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Association of anxiolytic drugs with Torsade de Pointes: a pharmacovigilance study of the Food and Drug Administration Adverse Event Reporting System

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ABSTRACT

Background: This study aimed to determine the association of Torsade de Pointes (TdP) with anxiolytic drugs and present a detailed overview of anxiolytic-induced cases of TdP reported to the Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: All cases of anxiolytic-induced TdP ($n = 260$) between 1990 and 2020 were retrieved from the FAERS database using the Preferred Term 'Torsade de Pointes, code: 10044066' from the Medical Dictionary for Regulatory Activities (MedDRA version 22). Four data-mining algorithms were used for disproportionality analysis: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Empirical Bayes Geometric Mean (EBGM), and Information Content (IC). Anxiolytics with ≥3 TdP cases were included.

Results: Of a total of eight drugs, this study identified seven signals of TdP, of which six signals were new, namely for alprazolam, bromazepam, lorazepam, meprobamate, midazolam, and oxazepam. Based on disproportionality analysis, among new signals, the highest risk of TdP was observed with bromazepam and midazolam. Alprazolam showed the lowest risk for TdP, while diazepam did not reach significant disproportionality.

Conclusions: This study identified six new signals of TdP among anxiolytic drugs, so warranting stringent clinical studies to ascertain the actual risk of TdP and ensure patient safety.

Clinical Trial Registration: This study is registered at ClinicalTrials.gov (NCT.gov ID: NCT04293432).

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1. Introduction

Torsade de Pointes (TdP) is a life-threatening ventricular arrhythmia that has been associated with a number of commonly prescribed drugs. TdP is usually self-limited and subsides spontaneously following an episode of palpitations, dizziness, and/or light-headedness (Drew et al., 2010). However, it may lead to syncope and/or sudden cardiac death, mainly due to ventricular arrhythmia (Iragavarapu & Krishna, 2023). Ventricular arrhythmias, especially ventricular fibrillation, are considered the major underlying cause of sudden cardiac death (Ruiz Diaz et al., 2020; Tfelt-Hansen et al., 2023; Waldmann et al., 2020). Nearly one-fifth of TdP patients experiences sudden cardiac death due to ventricular fibrillation (Vandael, Vandenberk, Vandenberghe, Pincé, et al., 2017).

TdP is often preceded by QTc interval prolongation (QTIP), which is a widely used marker for the risk of TdP (Beach et al., 2013). QTIP may occur due to abnormal functioning of cardiac ion channels, i.e. potassium, sodium, and calcium (Garcia-Elias & Benito, 2018). The abnormal functioning of these channels may be attributed to various congenital and/or acquired factors. The latter, which are more common, predominantly involve drugs (Ali et al., 2020). To date, a number of cardiac and non-cardiac drugs have been associated with TdP. Currently, 59 marketed drugs are recognised for their TdP liability, of which 21 are not on the U.S. market, while 49 drugs can cause TdP under certain conditions such as a high dose, congenital long QT, hypokalaemia or drug–drug interactions (QTdrugs List & Clinical Factors Associated with Prolonged QTc and/or TdP, n.d.).

The presence of various pro-arrhythmic risk factors such as advanced age, female sex, electrolyte imbalance, liver/kidney failure, eating disorders, genetic predisposition, bradycardia, and structural cardiac diseases may further augment the risk of drug-induced TdP (Ali et al., 2020; Vandael, Vandenberk, Vandenberghe, Willems, et al., 2017). The presence of at least one risk factor has been documented in almost all cases of TdP, while two or more risk factors have been reported in three quarters of cases (Zeltser et al., 2003). Moreover, the co-administration of QT-prolonging drugs may increase the risk of TdP due to drug–drug interactions (Khan et al., 2019; Tisdale, 2016). A study reported that the simultaneous use of more than one QT-prolonging drug or concurrent use with a drug that alters the pharmacokinetics of the drug can lead to increased risk of ventricular arrhythmias (Coughtrie et al., 2017).

