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Ventricular Arrhythmias Associated With Over-the-Counter and Recreational Opioids

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ABSTRACT

BACKGROUND Epidemic increases in opioid deaths prompted policies limiting access to prescription opioids in North America. Consequently, the over-the-counter opioids loperamide (Imodium A-D) and mitragynine, the herbal ingredient in kratom, are increasingly used to avert withdrawal or induce euphoria. Arrhythmia events related to these nonscheduled drugs have not been systematically studied.

OBJECTIVES In this study, we sought to explore opioid-associated arrhythmia reporting in North America.

METHODS The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), and Canada Vigilance Adverse Reaction (CVAR) databases were searched (2015-2021). Reports involving nonprescription drugs (loperamide, mitragynine) and diphenoxylate/atropine (Lomotil) were identified. Methadone, a prescription opioid (full agonist), served as a positive control owing to its established arrhythmia risk. Buprenorphine (partial agonist) and naltrexone (pure antagonist), served as negative controls. Reports were classified according to Medical Dictionary for Regulatory Activities terminology. Significant disproportionate reporting required a proportional reporting ratio (PRR) of ≥2, ≥3 cases, and chi-square ≥4. Primary analysis used FAERS data, whereas CAERS and CVAR data were confirmatory.

RESULTS Methadone was disproportionately associated with ventricular arrhythmia reports (PRR: 6.6; 95% CI: 6.2-7.0; n = 1,163; chi-square = 5,456), including 852 (73%) fatalities. Loperamide was also significantly associated with arrhythmia (PRR: 3.2; 95% CI: 3.0-3.4; n = 1,008; chi-square = 1,537), including 371 (37%) deaths. Mitragynine demonstrated the highest signal (PRR: 8.9; 95% CI: 6.7-11.7; n = 46; chi-square = 315), with 42 (91%) deaths. Buprenorphine, diphenoxylate, and naltrexone were not associated with arrhythmia. Signals were similar in CVAR and CAERS.

CONCLUSIONS The nonprescription drugs loperamide and mitragynine are associated with disproportionate reports of life-threatening ventricular arrhythmia in North America. (J Am Coll Cardiol 2023;81:2258-2268) © 2023 by the American College of Cardiology Foundation.

More than a half-million unintentional deaths occurred during the prescription opioid epidemic of the past 2 decades. Despite more stringent opioid prescribing policies, >80,000 American deaths still occurred in 2021 alone.[1] Public health interventions have principally involved addiction medicine, primary care, and pain-management communities. However, the American College of Cardiology issued a Call to Action in 2020, noting that cardiovascular medicine is not immune to the impact of this epidemic.[2] Although opioids are generally considered to be devoid of direct

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cardiovascular toxicity, emerging data suggest that they are associated with acute coronary syndrome, heart failure hospitalization, atrial fibrillation, and even malignant ventricular arrhythmias such as torsade de pointes resulting in sudden cardiac death.[3] Stricter prescription-opioid guidelines appear to be effective in reducing consumption of regulated agents, but an unintended dramatic increase in misuse of intravenous heroin, illicitly manufactured fentanyl, loperamide (Imodium A-D), and mitragynine in the form of kratom products has been observed, likely reflecting attempts to relieve opioid withdrawal symptoms and, in very high doses, to induce euphoria.[4,5] The most obvious result of this "illicit shift" is a sharp global increase in infective endocarditis, with incidence rates now exceeding 1 million per year in the United States, which is the highest burden worldwide.[6] In contrast, the potential cardiac arrhythmic sequelae of this shift in opioid utilization patterns have not been well studied.

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Regarding over-the-counter opioids, the Consumer Healthcare Products Association warned in 2019 of rising loperamide misuse and the potential for ventricular arrhythmia.[7] Loperamide can be purchased in bulk online and in drugstores and supermarkets worldwide for as little as a few cents per pill. In response, the U.S. Food and Drug Administration (FDA) issued a health professional advisory regarding QTc-prolongation and torsade de pointes and is now working closely with drug manufacturers to institute blister packs or single-dose packaging to limit availability and toxic exposure.[8]

Analogously to loperamide, >5 million people in the United States reported using mitragynine to alleviate opioid withdrawal or as a substitute for prescription opioids.[9] Mitragynine is an herbal opioid with stimulant properties, extracted from an evergreen tree (*Mitragyna speciosa*) in southeast Asia, and its use is increasing in the form of kratom products such as tea, powder, and capsules. Although kratom is banned in parts of Asia, carrying a risk of imprisonment, it is now widely available in the U.S. and Canada in head shops, vaping establishments, gas stations, and other markets and via online websites. Similar to loperamide, kratom is inexpensive, creating enormous opportunity for misuse. The U.S. Drug Enforcement Agency (DEA) initially proposed to list kratom as a Schedule 1 narcotic akin to heroin; but ultimately dropped the scheduling attempt following public backlash.[9] In 2022 the FDA issued a consumer alert regarding its abuse potential, as U.S. Marshals seized >25,000 pounds of raw kratom and 90,000 bottled supplements.[10] However, to date, no regulatory agency has issued warnings regarding proarrhythmic properties of kratom despite scattered reports of unexplained sudden cardiac death. Given this background, we investigated for signals of ventricular arrhythmia associated with nonprescription opioids in North American pharmacovigilance systems.

