations in the open database of drug-related TdP case literature. $\Omega_{025,}$ the signal value of the Ω Shrinkage measure model. AM, the signal value of the Additive model. CRR, Combination risk ratio. PRR, proportional reporting ratio of drug D1 ∩ drug D2. χ^2, Chi-squared of drug D1 ∩ drug D2. χ, the signal value of the Chi-square statistics model.

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Shariff, A., et al. (2021). "Assessing Consistency of Drug-Drug Interaction-Related Information Across Various Drug Information Resources." Cureus 13(3): e13766.

Background Information related to drug-drug interactions (DDIs) varies significantly from one drug information (DI) resource to another. These variations pose challenges for healthcare professionals in making the right decisions regarding using some of the drug combinations in needy patients. The objective of this study was to review eight different DI resources for scope, completeness, and consistency of information related to DDIs. Methodology A total of eight DI resources, namely, Micromedex(®), Portable Electronic Physician Information Database(©), UpToDate(®), Medscape.com drug interaction checker, Drugs.com drug interaction checker, Stockley's Drug Interactions (ninth edition, 2010), Drug Interactions Analysis & Management: Facts and Comparisons 2014 (ninth edition, 2014), and the drug interaction appendix of the British National Formulary-76, were compared. Each DI resource was scored for scope by calculating the percentage of interactions that had an entry in each resource. A completeness score was calculated for each resource describing severity, clinical effects, mechanism, and DDI management. The consistency of the information was assessed using Fleiss Kappa (k) score estimated using ReCal3 0.1 (alpha) web service and Statistical Package for the Social Sciences version 24. Results The scope score was the highest (100%) for UpToDate(®) and Portable Electronic Physician Information Database(©), whereas the completeness score was the highest (100%) for Drug Interaction Analysis & Management: Facts and comparisons 2014. The inter-source reliability scores among the eight different DI sources were poor ($k < 0.20$, $p < 0.05$) for documentation of information related to severity, clinical effects, mechanism, and management of DDIs. Conclusions Variations in the information cause uncertainty among healthcare professionals concerning interacting drug pairs in clinical practice. This may also increase the possibility of adverse drug outcomes when interacting drug pairs are used in at-risk patients. We recommend comprehensive

drug not only induces adverse events (AEs) but also increases the risk of AEs due to drug-drug interactions (DDIs). The proportion of AEs caused by DDIs is estimated to be around 30% of unexpected AEs. The randomized clinical trials in pre-marketing typically focus emphasis on the verification of single drug safety and efficacy rather than the surveys of DDI, and therefore, patients on multiple drugs are usually excluded. However, unlike pre-marketing randomized clinical trials, in clinical practice (= post marketing), many patients use multiple drugs. The spontaneous reporting system is one of the significant sources drug safety surveillance in post-marketing. Commonly, signals of potential drug-induced AEs detected from this source are validated in real-world settings. Recently, not only methodological studies on signal detection of "single" drug, but also on several methodological studies on signal detection of DDIs have been conducted. On the other hand, there are few articles that systematically summarize the statistical methodology for signal detection of DDIs. Therefore, this article reviews the studies on the latest statistical methodologies from classical methodologies for signal detection of DDIs using spontaneous reporting system. This article describes how to calculate for each detection method and the major findings from the published literatures about DDIs. Finally, this article presented several limitations related to the currently used methodologies for signal detection of DDIs and suggestions for further studies.

Noguchi, Y., et al. (2021). "Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source." Brief Bioinform 22(6).

Continuous evaluation of drug safety is needed following approval to determine adverse events (AEs) in patient populations with diverse backgrounds. Spontaneous reporting systems are an important source of information for the detection of AEs not identified in clinical trials and for safety assessments that reflect the real-world use of drugs in specific populations and clinical settings. The use of spontaneous reporting systems is expected to detect drug-related AEs early after the launch of a new drug. Spontaneous reporting systems do not contain data on the total number of patients that use a drug; therefore, signal detection by disproportionality analysis, focusing on differences in the ratio of AE reports, is frequently used. In recent years, new analyses have been devised, including signal detection methods focused on the difference in the time to onset of an AE, methods that consider the patient background and those that identify drug-drug interactions. However, unlike commonly used statistics, the results of these analyses are open to misinterpretation if the method and the characteristics of the spontaneous reporting system cannot be evaluated properly. Therefore, this review describes signal detection using data mining, considering traditional methods and the latest knowledge, and their limitations.

Norén, G. N., et al. (2008). "A statistical methodology for drug-drug interaction surveillance." Stat Med 27(16): 3057-3070.

Interaction between drug substances may yield excessive risk of adverse drug reactions (ADRs) when two drugs are taken in combination. Collections of individual case safety reports (ICSRs) related to suspected ADR incidents in clinical practice have proven to be very useful in post-marketing surveillance for pairwise drug--ADR associations, but have yet to reach their full potential for drug-drug interaction surveillance. In this paper, we implement and evaluate a shrinkage observed-to-expected ratio for exploratory analysis of suspected drug-drug interaction in ICSR data, based on comparison with an additive risk model. We argue that the limited success of previously proposed methods for drug-drug interaction detection based on ICSR data may be due to an underlying assumption that the absence of interaction is equivalent to having multiplicative risk factors. We provide empirical examples of established drug-drug interaction highlighted with our proposed approach that go undetected with logistic regression. A database wide screen for suspected drug-drug interaction in the entire WHO database is carried out to demonstrate the feasibility of the proposed approach. As always in the analysis of ICSRs, the clinical validity of hypotheses raised with the proposed method must be further reviewed and evaluated by subject matter experts.

Noguchi, Y., et al. (2020). "Comparison of Signal Detection Algorithms Based on Frequency Statistical Model for Drug-Drug Interaction Using Spontaneous Reporting Systems." Pharm Res 37(5): 86.