Despite, clinical advancement drug-induced QTIP is a matter of great concern. Various classes of drugs including antiarrhythmics, antihistamines, antifungal, anticancer, antibiotics are associated with QTIP and subsequent TdP (Ali et al., 2021; Khatib et al., 2021; Schwartz & Woosley, 2016). Notably, during the past two decades, in the medication safety, drug-induced QTIP has been an important factor behind the removal or restricted use of medications (Tan et al., 2024; Vargas et al., 2021). Anxiolytic drugs are widely used in the treatment of anxiety disorders as well as depression because the acute phase of depression is often accompanied by anxiety, irritability, and insomnia (Kanba, 2004). However, literature is scarce regarding the association of anxiolytic drugs with TdP. Currently, none of the studies attempted to use big data mining in real-world pharmacovigilance to monitor the association of TdP with anxiolytics using Food and Drug Administration Adverse Event Reporting System (FAERS). FAERS is a spontaneous reporting system that collects a large number of adverse drug events (ADEs) reported with drugs and biologicals to assist the post-marketing safety surveillance program (Alomar et al., 2020; Roger et al., 2021). Therefore, this study aimed to determine the association of TdP with various anxiolytic drugs using four algorithms for disproportionality analysis. Moreover, we aimed to present a comprehensive overview and comparative analyses of various parameters of TdP cases for various anxiolytic drugs reported to the FAERS.

2. Methods

2.1. Data source

Anxiolytic-induced TdP cases from inception till midway through 2020 (June 30) were obtained from the public dashboard of FAERS, which is a web-based database that receives adverse event reports through post-marketing surveillance programs of biologics and drugs from healthcare professionals, manufacturers, and consumers across the globe (Food and Drug Administration adverse event reporting system (FAERS) public dashboard, n.d.). Each adverse event report is coded using the standardised Medical Dictionary for Regulatory Activities (MedDRA) and is assigned a unique Case ID (Medical Dictionary for Regulatory Activities (MedDRA), n.d.) so it can be stored in compliance with the guidelines of the International Conference on Harmonization (ICH) on content and format (International Conference on Harmonization (ICH) Guidelines, n.d.). After receipt, these adverse event reports of drugs, and biologics, are evaluated by experts in the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER), respectively. If the FAERS identifies any potential safety concern, the FDA takes regulatory action in the form of changing a product's label or removing it from the market (Stobaugh et al., 2013).

2.2. Data retrieval

Anxiolytic-induced TdP cases were retrieved from the FAERS database using the Preferred Term 'Torsade de Pointes, code: 10044066' of MedDRA version 22 ('Medical Dictionary for Regulatory Activities (MedDRA),'). The TdP cases of each anxiolytic drug were obtained using generic names as search terms in the FAERS database, from which the patients demographics' and clinical characteristics such as age, sex, outcome, reactions, and concomitant QT-prolonging drugs, as well as reporters' type and country, were collected. Anxiolytics having ≥3 TdP cases were included in this study.

2.3. Signal detection

The association of TdP with anxiolytic drugs was calculated using four data-mining algorithms, because each algorithm differs in certain aspects and one may be preferred over another in a particular application: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Empirical Bayes Geometric Mean (EBGM), and Information Content (IC) (Bate et al., 1998; DuMouchel, 1999; Evans et al., 2001; Rothman et al., 2004). These algorithms calculate signal scores to ascertain a significant association between a drug and an adverse event of interest. In pharmacovigilance, disproportionality analysis is considered a fundamental method that compares reports of an adverse event between a drug of interest and all other drugs. In comparison with all other drugs, the increased likelihood of a particular adverse event with a drug results in a higher disproportionality score (Zorych et al., 2013). The term signal refers to a significant statistical association between a drug and an adverse event that is more frequently reported than expected. For this study, a drug will be considered a signal if it exceeds the threshold values of at least one of the data-mining algorithms, i.e. ROR (lower 95% CI = >1), PRR (lower 95% CI = ≥2 with chi-square = ≥4 and $n \geq 3$ reports), EBGM (lower 95% CI (EB05) = ≥ 2), or IC (lower 95% CI (IC025) = > 0) (Sakaeda et al., 2013).

2.4. New and old signals

The torsadogenic potential of all marketed drugs is closely monitored and maintained by the CredibleMeds database using pre-defined criteria (Woosley et al., n.d.), where each drug carrying the risk is categorised into three categories; known risk, possible risk, and conditional risk, based on the available scientific data. Therefore, an anxiolytic drug that is not enlisted by the CredibleMeds database and is detected as a signal will be considered a new signal, whereas an anxiolytic drug that is listed will be considered a previously known signal.

