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Ventricular Dysrhythmias Associated with Poisoning and Drug Overdose: A 10-Year Review of Statewide Poison Control Center Data from California

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Abstract

Background Ventricular dysrhythmias are a serious consequence associated with drug overdose and chemical poisoning. The risk factors for the type of ventricular dysrhythmia and the outcomes by drug class are not well documented.

Objective The aim of this study was to determine the most common drugs and chemicals associated with ventricular dysrhythmias and their outcomes.

Methods We reviewed all human exposures reported to a statewide poison control system between 2002 and 2011 that had a documented ventricular dysrhythmia. Cases were differentiated into two groups by type of arrhythmia: (1) ventricular fibrillation and/or tachycardia (VT/VF); and (2) torsade de pointes (TdP).

Results Among the 300 potential cases identified, 148 cases met the inclusion criteria. Of these, 132 cases (89 %) experienced an episode of VT or VF, while the remaining 16 cases (11 %) had an episode of TdP. The most commonly involved therapeutic classes of drugs associated with VT/VF were antidepressants (33/132, 25 %), stimulants (33/132, 25 %), and diphenhydramine (16/132, 12.1 %). Those associated with TdP were antidepressants (4/16, 25 %), methadone (4/16, 25 %), and antiarrhythmics (3/16, 18.75 %). Drug exposures with the greatest risk of death in association with VT/VF were antidepressant exposure [odds ratio (OR) 1.71; 95 % confidence interval (CI)

0.705–4.181] and antiarrhythmic exposure (OR 1.75; 95 % CI 0.304–10.05), but neither association was statistically significant. Drug exposures with a statistically significant risk for TdP included methadone and antiarrhythmic drugs. **Conclusions** Antidepressants and stimulants were the most common drugs associated with ventricular dysrhythmias. Patients with suspected poisonings by medications with a high risk of ventricular dysrhythmia warrant prompt ECG monitoring.

Key Points

The most commonly involved therapeutic classes of drugs associated with ventricular fibrillation and/or tachycardia (VT/VF) were antidepressants (25 %) and stimulants (25 %).

The drugs most commonly associated with torsade de pointes (TdP) were antidepressants (25 %) and methadone (25 %).

Drug exposures with the greatest risk of death in association with VT/VF were antidepressant exposure [odds ratio (OR) 1.71] and antiarrhythmic exposure (OR 1.75), but neither association was statistically significant.

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1 Introduction

Ventricular dysrhythmias, including ventricular tachycardia (VT), torsade de pointes (TdP) and ventricular fibrillation (VF), have been reported in association with therapeutic use of or overdose by a number of drugs, most

commonly antidepressant and antipsychotic agents [1–5]. Published clinical experience regarding ventricular arrhythmias and TdP in drug overdose is derived primarily from single case reports or small case series [6–10]. There are numerous drugs that can cause prolongation of the QTc interval in therapeutic doses, but it is unknown if the risk is dose dependent [11, 12]. The aim of this study was to determine the most common drugs and chemicals associated with ventricular dysrhythmias and their outcomes. A secondary aim was to determine risk factors for outcomes and specific types of dysrhythmias. To achieve these aims, we examined the cases involving ventricular dysrhythmias reported to a large statewide poison control center system over a 10-year period.

2 Methods

2.1 Study Setting

This was a retrospective observational study of cases reported to the California Poison Control System (CPCS). The CPCS has provided a 24-h hotline service to the entire population of California since 1997. It is consulted on over 300,000 cases annually involving exposure to drugs, chemicals, or other potentially toxic substances. Staff members include poison information providers, pharmacists certified as specialists in poison information (SPI) and medical toxicologists. The study was reviewed and approved by the University of California San Francisco Committee on Human Research.

2.2 Selection of Cases

Using the standardized coding system in the CPCS computerized database, patient data were collected for analysis from a 10-year period (2002–2011). For each case, the SPIs enter specific symptom, treatment, and outcome codes according to American Association of Poison Control Centers (AAPCC) criteria; initial and follow-up notes (the case report narrative) are also entered into a text field for individuals referred to a health care facility. Any case coded with ventricular dysrhythmia (VT or VF) was further reviewed in detail, including review of the case progress notes, by three separate evaluators with expertise in clinical toxicology, who used a consensus method to determine the following: (1) that a ventricular dysrhythmia had occurred; (2) that the ventricular dysrhythmia was likely to be related to the exposure; (3) the most likely agent causing the dysrhythmia; and (4) whether the ventricular dysrhythmia was due to a primary (direct) effect of the drug or a secondary (indirect) effect caused by medical complications related to the drug exposure (e.g., hypoxia, severe acidosis,