"suspect drugs" in JADER, and the AEs targeted for this study were the same as those in a previous study on Stevens-Johnson syndrome (SJS). RESULTS: Of 3924 pairs that reported SJS, the number of signals detected by the Ω shrinkage measure, additive, multiplicative, combination risk ratio, and chi-square statistics models was 712, 3298, 2252, 739, and 1289 pairs, respectively. Among the five models, the Ω shrinkage measure model showed the most conservative signal detection tendency. CONCLUSION: Specifically, caution should be exercised when the number of reports is low because results differ depending on the statistical models. This study will contribute to the selection of appropriate statistical models to detect signals of potential DDIs.

Thakrar, B. T., et al. (2007). "Detecting signals of drug-drug interactions in a spontaneous reports database." Br J Clin Pharmacol 64(4): 489-495.

AIMS: The spontaneous reports database is widely used for detecting signals of ADRs. We have extended the methodology to include the detection of signals of ADRs that are associated with drug-drug interactions (DDI). In particular, we have investigated two different statistical assumptions for detecting signals of DDI. METHODS: Using the FDA's spontaneous reports database, we investigated two models, a multiplicative and an additive model, to detect signals of DDI. We applied the models to four known DDIs (methotrexate-diclofenac and bone marrow depression, simvastatin-ciclosporin and myopathy, ketoconazole-terfenadine and torsades de pointes, and cisapride-erythromycin and torsades de pointes) and to four drug-event combinations where there is currently no evidence of a DDI (fexofenadine-ketoconazole and torsades de pointes, methotrexade-rofecoxib and bone marrow depression, fluvastatin-ciclosporin and myopathy, and cisapride-azithromycine and torsade de pointes) and estimated the measure of interaction on the two scales. RESULTS: The additive model correctly identified all four known DDIs by giving a statistically significant ($P < 0.05$) positive measure of interaction. The multiplicative model identified the first two of the known DDIs as having a statistically significant or borderline significant ($P < 0.1$) positive measure of interaction term, gave a nonsignificant positive trend for the third interaction ($P = 0.27$), and a negative trend for the last interaction. Both models correctly identified the four known non interactions by estimating a negative measure of interaction. CONCLUSIONS: The spontaneous reports database is a valuable resource for detecting signals of DDIs. In particular, the additive model is more sensitive in detecting such signals. The multiplicative model may further help qualify the strength of the signal detected by the additive model.

Gosho, M., et al. (2017). "Utilization of chi-square statistics for screening adverse drug-drug interactions in spontaneous reporting systems." Eur J Clin Pharmacol 73(6): 779-786.

PURPOSE: We proposed a statistical criterion to detect drug-drug interactions causing adverse drug reactions in spontaneous reporting systems. METHODS: The used criterion quantitatively measures the discrepancy between the observed and expected number of adverse events via chi-square statistics. We compared the performance of our method with that of Norén et al. (Stat Med 2008; 27 (16): 3057-3070) through a simulation study. RESULTS: When the number of events for a combination of two drugs was equal to or lower than two, the false positive rate for our method ranged from 0.01 to 0.08, whereas the rate for Norén's method ranged from 0.01 to 0.06. The sensitivity for our method ranged from 0.09 to 0.29, whereas the sensitivity for Norén's method ranged from 0.03 to 0.24. The area-under-the-receiver operating characteristic curve for our method was significantly larger than that for Norén's methods regardless of simulation settings. The proposed method was also applied to the Food and Drug Administration Adverse Event Reporting System database, and a recognized drug-drug interaction was detected. CONCLUSIONS: The proposed criterion controlled false positives at an acceptable level and had higher sensitivity than that of Norén's method had when events were rare.

Matsuo, J. and S. Yamaori (2022). "Detecting drug-drug interactions that increase the incidence of long QT syndrome using a spontaneous reporting system." J Clin Pharm Ther 47(1): 70-80.

requiring precaution for concomitant use in at least one of the package inserts in Japan, the United States and the United Kingdom, respectively, although no such precautions were described for the remaining combinations. On the contrary, a combination of bepridil & clarithromycin was categorized as "X (avoid combination)" and two combinations (chlorpromazine & haloperidol, amiodarone & metildigoxin) were classified as "D (modify regimen)" in the Lexicomp(®) risk rating. WHAT IS NEW AND CONCLUSION: This study identified 31 combinations of drugs that may elevate the risk of diLQTS. The use of these drug combinations should be monitored more carefully in future.

Landerholm, A., et al. (2023). "C-L Case Conference: Torsades de Pointes in a Patient With Lifelong Medical Trauma, COVID-19, Remdesivir, Citalopram, Quetiapine, and Hemodialysis." J Acad Consult Liaison Psychiatry 64(2): 147-157.

We present a case of Torsades de Pointes (TdP) in a patient with COVID-19 infection and multiple TdP risk factors including QT-interval prolongation, hemodialysis, bradycardia, and treatment with remdesivir, citalopram, and quetiapine. The case was complicated by post-resuscitation anxiety superimposed on a history of medical trauma since childhood. Top experts in the field of consultation-liaison psychiatry, trauma informed care, and cardiac electrophysiology provide perspectives on this case with a review of the literature. Key teaching topics include identification of TdP risk factors in patients with a complex illness; the necessity for prompt electrophysiology consultation in clinical scenarios with high risk for TdP; and the approach to patients with medical trauma using a trauma-informed lens. We highlight the contributions of COVID-19, the pharmacokinetics of QT-interval-prolonging psychotropic medications, the risks of hemodialysis, and the role of remdesivir-induced bradycardia in this first reported case of TdP in a patient treated with remdesivir.

Devaux, F., et al. (2019). "[Torsade de pointe resulting from a drug interaction between sotalol and ciprofloxacin]." Rev Med Liege 74(7-8): 382-387.