2.5. Descriptive analysis

Descriptive analyses were performed for age, gender, seriousness of reaction, outcome of reaction, type of reporter and region of report. Moreover, each drug was stratified with respect to gender, age, number of all co-prescribed drugs, number of concomitant QT-prolonging drugs, number of pro-arrhythmic factors and outcome of TdP. Further, each drug was also stratified with respect to QTIP, cardiac reactions/factors, electrolyte abnormalities, and other reactions/factors.

3. Results

A total of 260 cases of TdP were obtained for anxiolytic drugs during the study period, of which 63.1% were in females and 64.2% in patients aged between 19 and 64 years old (Table 1). The most frequent reaction outcomes were hospitalisation ($n = 186$; 71.5%) and life-threatening events ($n = 110$; 42.3%). All cases of TdP ($n = 260$; 100%) were of a serious nature, while death was reported in 19.6% of cases. The majority of cases were reported by healthcare professionals ($n = 206$; 79.2%). The reporting region was

Table 1. General characteristics.

Variables	*n* (%)
Gender	
Female	164 (63.1)
Male	83 (31.9)
Not specified	13 (5)
Age (years)	
≤18	5 (1.9)
19–64	167 (64.2)
≥65	64 (24.6)
Not specified	24 (9.2)
Outcomes	
Hospitalised	186 (71.5)
Life threatening	110 (42.3)
Died	51 (19.6)
Required intervention	10 (3.8)
Disabled	2 (0.8)
Other outcomes	139 (53.5)
Seriousness of reaction	
Serious	260 (100)
Non-serious	0 (0)
Reporter type	
Healthcare professional	206 (79.2)
Consumer	18 (6.9)
Not specified	36 (13.8)
Region of reports	
Europe	96 (36.9)
North America	77 (29.6)
Asia	12 (4.6)
Oceania/Australia	2 (0.8)
Not specified	73 (28.1)

Table 2. Disproportionality analysis.

Drug	TdP cases Reports	Disproportionality analysis ROR (95%CI)	PRR (Chi)^2	EBGM (EB05)	IC (IC05)
Alprazolam	49	2.5 (1.9–3.3)	2.5 (42.4)	2.5 (1.9)	1.3 (0.9)
Bromazepam	20	11.2 (7.2–17.4)	11.2 (184.9)	11.2 (7.2)	2.9 (2.3)
Diazepam	13	0.9 (0.5–1.6)	0.9 (0.1)	0.9 (0.5)	−0.1 (−0.9)
Hydroxyzine	79	17 (13.6–21.2)	16.9 (1170.8)	16.7 (13.4)	3.8 (3.5)
Lorazepam	45	3.8 (2.8–5.1)	3.8 (92.1)	3.8 (2.8)	1.8 (1.4)
Meprobamate	3	4.4 (1.4–13.7)	4.4 (7.8)	4.4 (1.4)	1.2 (−0.2)
Midazolam	33	7.3 (5.2–10.3)	7.3 (178.5)	7.3 (5.2)	2.6 (2.1)
Oxazepam	18	6.1 (3.8–9.7)	6 (75.6)	6 (3.8)	2.3 (1.6)

EBGM: Empirical Bayes Geometric Mean; IC: information content; PRR: proportional reporting ratio; ROR: reporting odds ratio; TdP: Torsade de Pointes.

Europe in 36.9% of cases, North America in 29.6%, and Asia in 4.6%, while it was not specified in 28.1% of cases.

Table 2 shows the disproportionality analysis of individual anxiolytic drugs using ROR, PRR, EBGM, and IC data-mining algorithms, along with the frequency of TdP cases. All drugs included in the analyses were detected as signals by all data-mining algorithms except diazepam. Based on disproportionality analysis, the highest risk of TdP was observed with hydroxyzine, which is a previously known signal, whereas bromazepam, and midazolam, had the highest risk of TdP among new signals (Figure 1).