hypotension, etc.). If more than one drug or chemical substance was involved, the reviewers indicated the primary causative agent on the basis of patient exposure history (e.g., amount ingested), symptomology (e.g., anticholinergic, sympathomimetic), and the dysrhythmic properties (e.g., membrane stabilizer) of the agents. Cases were excluded if at least two of the three evaluators concluded that (1) no ventricular arrhythmia had occurred; (2) the ventricular arrhythmia was not related to the drug exposure (e.g., it was due to underlying cardiac disease); (3) no drug or chemical could be identified as the cause of the dysrhythmia; or (4) the ventricular dysrhythmia was caused by a medical complication of the drug exposure, such as respiratory arrest leading to hypoxia, metabolic acidosis, hypotension, hyperthermia, or hepatic failure; (5) there was no agreement between at least two of the three evaluators about the primary agent on multiple drug exposure. Duplicate cases were also excluded (see Fig. 1). The study cases were divided into two subgroups: (1) VT, VF or unspecified ventricular dysrhythmia (VT/VF) and (2) TdP.

3 Study Definitions

A primary cause of ventricular dysrhythmia was defined as a direct action of the drug, such as sodium channel blockade impairing cardiac conduction; potassium channel blockade impairing repolarization; intracellular calcium buildup; or adrenergic excess leading to increased ectopy, coronary vasospasm or serious electrolyte disturbance. Outcomes were classified as death, morbidity, recovery or unknown. Morbidity was defined as medical complications

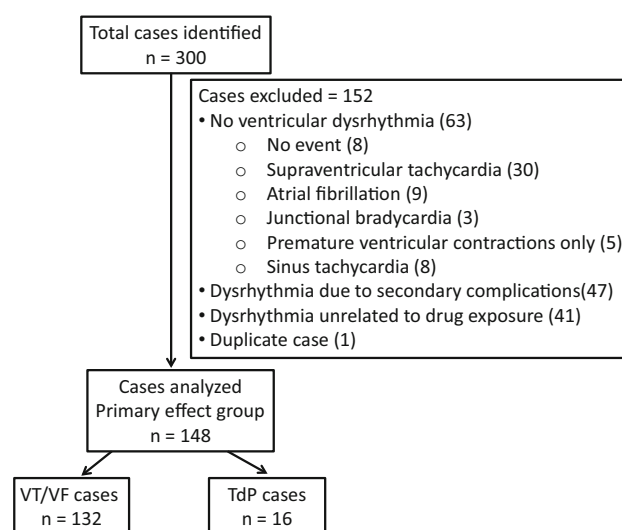


Fig. 1 Study flow chart. *TdP* torsade de pointes, *VT/VF* ventricular fibrillation and/or tachycardia

leading to prolonged admission, such as anoxic brain injury, aspiration pneumonia, ventilator-associated complications, rhabdomyolysis, renal failure, and sepsis. Recovery was defined as resolution of toxicity and discharge from hospital within 3 days.

4 Outcome Measures

The primary outcome measured was the drug or chemical cause of the ventricular dysrhythmias. We also compared morbidity and mortality between drug and chemical classes.

5 Data Analysis

We used standard statistical tests to analyze the comparative demographics between the groups for gender and age. Means and medians were calculated for continuous variables. Categorical variables were compared by χ^2 test. Associations between drug and substance categories, dysrhythmia type, and outcomes were analyzed by univariate analysis to determine odds ratios (ORs), 95 % confidence intervals (CIs), and associated *P* values. The significance threshold was $P < 0.05$ in all tests. Data were analyzed using MicrosoftTM ExcelTM 2010 (version 14.0.6123.5001).