Sotalol is a bêta-blocker and class 3 anti-arrhythmic. Ciprofloxacin is a fluoroquinolone antibiotic used against Gram - germs. Both drugs have a common adverse effect : they increase QT interval with a risk of torsade de pointe. The risk increases even more if other risk factors are present such as old age, female gender, renal failure, high blood pressure and ionic disturbances. Because a long QT interval is not associated with symptoms, only an electrocardiogram can establish the diagnosis. However, it's not rare that a torsade de pointe will reveal it. We report a clinical case of a long QT interval due to the association of sotalol and ciprofloxacin, which led to a torsade de pointe. Intravenous magnesium sulphate is the recommended treatment if haemodynamic parameters are good. If not, an external electric shock may be needed.

Wei, A., et al. (2017). "QTc prolongation and torsades de pointes due to a coadministration of fluoxetine and amiodarone in a patient with implantable cardioverter-defibrillator: Case report and review of the literature." Medicine (Baltimore) 96(49): e9071.

RATIONALE: Drug-induced prolongation of the corrected QT interval (QTc) may lead to serious and potentially life-threatening ventricular tachyarrhythmia, such as torsades de pointes (Tdp), which is worthy of clinical attention. Here, we report 1 case of Tdp after a coadministration of fluoxetine and amiodarone. PATIENT CONCERNS: A 62-year-old Chinese male who placed with the implanted cardioverter-defibrillator (ICD) appeared the QTc prolongation and Tdp after the concurrent administration of fluoxetine and amiodarone. DIAGNOSES: Torsades de pointes (Tdp). INTERVENTIONS: The patient was treated with magnesium and potassium immediately. Her ICD-brady pacing mode was reprogrammed to 90 bpm. Meanwhile, both of fluoxetine and amiodarone were discontinued. OUTCOMES: The further episodes of Tdp were prevented. After a few days, the QTc gradually decreased without clinically significant arrhythmias. LESSONS: The present case demonstrates that a potential drug-drug interaction (DDI) may lead to a

BACKGROUND: Acquired prolonged corrected QT (QTc) interval can lead to life-threatening Torsade de Pointes (TdP) arrhythmia. Multiple risk factors including medications, comorbidities, and electrolyte imbalances contribute significantly to acquired manifestations of the QTc prolongation. Critically ill patients are particularly more vulnerable to TdP due to complex medical conditions, aging, and polypharmacy. OBJECTIVE: This study aimed to assess the prevalence of TdP-associated medication prescribing, identify risk factors for QTc prolongation and TdP, and determine primary predictors of high TdP medication usage in critically ill patients in Jordan. METHODS: We conducted a retrospective cross-sectional analysis of electronic medical records for patients from King Abdullah University Hospital who were admitted to Intensive Care Unit (ICU) between (July 2012-July 2022). We collected data on patients' demographics, clinical characteristics, comorbidities, laboratory results, and prescribed medications. Medications were categorized into three TdP risk levels according to CredibleMeds(®) assessment tool. Data were analyzed using descriptive statistics and a binary logistic regression model. RESULTS: Of the 13,300 patients (58.2% male, median age 62 years). Prescribing prevalence for medications with known TdP risk was 19%, possible risk (24.7%), conditional risk (21.6%), and confirmed conditional risk (8.3%). Common comorbidities included hypertension (40.9%), diabetes (33.3%), and cancer (15.4%). Drugs with known TdP risk included citalopram, amiodarone, clarithromycin, and ciprofloxacin. A binary regression model revealed that as age increased, the odds of TdP associated medication prescribing decreased (OR = 0.989, $p < 0.001$), while patients on more than five medications had higher odds (OR = 4.281, $p < 0.001$). CONCLUSION: The study identified a notable prevalence of prescribing for medications with QTc prolongation/TdP risk in critically ill patients. Healthcare providers in the ICU should exercise caution to minimize the inadvertent prescription of TdP associated medications especially among older patients and those with polypharmacy.

Khederlou, H. and V. Azimi Pirsaraei (2024). "Torsades de Pointe Associated with Trazodone Consumption." Case Rep Crit Care 2024: 5759229.

INTRODUCTION: Trazodone is a serotonin receptor antagonist and reuptake inhibitor commonly used to treat major depression disorder (MDD), anxiety, and sleep disorders. It is considered safe for the heart due to minimal anticholinergic effects. Prolonged QT intervals can cause polymorphic ventricular tachycardia, known as torsades de pointe (TdP). We present a case of a 67-year-old female with a history of MDD who developed trazodone-induced TdP. Case Presentation. The patient was referred to a tertiary hospital with a ten-hour history of nausea and vomiting. Trazodone (50 mg daily) was started for her six days ago due to her past medical history of MDD. The initial electrocardiography (ECG) revealed a prolonged corrected QT interval (QTc = 586 ms) due to a long ST segment and generalized T wave inversion. A few moments after admission to the intensive care unit, she suddenly lost consciousness. ECG monitoring showed a TdP, which terminated immediately with the asynchronous defibrillation. A temporary pacemaker was implanted due to repeated arrhythmias and bradycardia. Arrhythmia did not recur for hours and days later. After four days of stopping trazodone, all abnormal ECG findings were resolved, and she was discharged with a normal ECG. She was followed up six months later; the ECG was normal, and she had no complaints. CONCLUSION: Trazodone may lead to QTc prolongation and TdP, potentially fatal even without risk factors for QTc prolongation. Close monitoring is essential to prevent adverse complications in trazodone users.

Wang, L., et al. (2023). "Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder." J Clin Psychol 79(12): 2869-2883.