The frequency of top-10 frequently co-prescribed QT-prolonging drugs with anxiolytic drugs along with their TdP risks are presented in Table 3. The frequently used co-prescribed QT-prolonging drugs were methadone ($n = 61$; 23.5%), fluoxetine ($n = 40$; 15.4%), and haloperidol ($n = 40$; 15.4%). The majority of drugs were carrying known ($n = 182$; 70%) or conditional risks of TdP ($n = 104$; 40%).

Table 4 lists the frequencies of reactions/factors observed with TdP cases of individual anxiolytic drugs. Among signals, QTIP was frequently reported

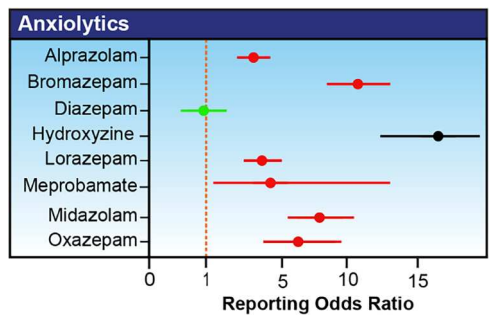

Figure 1. Disproportionality analysis of TdP cases of anxiolytic drugs using reporting odds ratio. Black indicates old signal, Red indicates new signal, Green indicates no signal.

Table 3. List of top 10 co-prescribed QT-prolonging drugs with anxiolytic drugs along with their TdP risks.

Drug	TdP risk	*n* (%)*
Methadone	Known	61 (23.5)
Fluoxetine	Conditional	40 (15.4)
Haloperidol	Known	40 (15.4)
Cocaine	Known	35 (13.5)
Famotidine	Conditional	34 (13.1)
Risperidone	Conditional	30 (11.5)
Saquinavir	Possible	30 (11.5)
Trimethoprim	Avoid in CQT	30 (11.5)
Amiodarone	Known	26 (10)
Flecainide	Known	20 (7.7)

CQT: Congenital long QT; *Percentage calculated in total of 260 TdP cases.

with bromazepam (65%), followed by oxazepam (55.6%), and alprazolam (53.1%). The frequencies of TdP-related cardiac reactions/factors such as cardiac arrest (49%), ventricular tachycardia (81.8%), ventricular fibrillation (33.8%), syncope/fall (66.7%), and atrial fibrillation (8.9%) were considerably higher with alprazolam, midazolam, hydroxyzine, meprobamate, and lorazepam. Moreover, hypokalaemia (54.5%) and hypomagnesaemia (27.3%) was most commonly reported with midazolam, while hypocalcaemia (20%) was most commonly reported with bromazepam. Furthermore, drug interactions (30.4%) were frequently observed with hydroxyzine, whereas overdose cases (65%) were commonly reported with bromazepam.

Table 5 shows the stratification of TdP cases of individual anxiolytic drugs with respect to demographics, all prescribed drugs, QT-prolonging drugs, risk factors, and reaction outcomes. Among signals, alprazolam was frequently used by females (85.7%), while diazepam, which is not detected as a signal, was frequently used by male patients (69.2%). The highest mean age was reported with meprobamate (69.3 years), while the lowest mean age was reported with diazepam (36.3 years). The highest number of pro-arrhythmic risk factors was reported for hydroxyzine (mean: 1.5) while the risk factors were lowest for diazepam (mean: 0.2). As far as reaction outcomes are concerned, the highest number of deaths was reported with midazolam (36.4%), followed by lorazepam (35.6%), and hydroxyzine (20.3%). The highest number of hospitalisations was reported with meprobamate (100%), followed by bromazepam (90%), alprazolam (85.7%), and lorazepam (77.8%), whereas no deaths were reported with diazepam or meprobamate.

4. Discussion

The present pharmacovigilance study has identified six new signals of TdP for anxiolytic drugs by retrieving almost 30 years of data from the FAERS database and validated one previously known signal. Further, four data-mining

Table 4. Frequencies of various reactions/factors observed with TdP cases of individual anxiolytic drug.