6 Results

Among the 300 potential cases in the CPCS computerized database with a code for ventricular arrhythmia, 148 met the inclusion criteria. Figure 1 is an algorithm of cases reviewed and provides a summary of reasons for exclusion of cases. Of these, 132 cases (89 %) experienced an episode of VT or VF, while the remaining 16 cases (11 %) had an episode of TdP. Table 1 compares the age and gender of the patients between the dysrhythmia groups. In both groups, VT/VF versus TdP, 59.8 and 81.3 % of exposures

Table 1 Summary of drug-induced ventricular dysrhythmia cases ($n = 148$)

	Ventricular tachycardia or fibrillation cases	Torsade de pointes cases	Total
Number	132	16	148
Age range, years	0.83–92	23–65	0.83–92
Age (mean), years	40.4	45	40.8
Age (median), years	40	42.5	40
Male, n (%)	53 (40.2)	3 (18.7)	56 (37.8)
Female, n (%)	79 (59.8)	13 (81.3)	92 (62.2)

involved females, respectively. The average age of individuals in the VT/VF group was 40.4 years (range 10 months–92 years) and, in the TdP group, 45 years (range 23–65 years). Table 2 summarizes the drug and chemical categories and outcomes associated with VT or VF. Table 3 summarizes the drug and chemical categories and outcomes associated with TdP.

Outcomes for all 148 analyzed cases were as follows: death in 32/148 (21.7 %), morbidity in 15/148 (10.1 %), recovery in 92/148 (62.1 %), and unknown outcome in 9/148 (6.1 %). There were 30 reported deaths in the VT/VF group and two in the TdP group (overall mortality 21.6 % for any ventricular dysrhythmia). Table 4 summarizes drug exposures with the greatest risk of death in association with VT/VF, and were antidepressant exposure (OR 1.71; 95 % CI 0.705–4.181) and antiarrhythmic exposure (OR 1.75; 95 % CI 0.304–10.05), but neither association was statistically significant. Figure 2 illustrates the frequency of cases by type of dysrhythmia for each drug and chemical class. The most commonly involved classes of drugs associated with VT/VF were antidepressants (33/132, 25 %), stimulants (33/132, 25 %), and diphenhydramine (16/132, 12.1 %). The most common classes of agents associated with TdP were antidepressants (4/16, 25 %), methadone (4/16, 25 %), and antiarrhythmics (3/16, 18.75 %).

Drug exposures with a statistically significant risk for TdP included methadone (OR 5.95; 95 % CI 1.52–23.28) and antiarrhythmic drugs (OR 4.84; 95 % CI 1.08–21.69). Females had a higher risk of TdP (OR 2.90; 95 % CI 0.79–10.69), but this association was not statistically significant.

7 Discussion

During a 10-year period, CPCS managed around 2,258,776 cases, and ventricular dysthymia was found to be a rare event in reported cases. Our study describes the types of ventricular dysrhythmias among classes of drug and chemical overdoses and poisonings reported to a large statewide poison control center over a decade. Antidepressants accounted for 25 % of the agents causing VF/VT, and most of these (22/33) were tricyclic antidepressants (TCAs), including amitriptyline, nortriptyline, desipramine and doxepin. TCA overdose remains an important cause of poisoning; according to the national database of poison center calls maintained by the AAPCC, there were 10,549 TCA exposures in 2012, the majority of which were to amitriptyline [13]. TCAs have been well documented to be a major cause of ventricular arrhythmias due to their sodium channel blocker effect [14, 15]. Selective serotonin reuptake inhibitors (SSRIs) and other newer

Table 2 Outcomes associated with ventricular tachycardia or fibrillation ($n = 132$)