IMPORTANCE: More than 109,000 Americans died of drug overdose in 2022, with 81,231 overdose deaths involving opioids. Methadone, buprenorphine and naltrexone are the most widely used medications for opioid use disorders (MOUD) and the most effective intervention for preventing overdose deaths. However, there is a concern that methadone results in long QT syndrome, which increases the risk for fatal cardiac arrythmias. Currently few studies have systematically evaluated both the short-term and long-term differences in cardiac and mortality outcomes between MOUD. OBJECTIVES: To compare the risks of cardiac arrythmias, long QT syndrome and overall mortality between patients with opioid use disorders (OUD) who were prescribed methadone, buprenorphine or naltrexone. DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study based on a multicenter and nationwide database of electronic health records (EHRs) in the United States. The study population was comprised of 144,141 patients who

syndrome and death compared with propensity-score matched patients with OUD who were prescribed buprenorphine or naltrexone. For the 1-month follow-up, the overall risk for cardiac arrythmias was 1.03% in the Methadone cohort, higher than the 0.87% in the matched Buprenorphine cohort (HR: 1.20, 95% CI: 1.04-1.39); The overall risk for long QT syndrome was 0.35% in the Methadone cohort, higher than the 0.15% in the matched Buprenorphine cohort (HR: 2.40, 95% CI: 1.75-3.28); The overall mortality was 0.59% in the Methadone cohort, higher than the 0.41% in the matched Buprenorphine cohort (HR: 1.48, 95% CI: 1.21-1.81). The increased risk persisted for 5 years: cardiac arrhythmias (HR: 1.31, 95% CI: 1.23-1.38), long QT syndrome (HR: 3.14, 95% CI: 2.76-3.58), death (HR: 1.50, 95% CI: 1.41-1.59). CONCLUSIONS AND RELEVANCE: Methadone was associated with a significantly higher risk for cardiac and mortality outcomes than buprenorphine and naltrexone. These findings are relevant to the development of guidelines for medication selection when initiating MOUD treatment and inform future medication development for OUD that minimizes risks while maximizing benefits.

Nair, M. K., et al. (2008). "Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient." Addiction 103(12): 2062-2064.

ABSTRACT Background Methadone has been associated with QT prolongation and Torsades de pointes. Ciprofloxacin may prolong QT interval and induce Torsades de pointes when other risk factors are present. Case description A case is described in which a patient receiving methadone treatment developed Torsades de pointes following the addition of ciprofloxacin. Conclusion Ciprofloxacin should be used with caution in patients receiving methadone.

NoorZurani, M. H., et al. (2009). "Itraconazole-induced torsade de pointes in a patient receiving methadone substitution therapy." Drug Alcohol Rev 28(6): 688-690.

ISSUES: Methadone, a pharmacological agent used to treat heroin dependence is relatively safe, but may cause cardiac arrhythmias in the concurrent presence of other risk factors. APPROACH AND KEY FINDINGS: This case report highlights the risk of torsade de pointes, a life-threatening cardiac arrhythmia, in a heroin-dependent patient receiving methadone substitution therapy who was prescribed itraconazole for vaginal thrush. The patient presented to the accident and emergency department for chest discomfort and an episode of syncope following two doses of itraconazole (200 mg). Electrocardiogram monitoring at the accident and emergency department showed prolonged rate-corrected QT interval leading to torsade de pointes. The patient was admitted for cardiac monitoring, and electrocardiogram returned to normal upon discontinuation of methadone. IMPLICATION: This cardiac arrhythmia was most likely as a result of a drug interaction between methadone and itraconazole because the patient presented with no other risk factors. CONCLUSION: Given the benefits of methadone as a substitution treatment for heroin-dependent individuals, the association between methadone and cardiac arrhythmias is of great concern. Physicians treating heroin-dependent patients on methadone substitution therapy should therefore be cautious of the potential risk of drug interactions that may lead to fatal cardiac arrhythmias.

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Norén, G. N., Sundberg, R., Bate, A., & Edwards, I. R. (2008). A statistical methodology for drug-drug interaction surveillance. Stat Med, 27(16), 3057-3070. doi:10.1002/sim.3247

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Thakrar, B. T., Grundschober, S. B., & Doessegger, L. (2007). Detecting signals of drug-drug interactions in a spontaneous reports database. Br J Clin Pharmacol, 64(4), 489-495. doi:10.1111/j.1365-2125.2007.02900.x

Gosho, M., Maruo, K., Tada, K., & Hirakawa, A. (2017). Utilization of chi-square statistics for screening adverse drug-drug interactions in spontaneous reporting systems. Eur J Clin Pharmacol, 73(6), 779-786. doi:10.1007/s00228-017-2233-3

Matsuo, J., & Yamaori, S. (2022). Detecting drug-drug interactions that increase the incidence of long QT syndrome using a spontaneous reporting system. J Clin Pharm Ther, 47(1), 70-80. doi:10.1111/jcpt.13539

Landerholm, A., Fedotova, N. O., Levy-Carrick, N. C., Chung, R., & Funk, M. C. (2023). C-L Case Conference: Torsades de Pointes in a Patient With Lifelong Medical Trauma, COVID-19, Remdesivir, Citalopram, Quetiapine, and Hemodialysis. J Acad Consult Liaison Psychiatry, 64(2), 147-157. doi:10.1016/j.jaclp.2022.11.001

Devaux, F., Fillet, M., & Krzesinski, F. (2019). [Torsade de pointe resulting from a drug interaction between sotalol and ciprofloxacin]. Rev Med Liege, 74(7-8), 382-387.

Wei, A., Peng, J., Gu, Z., & Li, J. (2017). QTc prolongation and torsades de pointes due to a coadministration of fluoxetine and amiodarone in a patient with implantable cardioverter-defibrillator: Case report and review of the literature. Medicine (Baltimore), 96(49), e9071. doi:10.1097/md.0000000000009071

Al-Azayzih, A., Al-Qerem, W., Al-Azzam, S., Muflih, S., Al-Husein, B. A., Kharaba, Z., . . . Rahhal, D. (2024). Prevalence of Medication Associated with QTc Prolongation Used Among Critically Ill Patients. Vasc Health Risk Manag, 20, 27-37. doi:10.2147/vhrm.S438899

Khederlou, H., & Azimi Pirsaraei, V. (2024). Torsades de Pointe Associated with Trazodone Consumption. Case Rep Crit Care, 2024, 5759229. doi:10.1155/2024/5759229