	Anxiolytic drugs							
Reactions/factors ECG changes	Alprazolam *N* = 49 *n* (%)	Bromazepam *N* = 20 *n* (%)	Diazepam *N* = 13 *n* (%)	Hydroxyzine *N* = 79 *n* (%)	Lorazepam *N* = 45 *n* (%)	Meprobamate *N* = 3 *n* (%)	Midazolam *N* = 33 *n* (%)	Oxazepam *N* = 18 *n* (%)
QT interval prolongation	26 (53.1)	13 (65)	9 (69.2)	37 (46.8)	18 (40)	1 (33.3)	13 (39.4)	10 (55.6)
Cardiac reactions/factors						–		
Cardiac arrest	24 (49)	2 (10)	2 (15.4)	29 (36.7)	13 (28.9)	–	11 (33.3)	2 (11.1)
Ventricular tachycardia	19 (38.8)	7 (35)	6 (46.2)	24 (30.4)	20 (44.4)	1 (33.3)	27 (81.8)	9 (50)
Ventricular fibrillation	13 (26.3)	1 (5)	1 (7.7)	24 (30.4)	1 (2.2)	–	6 (18.2)	
Syncope/fall	2 (4.1)	6 (30)	4 (30.8)	9 (11.4)	3 (6.7)	2 (66.7)		6 (33.3)
Bradycardia	7 (14.3)	1 (5)	–	4 (5.1)	3 (6.7)	2 (66.7)	3 (9.1)	4 (22.2)
Atrial fibrillation	2 (4.1)	1 (5)	–	5 (6.3)	4 (8.9)	–	–	1 (5.6)
Myocardial infarction	–	–	1 (7.7)	–	–	–	–	–
Angina pectoris	–	–	1 (7.7)	–	–	–	–	–
Atrial ventricular block	–	–	–	–	–	–	1 (3)	–
Electrolytes abnormalities								
Hypokalaemia	13 (26.5)	1 (5)	1 (7.7)	23 (29.1)	15 (33.3)	1 (33.3)	18 (54.5)	1 (5.6)
Hypomagnesemia	4 (8.2)	–	2 (15.4)	10 (12.7)	11 (24.4)	–	9 (27.3)	–
Hypocalcaemia	2 (4.1)	4 (20)	–	1 (1.3)	1 (2.2)	–	3 (9.1)	–
Hyponatremia	–	–	–	1 (1.3)	–	–	1 (3)	–
Other reactions/factors						–		
Drug–drug interactions	5 (10.2)	4 (20)	1 (7.7)	24 (30.4)	12 (26.7)	–	5 (15.2)	2 (11.1)
Overdose	25 (51)	13 (65)	1 (7.7)	6 (7.6)	1 (2.2)	–	–	1 (5.6)
Hepatic function abnormal/failure	–	–	–	2 (2.5)	1 (2.2)	–	1 (3)	4 (22.2)
Renal failure/impairment	–	–	–	9 (11.4)	–	–	1 (3)	–
Hyperglycaemia	–	–	–	1 (1.3)	–	–	–	–
Sepsis	–	–	–	–	4 (8.9)	–	–	–

Table 5. Stratification of TdP cases of individual anxiolytic drug with respect to gender, age, number of all prescribed drugs, QT-prolonging drugs and risk factors.