Drugs classes	Death 30/132 (22.7 %)	Morbidity ^a 13/132 (9.9 %)	Recovery ^b 80/132 (60.6 %)	Outcome unknown 9/132 (6.8 %)
Antidepressants ($n = 33$)	10/33 (30.3 %)	4/33 (12.1 %)	17/33 (51.5 %)	2/33 (6.1 %)
Tricyclic antidepressants	6/22	2/22	13/22	1/22
SSRIs	1/4	1/4	1/4	1/4
Bupropion	2/4	0/4	2/4	0/4
Venlafaxine and metabolites	1/3	1/3	1/3	0/3
Stimulants ($n = 33$)	7/33 (21.2 %)	1/33 (3 %)	23/33 (69.7 %)	2/33 (6.1 %)
Amphetamine/methamphetamine	2/11	0/11	8/11	1/11
Methylxanthines (e.g., caffeine)	1/7	0/7	5/7	1/7
Cocaine	1/5	0/5	4/5	0/5
MDMA/ecstasy	2/3	1/3	0/3	0/3
Other (e.g., pseudoephedrine)	1/7	0/7	6/7	0/7
Antihistamines ($n = 16$)	2/16 (12.5 %)	1/16 (6.3 %)	13/16 (81.2 %)	0/16 (0 %)
Diphenhydramine	2/16	1/16	13/16	0/16
Antipsychotics ($n = 11$)	2/11 (18.2 %)	2/11 (18.2 %)	7/11 (63.6 %)	0/11 (0 %)
Quetiapine	2/6	1/6	3/6	0/6
Ziprasidone	0/1	0/1	1/1	0/1
Other atypical agents	0/2	1/2	1/2	0/2
Chlorpromazine	0/1	0/1	1/1	0/1
Thioridazine	0/1	0/1	1/1	0/1
Cardiac glycosides ($n = 9$)	3/9 (33.3 %)	1/9 (11.1 %)	2/9 (22.3 %)	3/9 (33.3 %)
Digoxin	3/9	1/9	2/9	3/9
Opioids ($n = 7$)	1/7 (14.3 %)	1/7 (14.3 %)	4/7 (57.1 %)	1/7 (14.3 %)
Methadone	0/1	0/1	1/1	1/1
Propoxyphene	1/3	1/3	1/3	0/3
Tramadol	0/2	0/2	2/2	0/2
Antiarrhythmic drugs ($n = 6$)	2/6 (33.3 %)	0/6 (0 %)	4/6 (66.7 %)	0/6 (0 %)
Propafenone	0/1	0/1	1/1	0/1
Flecainide	1/3	0/3	2/3	0/3
Propranolol	1/2	0/2	1/2	0/2
Halogenated hydrocarbons ($n = 5$) (e.g., trichloroethane)	1/5 (20 %)	1/5 (20 %)	3/5 (60 %)	0/5 (0 %)
Anticonvulsants ($n = 4$)	0/4 (0 %)	1/4 (25 %)	3/4 (75 %)	0/4 (0 %)
Lamotrigine	0/3	1/3	2/3	0/3
Valproic acid	0/1	0/1	1/1	0/1
Cellular asphyxiants ($n = 3$)	1/3 (33.3 %)	0/3 (0 %)	2/3 (66.7 %)	0/3 (0 %)
Carbon monoxide	1/2	0/2	1/2	0/2
Zinc phosphide	0/1	0/1	1/1	0/1
Others ($n=5$)	1/5 (20 %)	1/5 (20 %)	2/5 (40 %)	1/5 (20 %)
Local anesthetics	0/3	1/3	1/3	1/3
Fluoroquinolones	0/1	0/1	1/1	0/1
Hydrofluoric acid	1/1	0/1	0/1	0/1

MDMA 3,4-methylenedioxy-methamphetamine, SSRI selective serotonin reuptake inhibitor

^a Morbidity was defined as medical complications leading to prolonged admission, such as anoxic brain injury, aspiration pneumonia, ventilator-associated complications, rhabdomyolysis, renal failure, and sepsis

^b Recovery was defined as resolution of toxicity and discharge from hospital within 3 days

antidepressants, including venlafaxine and bupropion, have been associated with cardiotoxicity in overdose [16–23], but accounted for only a small number of our VT/VF cases

and none of the TdP cases. TCAs and trazodone accounted for 25 % of the TdP cases; these drugs have previously been reported to cause TdP [24, 25].

Table 3 Outcomes associated with torsade de pointes ($n = 16$)

Drug category	Death 2/16 (12.5 %)	Morbidity ^a 2/16 (12.5 %)	Recovery ^b 12/16 (75 %)
Antidepressants ($n = 4$)	0/4 (0 %)	0/4 (0 %)	4/4 (100 %)
Tricyclic antidepressants	0/3	0/3	3/3
Trazodone	0/1	0/1	1/4
Antihistamines ($n = 1$)	0/1 (0 %)	0/1 (0 %)	1/1 (100 %)
Diphenhydramine			
Antipsychotics ($n = 1$)	0/1 (0 %)	0/1 (0 %)	2/2 (100 %)
Ziprasidone			
Opioids ($n = 4$)	¼ (25 %)	¼ (25 %)	2/4 (50 %)
Methadone			
Antiarrhythmics ($n = 3$)	1/3 (33.3 %)	0/3 (0 %)	2/3 (66.7 %)
Propafenone	0/1	0/1	1/1
Flecainide	0/1	0/1	1/1
Sotalol	0/1	1/1	0/1
Stimulants ($n = 1$)	0/1 (0 %)	0/1 (0 %)	1/1 (100 %)
Herbal Ma Huang			
Other ($n = 1$)	1/1 (100 %)	0/1 (0 %)	0/1 (0 %)
Sulfuryl fluoride			