Wang, L., Volkow, N. D., Berger, N. A., Davis, P. B., Kaelber, D. C., & Xu, R. (2023). Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder. J Clin Psychol, 79(12), 2869-2883. doi:10.1002/jclp.23582

Nair, M. K., Patel, K., & Starer, P. J. (2008). Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient. Addiction, 103(12), 2062-2064. doi:10.1111/j.1360-0443.2008.02390.x

Reference Type: Journal Article
Record Number: 1688
Author: Thakrar, B. T., Grundschober, S. B. and Doessegger, L.
Year: 2007
Title: Detecting signals of drug-drug interactions in a spontaneous reports database
Journal: Br J Clin Pharmacol
Volume: 64
Issue: 4
Pages: 489-95
Epub Date: 20070515
Date: Oct
Short Title: Detecting signals of drug-drug interactions in a spontaneous reports database
ISSN: 0306-5251 (Print)
0306-5251
DOI: 10.1111/j.1365-2125.2007.02900.x
PMCID: PMC2048563
Accession Number: 17506784
Keywords: Adverse Drug Reaction Reporting Systems
Drug Interactions/*physiology
*Drug-Related Side Effects and Adverse Reactions
Models, Chemical

Abstract: AIMS: The spontaneous reports database is widely used for detecting signals of ADRs. We have extended the methodology to include the detection of signals of ADRs that are associated with drug-drug interactions (DDI). In particular, we have investigated two different statistical assumptions for detecting signals of DDI. METHODS: Using the FDA's spontaneous reports database, we investigated two models, a multiplicative and an additive model, to detect signals of DDI. We applied the models to four known DDIs (methotrexate-diclofenac and bone marrow depression, simvastatin-ciclosporin and myopathy, ketoconazole-terfenadine and torsades de pointes, and cisapride-erythromycin and torsades de pointes) and to four drug-event combinations where there is currently no evidence of a DDI (fexofenadine-ketoconazole and torsades de pointes, methotrexade-rofecoxib and bone marrow depression, fluvastatin-ciclosporin and myopathy, and cisapride-azithromycine and torsade de pointes) and estimated the measure of interaction on the two scales. RESULTS: The additive model correctly identified all four known DDIs by giving a statistically significant ($P < 0.05$) positive measure of interaction. The multiplicative model identified the first two of the known DDIs as having a statistically significant or borderline significant ($P < 0.1$) positive measure of interaction term, gave a nonsignificant positive trend for the third interaction ($P = 0.27$), and a negative trend for the last interaction. Both models correctly identified the four known non interactions by estimating a negative measure of interaction. CONCLUSIONS: The spontaneous reports database is a valuable resource for detecting signals of DDIs. In particular, the additive model is more sensitive in detecting such signals. The multiplicative model may further help qualify the strength of the signal

Comparative Study
Journal Article
England
2007/05/18
Br J Clin Pharmacol. 2007 Oct;64(4):489-95. doi: 10.1111/j.1365-2125.2007.02900.x. Epub 2007 May 15.
Author Address: Drug Safety Risk Management, F. Hoffman-La Roche Ltd, Basel, Switzerland. bharat.thakrar@roche.com
Database Provider: NLM
Language: eng

Reference Type: Journal Article
Record Number: 1689
Author: Gosho, M., Maruo, K., Tada, K. and Hirakawa, A.
Year: 2017
Title: Utilization of chi-square statistics for screening adverse drug-drug interactions in spontaneous reporting systems
Journal: Eur J Clin Pharmacol
Volume: 73
Issue: 6
Pages: 779-786
Epub Date: 20170309
Date: Jun
Short Title: Utilization of chi-square statistics for screening adverse drug-drug interactions in spontaneous reporting systems
ISSN: 0031-6970
DOI: 10.1007/s00228-017-2233-3
Accession Number: 28280890
Keywords: *Adverse Drug Reaction Reporting Systems
Chi-Square Distribution
Computer Simulation
Databases, Factual/statistics & numerical data
*Drug Interactions
Drug-Related Side Effects and Adverse Reactions/*diagnosis/epidemiology

United States Food and Drug Administration
Adverse event reporting system
False positive
Sensitivity
Signal detection

Abstract: PURPOSE: We proposed a statistical criterion to detect drug-drug interactions causing adverse drug reactions in spontaneous reporting systems. METHODS: The used criterion quantitatively measures the discrepancy between the observed and expected number of adverse events via chi-square statistics. We compared the performance of our method with that of Norén et al. (Stat Med 2008; 27 (16): 3057-3070) through a simulation study. RESULTS: When the number of events for a combination of two drugs was equal to or lower than two, the false positive rate for our method ranged from 0.01 to 0.08, whereas the rate for Norén's method ranged from 0.01 to 0.06. The sensitivity for our method ranged from 0.09 to 0.29, whereas the sensitivity for Norén's method ranged from 0.03 to 0.24. The area-under-the-receiver operating characteristic curve for our method was significantly larger than that for Norén's methods regardless of simulation settings. The proposed method was also applied to the Food and Drug Administration Adverse Event Reporting System database, and a recognized drug-drug interaction was detected. CONCLUSIONS: The proposed criterion controlled false positives at an acceptable level and had higher sensitivity than that of Norén's method had when events were rare.