	Anxiolytic drugs							
Variables Gender	Alprazolam *n* (%)	Bromazepam *n* (%)	Diazepam *n* (%)	Hydroxyzine *n* (%)	Lorazepam *n* (%)	Meprobamate *n* (%)	Midazolam *n* (%)	Oxazepam *n* (%)
Female	42 (85.7)	17 (85)	3 (23.1)	50 (63.3)	24 (53.3)	3 (100)	16 (48.5)	9 (50)
Male	4 (8.2)	0 (0)	9 (69.2)	25 (31.6)	19 (42.2)	0 (0)	17 (51.5)	9 (50)
Not specified	3 (6.1)	3 (15)	1 (7.7)	4 (5.1)	2 (4.4)	0 (0)	0 (0)	0 (0)
Age (years)	Mean: 46.4	Mean: 56	Mean: 36.3	Mean: 51.4	Mean: 37.4	Mean: 69.3	Mean: 40.4	Mean: 43.5
≤18	0 (0)	0 (0)	1 (7.7)	1 (1.3)	3 (6.7)	0 (0)	1 (3)	0 (0)
19–64	41 (83.7)	13 (65)	12 (92.3)	37 (46.8)	26 (57.8)	2 (66.7)	27 (81.8)	9 (50)
≥65	5 (10.2)	4 (20)	0 (0)	36 (45.6)	9 (20)	1 (33.3)	4 (12.1)	5 (27.8)
Not specified	3 (6.1)	3 (15)	0 (0)	5 (6.3)	7 (15.6)	0 (0)	1 (3)	4 (22.2)
All prescribed drugs	Mean: 5.1	Mean: 7.2	Mean: 6.2	Mean: 8	Mean: 10.6	Mean: 6	Mean: 12	Mean: 7.1
1–3	15 (30.6)	0 (0)	1 (7.7)	23 (29.1)	6 (13.3)	2 (66.7)	1 (3)	1 (5.6)
4–6	19 (38.8)	12 (60)	6 (46.2)	27 (34.2)	11 (24.4)	0 (0)	9 (27.3)	7 (38.9)
>6	15 (30.6)	8 (40)	6 (46.2)	29 (36.7)	28 (62.2)	1 (33.3)	23 (69.7)	10 (55.6)
QT drugs	Mean: 2.4	Mean: 2.5	Mean: 2.5	Mean: 2	Mean: 4.1	Mean: 1.7	Mean: 3.7	Mean: 2.8
0	0 (0)	0 (0)	1 (7.7)	16 (20.3)	13 (28.9)	0 (0)	4 (12.1)	0 (0)
1	17 (34.7)	0 (0)	1 (7.7)	32 (40.5)	6 (13.3)	2 (66.7)	3 (9.1)	3 (16.7)
2	17 (34.7)	15 (75)	3 (23.1)	8 (10.1)	5 (11.1)	0 (0)	8 (24.2)	6 (33.3)
>2	15 (30.6)	5 (25)	8 (61.5)	23 (29.1)	33 (73.3)	1 (33.3)	18 (54.5)	9 (50)
Risk factors	Mean: 1	Mean: 1.2	Mean: 0.2	Mean: 1.5	Mean: 1	Mean: 1.3	Mean: 0.8	Mean: 0.9
0	7 (14.3)	3 (15)	10 (76.9)	17 (21.5)	13 (28.9)	0 (0)	15 (45.5)	6 (33.3)
1	37 (75.5)	13 (65)	3 (23.1)	27 (34.2)	23 (51.1)	2 (66.7)	13 (39.4)	8 (44.4)
≥2	5 (10.2)	4 (20)	0 (0)	35 (44.3)	9 (20)	1 (33.3)	5 (15.2)	4 (22.2)
Outcomes								
Died	1 (2)	3 (15)	0 (0)	16 (20.3)	16 (35.6)	0 (0)	12 (36.4)	3 (16.7)
Hospitalised	42 (85.7)	18 (90)	7 (53.8)	48 (60.8)	35 (77.8)	3 (100)	20 (60.6)	13 (72.2)
Life-threatening	24 (49)	11 (55)	6 (46.2)	29 (36.7)	14 (31.1)	0 (0)	13 (39.4)	13 (72.2)
Other outcomes	26 (53.1)	13 (65)	4 (30.8)	45 (57)	24 (53.3)	1 (33.3)	13 (39.4)	13 (72.2)
Required intervention	2 (2)	–	–	4 (5.1)	–	0 (0)	3 (9.1)	1 (5.6)
Disabled	–	–	1 (7.7)	–	–	0 (0)	–	–

algorithms were employed for disproportionality analysis to make the findings more generalisable.

In this study, six anxiolytics – bromazepam, midazolam, oxazepam, meprobamate, lorazepam, and alprazolam – were identified as new signals, whereas diazepam was not detected as a signal. Based on ROR, among new signals, the highest risk of TdP was observed with bromazepam and midazolam, whereas alprazolam showed minimal risk of TdP. Though literature regarding the association of bromazepam with QTIP and subsequent TdP is scarce, bromazepam may induce tachycardia by decreasing the vagal tone (Costa et al., 2019), which is in line with a study conducted in dogs (Gerold et al., 1976). Another study conducted recently (Rahman et al., 2018) reported that bromazepam can induce QTIP in higher doses which is consistent with our study's finding. In our study, bromazepam induced QTIP in 65% of patients, and it was overdosed among 65% of patients, supporting the association of higher doses of bromazepam with QTIP and subsequent TdP. Another possible mechanism of bromazepam inducing TdP may be attributed to hypocalcaemia, which was frequently observed with bromazepam among new signals, whereas the higher risk of midazolam for TdP may be attributed to electrolyte disturbances because midazolam was frequently involved in causing hypokalaemia and hypomagnesemia.