^a Morbidity was defined as medical complications leading to prolonged admission, such as anoxic brain injury, aspiration pneumonia, ventilator-associated complications, rhabdomyolysis, renal failure, and sepsis

^b Recovery was defined as resolution of toxicity and discharge from hospital within 3 days

Table 4 Association of drug exposure by therapeutic class with highest risk of death among cases with ventricular fibrillation or tachycardia

Factor	OR	95 % CI (lower, higher)	<i>P</i>
Antidepressant exposure (yes/no)	1.71	(0.705, 4.181)	0.233
Antiarrhythmic exposure (yes/no)	1.75	(0.304, 10.05)	0.530

CI confidence interval, OR odds ratio

Sympathomimetics, including amphetamine, methamphetamine, methylxanthines and cocaine, accounted for another 25 % of the VF/VT cases. The mechanism of the cardiotoxicity in most of these agents is most likely due to catecholamine excess. These agents are known to stimulate catecholamine release, particularly dopamine and norepinephrine [26, 27]. One common source of caffeine is the caffeinated energy drinks that have been reported recently to cause toxicity [28, 29]. Cocaine has been well described to be associated with cardiovascular toxicity due to both catecholamine mediated effects as well as direct sodium channel blockade [30, 31].

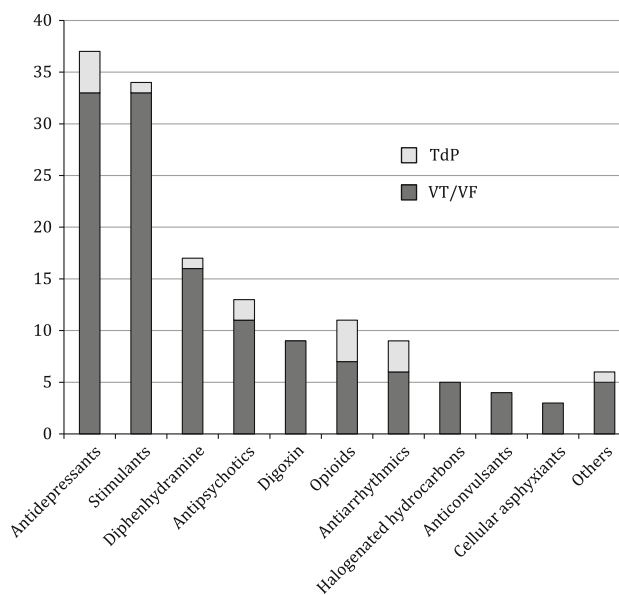


Fig. 2 Distribution of VT/VF and TdP with different drug classes. TdP torsade de pointes, VT/VF ventricular fibrillation and/or tachycardia

Although diphenhydramine was the primary cause of the ventricular arrhythmia in 17 cases, only one case had TdP. Sodium channel blockade has been reported in massive diphenhydramine overdose [32]. QT prolongation and TdP have also been described with diphenhydramine overdose [33–35].

Among the antipsychotic drugs causing dysrhythmias, quetiapine was the most common (six cases, with two deaths). Quetiapine has been reported to cause sudden cardiac death [36], but in one large retrospective review of quetiapine overdoses, this was uncommon (2/945 cases) [37]. There were only two cases of TdP in the antipsychotic drug group, both associated with ziprasidone overdose. This is consistent with previous reports that ziprasidone appears to prolong QTc to a greater extent than other antipsychotics, including quetiapine, risperidone, olanzapine and haloperidol [38–41].

Opioids accounted for 11 cases. Methadone was the cause of TdP in four cases. Methadone has been associated with an increased risk of TdP, especially in higher doses [42–44]. There were five cases of VT/VF associated with tramadol and propoxyphene. Tramadol toxicity has been reported to cause both QRS and QT prolongation [45]. Propoxyphene is well known to cause sodium channel blockade [46].