METHODS

DATA AVAILABILITY AND DESIGN STATEMENT. The data, analytic methods, and study materials used for this analysis are within the public domain and are available free of charge. Because the data are completely deidentified and access is unrestricted to the public via electronic download, this analysis was considered to be exempt from human subjects research (category 4) by the U.S. Department of Health and Human Services and was not subject to local review by Institutional Review Board or ethics committee.

POPULATION AND DRUGS ANALYZED. Publicly available data were obtained for the years 2015 to 2021 through the FDA Adverse Event Reporting System (FAERS),[11] the Canadian Vigilance Adverse Reaction Online Database (CVAR),[12] and the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS).[13] CAERS was included because it tracks product complaints submitted to the FDA for foods, dietary supplements, and cosmetics including kratom, which is both nonprescription and outside of standard over-the-counter FDA labeling.

This study focused on the antidiarrheal agents loperamide and diphenoxylate-atropine as well as mitragynine, the primary active ingredient in the herbal supplement kratom. We included analyses of reports involving methadone as a quasiexperimental positive control owing to its known proarrhythmic potential.[14] We also evaluated reports involving buprenorphine, a partial μ-opioid agonist as a negative control.[15] Naltrexone, a pure μ-opioid antagonist, was also included as a negative control owing to no cardiotoxicity signal for naloxone in previous pharmacovigilance studies.[16] Control drugs were used to augment inferences regarding potential arrhythmia signals among uncharacterized nonprescription agents.

FAERS is the largest North American pharmacovigilance system and was therefore selected for primary analysis of signals of disproportionate

ABBREVIATIONS AND ACRONYMS

CAERS = Center for Food Safety and Applied Nutrition Adverse Event Reporting System

CVAR = Canada Vigilance Adverse Reaction database

DEA = Drug Enforcement Agency

FAERS = U.S. Food and Drug Administration Adverse Event Reporting System

FDA = U.S. Food and Drug Administration

hERG = human ether-a-go-go

I_{Kr} = delayed rectifier potassium ion channel

QTc = rate-corrected QT interval

reporting for opioid-associated arrhythmia events as previously described. FAERS, CAERS, and CVAR are all relational databases of spontaneous adverse event reports collected from individuals, clinicians, and pharmaceutical companies through voluntary postmarketing surveillance. Reports are individually assigned a unique identifier. When multiple reports refer to the same event, they are linked via a unique case identifier. For the present study, redundant counting was minimized by using the case identifier, because life-threatening arrhythmia events are clinically remarkable, creating the potential to prompt multiple constituent reports. In both FAERS and CVAR, drug names were then linked by means of string matching to standardized active ingredients contained in the Drugs@FDA database. There is no specific reference terminology for CAERS reporting, and cases involving mitragynine were identified by the presence of the substrings "mitrag" or "krato." Only reports with specific product names were included to provide robust frequency estimates. Adverse drug reactions were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.1), a standardized lexicon developed by the International Conference on Harmonization. Access to the ingredient-normalized FAERS, CVAR, and CAERS databases is available from the authors on request.

ENDPOINTS. Adverse events in all 3 databases are reported with MedDRA Preferred Terms. MedDRA also has a formal hierarchy consisting of "high-level terms," "high-level group terms," and "system organ classes," which provide standardized aggregation of related Preferred Terms across studies. The primary outcome was the MedDRA composite high-level term "ventricular arrhythmia and cardiac arrest."[17] The secondary endpoint was reports of "QTc-prolongation and torsade de pointes," given the mechanistic potential for proarrhythmia to result from blockade of the human ether-a-go-go (hERG) ion channel, responsible for the delayed rectifier potassium current.[3] Endpoint events were further categorized as resulting in death or hospitalization within each database. The role of the opioids of interest were then classified according to database nomenclature. In FAERS and CAERS, this corresponded to "primary suspect," "secondary suspect," "concomitant," and "interacting." In CVAR, classifications were suspect, concomitant, and interacting. Concomitant medications associated with the primary and secondary outcomes were tabulated, because drug-induced arrhythmia often results from a confluence of factors.[18] All concomitant drugs in FAERS and CVAR were cross-referenced with a dynamic registry (CredibleMeds) of QTc-prolonging drugs[19] and quantified for each case.

The "hERG safety margin," defined as the ratio of 50% in vitro inhibitory concentration (IC_{50}) of I_{Kr}-current relative to the maximum serum concentration,[3] was calculated through targeted literature review to assess biologic plausibility of any signals of ventricular arrhythmia. The hERG safety margin is an experimental predictor of the clinical risk for torsade de pointes, a distinct polymorphic subtype of the higher-level category of ventricular arrhythmia. Data on opioid-associated mortality from 1999 to 2020 from the Centers for Disease Control and Prevention[1,4] were then tabulated to provide a temporal framework for interpretation of emerging signals of opioid-associated arrhythmia.