Diazepam was not significantly associated with TdP, although QTIP was most frequently reported with diazepam compared to all other included drugs. This insignificant association of diazepam with TdP may be due to the following reasons: absence of QT-prolonging risk factors in the majority of patients (76.9%) and the majority of patients being males with a lower mean age.

In this study, females were more highly exposed to TdP than males, which are in line with other studies (Ali et al., 2021; Chorin et al., 2017; Johannesen et al., 2018). However, there are mixed results on this; a recently conducted study reported a higher risk of QTIP and subsequent TdP among males (Ali et al., 2020). The mean age of the patients was 47.6 years, which is not consistent with a study that reported a significant risk of TdP in patients aged over 60 (Kanba, 2018). All cases of TdP were of a serious nature and caused hospitalisation in the majority of cases (71.5%), of which 42.3% of patients experienced a life-threatening situation, while 19.6% died as a result. Based on the study findings and current literature, patients of either gender, and aged 47 years or above, are at higher risk of developing TdP with a serious outcome.

The risk of TdP increases with an escalating number of QT-prolonging risk factors. At least one QT-prolonging risk factor has been reported in 90% of TdP cases, while $\geq$2 QT-prolonging risk factors have been documented in 71% of cases (Kanba, 2018). Based on our data, new signals possess the greater potential for TdP as compared to hydroxyzine (a previously known

signal) because fewer QT-prolonging risk factors have been reported with all new signals. Of the new signals, the least number of risk factors were observed with midazolam and oxazepam, supporting their greater potential for preventing TdP. The association of QTIP with TdP is well established and is considered a surrogate marker of TdP (Kanba, 2018), which is consistent with the finding of our study where all signals caused QTIP in 47.6% TdP cases. In our study, we found abnormal electrolyte levels in a considerable number of TdP cases: hypokalaemia (26.8%) was caused by all signals, hypomagnesaemia (18.2%) by four signals (alprazolam, hydroxyzine, lorazepam, and midazolam) and hypocalcaemia (7.3%) by five signals, namely alprazolam, bromazepam, hydroxyzine, lorazepam, and midazolam. These findings are supported by the current literature which considered electrolyte abnormalities a risk factor for QTIP and subsequent TdP (Khan et al., 2018). Furthermore, drug–drug interactions were observed in 18.9% of patients with all signals except meprobamate, whereas higher doses of all signals except meprobamate and midazolam were observed among 26.3% of TdP cases, which is also consistent with the published literature (Khan et al., 2018). Therefore, all signals should be cautiously used, particularly in the presence of QT-prolonging risk factors, and further clinical studies are highly warranted to ascertain the actual TdP risk of these drugs to ensure patients' safety. Modifiable QT-prolonging risk factors such as electrolyte disturbances, QT drug–drug interactions, drug overdose, and co-administration of QT-prolonging drugs should be considered and corrected before prescribing to predisposed patients. Monitoring parameters, particularly the QTc interval measurement from an ECG, can be extremely helpful in early diagnosis of QTIP and subsequent prevention of TdP, which is usually overlooked in routine practice. Moreover, knowledge regarding the mechanisms of drugs causing QTIP/TdP, awareness of QT-prolonging drugs, and consideration of other patient-specific QT-prolonging risk factors are key parameters in the prevention of QTIP/TdP (Woosley & Schwartz, 2020).

To our knowledge, literature regarding the association of anxiolytic drugs with TdP is lacking, and no other study has reported the torsadogenic potential of these drugs. However, a recent study has reported QTIP in 2 patients, when overdosed with bromazepam, diazepam, and clonazepam (Rahman et al., 2018). Based on our findings, anxiolytic drugs have raised concerns regarding the risk of life-threatening arrhythmias, and subsequent sudden cardiac death. Such studies will strengthen practice guidelines regarding the use of anxiolytic drugs in specific populations. At present, cardiac drug safety is a major challenge for healthcare professionals and regulatory authorities. TdP is an unpredictable and multifactorial disease, so a better understanding of the mechanism of drug-related TdP may help in the development of safe and effective medicines. Furthermore, knowledge of the arrhythmic

potential of drugs and patients' risk of TdP may help physicians prescribe rational therapy, which is only possible through further clinical studies.