Among the antiarrhythmic group of drugs, most were sodium channel or potassium rectifier channel blockers. Flecainide has been reported to cause widening of the QRS complex responsive to sodium bicarbonate [47, 48]. Antiarrhythmic drugs are often used by patients with baseline cardiac disease like cardiomegaly, heart failure and previous known arrhythmia, which may contribute to the risk of

dysrhythmia after overdose [49]. Sotalol is a class III agent that can prolong the QTc and can induce TdP [50]. All the TdP cases associated with antiarrhythmic drugs occurred in female patients, which is in agreement with previous reports that female gender carries a greater risk of TdP [51]. Patients with congenital QT prolongation or known structural heart disease may be at greater risk of TdP when taking QT-prolonging drugs [49]. Although we excluded cases with known cardiac disease from our cohort, it is possible that some of our study patients had underlying risk factors that were not noted in the poison control center chart.

Digoxin is known to be associated with a variety of cardiac dysrhythmias, including VT [52, 53].

We had five cases of ventricular dysrhythmias associated with inhalation of chlorinated or fluorinated hydrocarbons. Sudden cardiac deaths may occur in these patients because of cardiac sensitization to the effects of circulating catecholamines or secondary to hypoxia from respiratory depression or airway obstruction [54, 55].

Sulfuryl fluoride (SO₂F₂) is not a hydrocarbon; its cardiotoxicity probably results from release of free fluoride ions, which rapidly bind to calcium in the blood, causing acute hypocalcemia [56].

In the anticonvulsant group, there were three cases of lamotrigine, which has been reported to have sodium channel-blocking effects [57, 58]. There was only one case of VT/VF associated with valproic acid overdose and no cases of TdP; previous case reports suggest that valproate may cause QTc prolongation, possibly due to hypocalcemia [59, 60].

Only three study cases were associated with agents causing cellular asphyxia: carbon monoxide and zinc phosphide. The direct effects of these agents on the heart as a result of inhibition of the mitochondrial respiration chain are thought to be the cause [61, 62].

There were three VT/VF cases from local anesthetic drugs and one case each from fluoroquinolones and hydrofluoric acid. Local anesthetic drugs are well known to cause cardiotoxicity, which is thought to be mainly due to their sodium channel-blocking effects [63–65]. Fluoroquinolones associated with cardiac arrhythmia have been mainly linked to the risk of prolongation of QTc and TdP [66]. Hydrofluoric acid cardiotoxicity, like that of sulfuryl fluoride, is mainly due to acute hypocalcemia and hypomagnesemia [67, 68].

In this study cohort, there were 16 cases of TdP, with more than 80 % female, which is in agreement with previous studies that have shown a female gender predilection for TdP [50, 69, 70]. We had an overall mortality of 21.7 %, with 65.7 % being female, and previous studies have shown that the risk of sudden cardiac death is more common in women [71].

7.1 Limitations

This study has several significant limitations. First, though a useful service, CPCS does not consult on all drug and/or chemical exposures treated in every hospital in California, nor are health-care providers required to report such exposures. As a result, the CPCS database only contains cases reported voluntarily. This could lead to a reporting bias where only unusual exposures or more complicated cases are reported. If the patient arrived in the emergency department dead or died within minutes of arrival, it is unlikely that the CPCS would be called. This was demonstrated in a study comparing poison control data with medical examiner determinations of death by poisoning [72].

Third, confirmation of the ventricular arrhythmia and the presence or absence of QTc prolongation was not always possible because CPCS staff rarely receive a copy of the ECG and information is often gathered from nursing staff or physicians, who may not have the ECG in front of them at the time of the call.

Fourth, retrospective data are often lacking key information that might have been gathered more reliably in a prospective study. This includes underlying medical histories, which might include cardiac diseases or congenital QTc prolongation. Fifth, TdP could have been misclassified as VT by the treating physicians, and this misclassification could have affected our results.

Finally, we did not have laboratory confirmation of the drugs suspected to have been involved in the poisonings, nor could we rule out the possible cardiotoxic effects of other, unknown co-ingested drugs because comprehensive drug screens were rarely performed in these patients and many cardiotoxic drugs are not included in comprehensive drug screens anyway [73].

8 Conclusions

Antidepressants, stimulants, diphenhydramine, and antiarrhythmic agents were the most common drugs associated with ventricular dysrhythmias after overdose or chronic toxicity, and poisoning by methadone and antiarrhythmic drugs is associated with a high risk of TdP. Patients with suspected poisonings to medications with a high risk of ventricular arrhythmias warrant prompt ECG monitoring and therapy tailored to the toxic mechanism of the etiologic agent and type of arrhythmia.

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