Notes: 1432-1041
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Comparative Study
Journal Article
Germany
2017/03/11
Eur J Clin Pharmacol. 2017 Jun;73(6):779-786. doi: 10.1007/s00228-017-2233-3. Epub 2017 Mar 9.
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Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8560, Japan.
Database Provider: NLM
Language: eng

Journal: J Clin Pharm Ther
Volume: 47
Issue: 1
Pages: 70-80
Epub Date: 20211019
Date: Jan
Short Title: Detecting drug-drug interactions that increase the incidence of long QT syndrome using a spontaneous reporting system
ISSN: 0269-4727
DOI: 10.1111/jcpt.13539
Accession Number: 34664726
Keywords: Adverse Drug Reaction Reporting Systems/*statistics & numerical data
Drug Interactions
Humans
Japan
Long QT Syndrome/*chemically induced
Pharmacovigilance
Risk Factors
disproportionality
drug-drug interaction
long QT syndrome
signal detection
spontaneous reporting system

Abstract: WHAT IS KNOWN AND OBJECTIVE: Drug-induced long QT syndrome (diLQTS) is a rare but serious adverse drug reaction. Drug-drug interaction (DDI) is one of the risk factors for the development of diLQTS. However, the combinations of drugs that increase the risk of diLQTS have not been extensively investigated. This study was performed to analyse the potential DDIs that elevate the incidence of diLQTS using a spontaneous reporting system. METHODS: The Japanese Adverse Drug Event Report database from April 2004 to January 2020 was used to assess adverse event reports. We calculated the reporting odds ratio and 95% confidence interval for signal detection. RESULTS AND DISCUSSION: Signals for concomitant use risk were detected in 31 drug combinations. Combinations of antipsychotics and antidepressants were the most common (olanzapine & fluvoxamine, olanzapine & trazodone, quetiapine & paroxetine, sulpiride & fluvoxamine, sulpiride & trazodone). Sixteen, 17 and 21 combinations were designated as requiring precaution for concomitant use in at least one of the package inserts in Japan, the United States and the United Kingdom, respectively, although no such precautions were described for the remaining combinations. On the contrary, a combination of bepridil & clarithromycin was categorized as "X (avoid combination)" and two combinations (chlorpromazine & haloperidol, amiodarone & metildigoxin) were classified as "D (modify regimen)" in the Lexicomp(®) risk rating. WHAT IS NEW AND CONCLUSION: This study identified 31 combinations of drugs that may elevate the risk of diLQTS.

Journal Article
England
2021/10/20
J Clin Pharm Ther. 2022 Jan;47(1):70-80. doi: 10.1111/jcpt.13539. Epub 2021 Oct 19.
Author Address: Department of Pharmacy, Shinshu University Hospital, Matsumoto, Japan.
Department of Biochemical Pharmacology and Toxicology, Graduate School of Medicine, Shinshu University, Matsumoto, Japan.
Database Provider: NLM
Language: eng

Reference Type: Journal Article
Record Number: 1680
Author: Devaux, F., Fillet, M. and Krzesinski, F.
Year: 2019
Title: [Torsade de pointe resulting from a drug interaction between sotalol and ciprofloxacin]
Journal: Rev Med Liege
Volume: 74
Issue: 7-8
Pages: 382-387
Date: Jul
Short Title: [Torsade de pointe resulting from a drug interaction between sotalol and ciprofloxacin]
ISSN: 0370-629X (Print)
0370-629x
Original Publication: Torsade de pointe sur interaction médicamenteuse entre sotalol et ciprofloxacine.
Accession Number: 31373450
Keywords: Anti-Arrhythmia Agents/adverse effects
Anti-Bacterial Agents/adverse effects
*Ciprofloxacin/adverse effects
*Drug Interactions
Electrocardiography
Female

Sotalol
Sudden cardiac death
Ventricular fibrillation
Torsade de pointe
Abstract: Sotalol is a bêta-blocker and class 3 anti-arrhythmic. Ciprofloxacin is a fluoroquinolone antibiotic used against Gram - germs. Both drugs have a common adverse effect : they increase QT interval with a risk of torsade de pointe. The risk increases even more if other risk factors are present such as old age, female gender, renal failure, high blood pressure and ionic disturbances. Because a long QT interval is not associated with symptoms, only an electrocardiogram can establish the diagnosis. However, it's not rare that a torsade de pointe will reveal it. We report a clinical case of a long QT interval due to the association of sotalol and ciprofloxacin, which led to a torsade de pointe. Intravenous magnesium sulphate is the recommended treatment if haemodynamic parameters are good. If not, an external electric shock may be needed.
Notes: Devaux, F
Fillet, M
Krzesinski, F
Case Reports
Journal Article
Belgium
2019/08/03
Rev Med Liege. 2019 Jul;74(7-8):382-387.
Author Address: Faculté de Médecine, ULiège, Belgique..
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Service de Cardiologie, CHR Huy, Belgique.
Database Provider: NLM
Language: fre

Reference Type: Journal Article
Record Number: 1681
Author: Wei, A., Peng, J., Gu, Z. and Li, J.
Year: 2017
Title: QTc prolongation and torsades de pointes due to a coadministration of fluoxetine and amiodarone in a patient with implantable cardioverter-defibrillator: Case report and review of the literature
Journal: Medicine (Baltimore)
Volume: 96
Issue: 49

DOI: 10.1097/md.0000000000009071
Legal Note: The authors report no conflicts of interest in this work.
PMCID: PMC5728935
Accession Number: 29245320
Keywords: Amiodarone/administration & dosage/*adverse effects
Anti-Arrhythmia Agents/administration & dosage/*adverse effects
Cardiomyopathy, Dilated/*therapy
*Defibrillators, Implantable
*Drug Interactions
Electrocardiography
Fluoxetine/administration & dosage/*adverse effects
Humans
Long QT Syndrome/*chemically induced
Male
Middle Aged
Selective Serotonin Reuptake Inhibitors/administration & dosage/*adverse effects
Torsades de Pointes/*chemically induced
Abstract: RATIONALE: Drug-induced prolongation of the corrected QT interval (QTc) may lead to serious and potentially life-threatening ventricular tachyarrhythmia, such as torsades de pointes (Tdp), which is worthy of clinical attention. Here, we report 1 case of Tdp after a coadministration of fluoxetine and amiodarone. PATIENT CONCERNS: A 62-year-old Chinese male who placed with the implanted cardioverter-defibrillator (ICD) appeared the QTc prolongation and Tdp after the concurrent administration of fluoxetine and amiodarone. DIAGNOSES: Torsades de pointes (Tdp). INTERVENTIONS: The patient was treated with magnesium and potassium immediately. Her ICD-brady pacing mode was reprogrammed to 90 bpm. Meanwhile, both of fluoxetine and amiodarone were discontinued. OUTCOMES: The further episodes of Tdp were prevented. After a few days, the QTc gradually decreased without clinically significant arrhythmias. LESSONS: The present case demonstrates that a potential drug-drug interaction (DDI) may lead to a life-threatening drug adverse reaction (ADR) especially in special subjects. Therefore, clinicians should closely monitor the electrocardiogram (ECG) when QTc-prolonging agents are given to patients with cardiac abnormalities, and avoid combining 2 QTc-prolonging drugs.
Notes: 1536-5964
Wei, Anhua
Peng, Jinlan
Gu, Zhichun
Li, Juan
Case Reports