Although post-marketing spontaneous adverse event reporting systems offer an important source of information providing real-world data, particularly regarding rare adverse events, the spontaneous adverse event reporting system including FAERS database has some limitations such as over- and under-reporting of adverse event reports, incomplete and replicate information, no guarantee of causal relationship, and existence of potential reporting biases (weber effect, notoriety effect, masking or cloaking effect, and ripple effect) (Noguchi et al., 2021). Overall, the spontaneous reporting does not guarantee that the drug-adverse event relationships are proven because the reported cases do not always contain sufficient details for proper evaluation. Furthermore, as reporting is voluntary, it is likely that not every adverse event observed with a product is reported, instead only the reported adverse events are registered resulting in under-reporting. There also exists higher possibility of duplicate reports of adverse events, as the same report submitted by a patient may be submitted by the sponsor. Other various factors such as the time of launch of drug in the market and publicity of a drug-associated adverse event can influence reporting of an event, and thus a recently marketed drug is expected to have more adverse event reports reported vs drugs reported old drugs in the market. Furthermore, there is significant heterogeneity among reports as it depends on individual reporting, potential bias based on physicians' preference of one drug over another, and patients' negative experience with a specific drug or lawyer's perception when defending a client prescribed that drug (Stobaugh et al., 2013). Additionally, information contained in the reports is not medically verified.

Although post-marketing spontaneous adverse event reporting systems offer an important source of information providing real-world data, particularly regarding rare adverse events, the FAERS database has some weaknesses. There is no certainty that the drug-adverse event relationships are proven because the reported cases do not always contain sufficient details for proper evaluation. Furthermore, as reporting is voluntary, it is likely that not every adverse event is reported. Various factors such as the time of the drug's market launch and publicity of a drug-associated adverse event can influence reporting of an event, and thus a recently marketed drug is expected to have more adverse event reports. Furthermore, there is significant heterogeneity among reports as it depends on individual reporting, potential bias based on physicians' preference of one drug over another, and patients' negative experience with a specific drug or lawyer's perception when defending a client prescribed that drug. Additionally, information contained in the reports is not medically verified.

There are several limitations of this study. First, we could not assess the influence of route of administration of drugs, which might have had some effect. Second, we excluded drugs with fewer than three TdP reports, thereby omitting signals, particularly new signals. Third, we only reported data from the FAERS database. Moreover, the detected signals in this study present a hypothesis for the presence of risk, and need confirmation through further clinical studies, as the predisposing clinical profile of the patient, and concomitant drugs may also potentially prolong QTc.

5. Conclusion

This study has identified the increased torsadogenic potential of numerous anxiolytic drugs, thereby warranting stringent clinical studies of these drugs to ascertain the actual risk of life-threatening arrhythmia, particularly in predisposed patients. Clinicians should exercise caution and assess patients for various pro-arrhythmic risk factors before prescribing these drugs. Moreover, adequate monitoring and preventive measures should be adopted in order to ensure patients' safety.

Author contributions

Conceptualisation, Mohammad Ismail Tajik; Formal analysis, Zahid Ali and Mohammad Ismail Tajik, Long Chiau Ming; Funding acquisition, Khang Wen Goh, Pakhrur Razi; Investigation, Zahid Ali; Methodology, Zahid Ali, Mohammad Ismail Tajik and Inayat Ur Rehman; Resources; Software, Zahid Ali, Inayat Ur Rehman, Khang Wen Goh, Pakhrur Razi and Long Chiau Ming; Validation, Mohammad Ismail Tajik, Inayat Ur Rehman, Long Chiau Ming; Visualisation, Zahid Ali; Writing – original draft, Zahid Ali and Mohammad Ismail Tajik; Writing – review & editing, Inayat Ur Rehman, Long Chiau Ming Khang Wen Goh and Pakhrur Razi.

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