Author Address: Department of Pharmacy, Tongji Hospital Department of Endocrinology, Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China.
Database Provider: NLM
Language: eng

Reference Type: Journal Article
Record Number: 1682
Author: Al-Azayzih, A., Al-Qerem, W., Al-Azzam, S., Muflih, S., Al-Husein, B. A., Kharaba, Z., Kanaan, R. J. and Rahhal, D.
Year: 2024
Title: Prevalence of Medication Associated with QTc Prolongation Used Among Critically Ill Patients
Journal: Vasc Health Risk Manag
Volume: 20
Pages: 27-37
Epub Date: 20240201
Short Title: Prevalence of Medication Associated with QTc Prolongation Used Among Critically Ill Patients
ISSN: 1176-6344 (Print)
1176-6344
DOI: 10.2147/vhrm.S438899
Legal Note: The authors declare no competing interest in this work.
PMCID: PMC10840412
Accession Number: 38318252
Keywords: Humans
Male
Middle Aged
Female
Retrospective Studies
Prevalence
Critical Illness
Cross-Sectional Studies
*Long QT Syndrome/chemically induced/diagnosis/epidemiology

QTc interval
critically ill patients
intensive care unit
torsade de pointes

Abstract: BACKGROUND: Acquired prolonged corrected QT (QTc) interval can lead to life-threatening Torsade de Pointes (TdP) arrhythmia. Multiple risk factors including medications, comorbidities, and electrolyte imbalances contribute significantly to acquired manifestations of the QTc prolongation. Critically ill patients are particularly more vulnerable to TdP due to complex medical conditions, aging, and polypharmacy. OBJECTIVE: This study aimed to assess the prevalence of TdP-associated medication prescribing, identify risk factors for QTc prolongation and TdP, and determine primary predictors of high TdP medication usage in critically ill patients in Jordan. METHODS: We conducted a retrospective cross-sectional analysis of electronic medical records for patients from King Abdullah University Hospital who were admitted to Intensive Care Unit (ICU) between (July 2012-July 2022). We collected data on patients' demographics, clinical characteristics, comorbidities, laboratory results, and prescribed medications. Medications were categorized into three TdP risk levels according to CredibleMeds(®) assessment tool. Data were analyzed using descriptive statistics and a binary logistic regression model. RESULTS: Of the 13,300 patients (58.2% male, median age 62 years). Prescribing prevalence for medications with known TdP risk was 19%, possible risk (24.7%), conditional risk (21.6%), and confirmed conditional risk (8.3%). Common comorbidities included hypertension (40.9%), diabetes (33.3%), and cancer (15.4%). Drugs with known TdP risk included citalopram, amiodarone, clarithromycin, and ciprofloxacin. A binary regression model revealed that as age increased, the odds of TdP associated medication prescribing decreased (OR = 0.989, $p < 0.001$), while patients on more than five medications had higher odds (OR = 4.281, $p < 0.001$). CONCLUSION: The study identified a notable prevalence of prescribing for medications with QTc prolongation/TdP risk in critically ill patients. Healthcare providers in the ICU should exercise caution to minimize the inadvertent prescription of TdP associated medications especially among older patients and those with polypharmacy.

Notes: 1178-2048

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Journal Article
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Author: Khederlou, H. and Azimi Pirsaraei, V.
Year: 2024
Title: Torsades de Pointe Associated with Trazodone Consumption
Journal: Case Rep Crit Care
Volume: 2024
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Short Title: Torsades de Pointe Associated with Trazodone Consumption
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Abstract: INTRODUCTION: Trazodone is a serotonin receptor antagonist and reuptake inhibitor commonly used to treat major depression disorder (MDD), anxiety, and sleep disorders. It is considered safe for the heart due to minimal anticholinergic effects. Prolonged QT intervals can cause polymorphic ventricular tachycardia, known as torsades de pointe (TdP). We present a case of a 67-year-old female with a history of MDD who developed trazodone-induced TdP. Case Presentation. The patient was referred to a tertiary hospital with a ten-hour history of nausea and vomiting. Trazodone (50 mg daily) was started for her six days ago due to her past medical history of MDD. The initial electrocardiography (ECG) revealed a prolonged corrected QT interval (QTc = 586 ms) due to a long ST segment and generalized T wave inversion. A few moments after admission to the intensive care unit, she suddenly lost consciousness. ECG monitoring showed a TdP, which terminated immediately with the asynchronous defibrillation. A temporary pacemaker was implanted due to repeated arrhythmias and bradycardia. Arrhythmia did not recur for hours and days later. After four days of stopping trazodone, all abnormal ECG findings were resolved, and she was discharged with a normal ECG. She was followed up six months later; the ECG was normal, and she had no complaints. CONCLUSION: Trazodone may lead to QTc prolongation and TdP, potentially fatal even without risk factors for QTc prolongation. Close monitoring is essential to prevent adverse complications in trazodone users.
Notes: 2090-6439
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Case Rep Crit Care. 2024 Apr 20;2024:5759229. doi: 10.1155/2024/5759229. eCollection 2024.
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Record Number: 1692
Author: Wang, L., Volkow, N. D., Berger, N. A., Davis, P. B., Kaelber, D. C. and Xu, R.
Year: 2023
Title: Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder
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Date: Dec
Short Title: Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder
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Accession Number: 37584532
Keywords: Humans
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Naltrexone/therapeutic use
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*Opioid-Related Disorders/drug therapy/epidemiology

substance dependence
treatment evaluation

Abstract: IMPORTANCE: More than 109,000 Americans died of drug overdose in 2022, with 81,231 overdose deaths involving opioids. Methadone, buprenorphine and naltrexone are the most widely used medications for opioid use disorders (MOUD) and the most effective intervention for preventing overdose deaths. However, there is a concern that methadone results in long QT syndrome, which increases the risk for fatal cardiac arrythmias. Currently few studies have systematically evaluated both the short-term and long-term differences in cardiac and mortality outcomes between MOUD. OBJECTIVES: To compare the risks of cardiac arrythmias, long QT syndrome and overall mortality between patients with opioid use disorders (OUD) who were prescribed methadone, buprenorphine or naltrexone. DESIGN, SETTING, AND PARTICIPANTS: Retrospective cohort study based on a multicenter and nationwide database of electronic health records (EHRs) in the United States. The study population was comprised of 144,141 patients who had medical encounters for OUD in 2016-2022, were prescribed MOUD within 1 month following a medical encounter for OUD diagnosis and had no diagnosis of cardiac arrythmias or long QT syndrome before any MOUD prescription. The study population was divided into three cohorts: (1) Methadone cohort (n = 40,938)-who were only prescribed methadone. (2) Buprenorphine cohort (n = 80,055)-who were only prescribed buprenorphine. (3) Naltrexone cohort (n = 5,738)-who were only prescribed naltrexone. EXPOSURES: methadone, buprenorphine, or naltrexone. MAIN OUTCOMES AND MEASURES: Cardiac arrythmias, long QT syndrome, and death. Hazard ratio (HR) and 95% confidence interval (CI) of outcomes at six different follow-up time frames (1-month, 3-month, 6-month, 1-year, 3-year, and 5-year) by comparing propensity-score matched cohorts using Kaplan-Meier survival analysis. RESULTS: Patients with OUD who were prescribed methadone had significantly higher risks of cardiac arrhythmias, long QT syndrome and death compared with propensity-score matched patients with OUD who were prescribed buprenorphine or naltrexone. For the 1-month follow-up, the overall risk for cardiac arrythmias was 1.03% in the Methadone cohort, higher than the 0.87% in the matched Buprenorphine cohort (HR: 1.20, 95% CI: 1.04-1.39); The overall risk for long QT syndrome was 0.35% in the Methadone cohort, higher than the 0.15% in the matched Buprenorphine cohort (HR: 2.40, 95% CI: 1.75-3.28); The overall mortality was 0.59% in the Methadone cohort, higher than the 0.41% in the matched Buprenorphine cohort (HR: 1.48, 95% CI: 1.21-1.81). The increased risk persisted for 5 years: cardiac arrhythmias (HR: 1.31, 95% CI: 1.23-1.38), long QT syndrome (HR: 3.14, 95% CI: 2.76-3.58), death (HR: 1.50, 95% CI: 1.41-1.59). CONCLUSIONS AND RELEVANCE: Methadone was associated with a significantly higher risk for cardiac and mortality outcomes than buprenorphine and naltrexone. These findings are relevant to the development of guidelines for medication selection when initiating MOUD treatment and inform future medication development for OUD that minimizes risks while maximizing benefits.

Notes: 1097-4679

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Journal Article
Multicenter Study
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Reference Type: Journal Article
Record Number: 1693
Author: Nair, M. K., Patel, K. and Starer, P. J.
Year: 2008
Title: Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient
Journal: Addiction
Volume: 103
Issue: 12
Pages: 2062-4
Date: Dec
Short Title: Ciprofloxacin-induced torsades de pointes in a methadone-dependent patient
ISSN: 0965-2140
DOI: 10.1111/j.1360-0443.2008.02390.x
Accession Number: 19469750
Keywords: Anti-Infective Agents/*adverse effects
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Male
Methadone/*adverse effects/therapeutic use
Middle Aged
Narcotics/*adverse effects/therapeutic use
Substance Abuse, Intravenous/*rehabilitation
Torsades de Pointes/*chemically induced
Abstract: ABSTRACT Background Methadone has been associated with QT prolongation and Torsades de pointes. Ciprofloxacin may prolong QT interval and induce Torsades de pointes when other risk factors

Starer, Perry J
Case Reports
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England
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Addiction. 2008 Dec;103(12):2062-4. doi: 10.1111/j.1360-0443.2008.02390.x.
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Record Number: 1694
Author: NoorZurani, M. H., Vicknasingam, B. and Narayanan, S.
Year: 2009
Title: Itraconazole-induced torsade de pointes in a patient receiving methadone substitution therapy
Journal: Drug Alcohol Rev
Volume: 28
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Pages: 688-90
Date: Nov
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ISSN: 0959-5236
DOI: 10.1111/j.1465-3362.2009.00128.x
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Heroin Dependence/*drug therapy/physiopathology
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Itraconazole/*adverse effects
Methadone/*therapeutic use

normal upon discontinuation of methadone. IMPLICATION: This cardiac arrhythmia was most likely as a result of a drug interaction between methadone and itraconazole because the patient presented with no other risk factors. CONCLUSION: Given the benefits of methadone as a substitution treatment for heroin-dependent individuals, the association between methadone and cardiac arrhythmias is of great concern. Physicians treating heroin-dependent patients on methadone substitution therapy should therefore be cautious of the potential risk of drug interactions that may lead to fatal cardiac arrhythmias.

Notes: 1465-3362

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2009/11/26
Drug Alcohol Rev. 2009 Nov;28(6):688-90. doi: 10.1111/j.1465-3362.2009.00128.x.

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14. Wang, L., et al., Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder. J Clin Psychol, 2023. 79(12): p. 2869-2883.

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Supplementary Files