STATISTICAL ANALYSIS. Summary statistics were presented for sociodemographic, clinical, and concurrent medication data. The primary outcome was ventricular arrhythmia/cardiac arrest, and the secondary outcome was QTc-prolongation/torsade de pointes, recognizing that torsade de pointes is subtended within the primary outcome. Given insufficient kratom cases in the CVAR database, confirmatory analyses of kratom-associated adverse event reports were performed in CAERS. The primary method to detect signals of disproportionate reporting for arrhythmia events was the proportionate reporting ratio (PRR), which was calculated with 95% CIs as

$$\frac{\textit{Arrhythmia events (drug of interest)}/\textit{All events (drug of interest)}}{\textit{Arrhythmia events (all other drugs)}/\textit{All events (all other drugs)}}$$

The empirical Bayes gamma poisson shrinker (GPS), and Bayesian confidence propagation neural network (BCPNN) were used for confirmation. The GPS model uses a Poisson data distribution (likelihood) to generate contingency tables in which rows represent drugs of interest and columns adverse events of interests.[20] The BCPNN model aims at automatic pattern recognition to identify adverse event clusters not known to occur with specific classes of drugs.[21] These models may be well suited for opioids, which are generally not considered to be proarrhythmic.

Raw data from all reporting systems were managed with the use of a MySQL server version 8.0.28-arm64 (Oracle Corporation) in the Google Cloud Platform. Statistical analyses were performed with the use of the R statistical package (RStudio). Analyses of

TABLE 1 Characteristics of Opioid-Associated Arrhythmia Reports in U.S. Food and Drug Administration Adverse Event Reporting System

	Mitragynine	Methadone	Loperamide	Buprenorphine	Diphenoxylate	Naltrexone	*P* Value
Ventricular arrhythmia/cardiac arrest	46	1,163	1,008	429	73	42	
Age, y	34 ± 9	40 ± 15	44 ± 18	40 ± 19	60 ± 19	39 ± 16	<0.001
Male	43 (94)	574 (55)	511 (56)	222 (54)	48 (73)	19 (53)	<0.001
Drug role							<0.001
Primary suspect	16 (35)	219 (19)	568 (56)	120 (28)	6 (7)	29 (69)	
Secondary suspect	30 (65)	783 (67)	138 (14)	232 (54)	13 (16)	1 (2)	
Concomitant	0 (0)	100 (9)	290 (29)	77 (18)	0 (0)	12 (29)	
Interacting	0 (0)	61 (5)	12 (1)	1 (0)	0 (0)	0 (0)	
Concomitant QTc-prolonging drugs							<0.001
0	18 (39)	352 (30)	467 (46)	162 (38)	4 (6)	28 (67)	
1	13 (28)	342 (29)	220 (22)	126 (29)	8 (11)	1 (3)	
≥2	15 (33)	469 (40)	321 (32)	141 (33)	61 (84)	13 (31)	
Clinical outcome							
Death	42 (91)	852 (73)	371 (37)	30 (7)	55 (75)	11 (26)	<0.001
Hospitalization	20 (44)	499 (43)	718 (71)	20 (5)	44 (60)	22 (52)	<0.001
QTc-prolongation/torsade de pointes	2	608	755	96	10	22	
Age, y	17	43 ± 17	40 ± 18	57 ± 19	64 ± 10	37 ± 13	<0.001
Male	2 (100)	323 (50)	332 (50)	33 (41)	4 (40)	4 (21)	<0.001
Drug role							<0.001
Primary suspect	1 (50)	231 (38)	513 (68)	43 (45)	1 (10)	5 (23)	
Secondary suspect	1 (50)	286 (47)	103 (14)	12 (12)	4 (40)	8 (36)	
Concomitant	0 (0)	41 (7)	112 (15)	40 (42)	1 (10)	8 (36)	
Interacting	0 (0)	101 (17)	22 (3)	1 (1)	4 (40)	1 (4)	
Concomitant QTc-prolonging drugs							<0.001
0	2 (100)	148 (24)	399 (53)	23 (24)	1 (10)	2 (9)	
1	0 (0)	171 (28)	142 (19)	16 (17)	2 (20)	3 (14)	
≥2	0 (0)	289 (48)	214 (28)	57 (59)	7 (70)	17 (77)	
Clinical outcome							0.007
Death	0 (0)	69 (11)	69 (9)	1 (1)	2 (20)	0 (0)	
Hospitalization	1 (50)	262 (43)	589 (78)	13 (14)	6 (60)	16 (73)	

Values are n, mean ± SD, or n (%).

pharmacovigilance signals of disproportionate reporting were performed with the use of the *mdsstat* package version 0.3.2 (ASM). We designated the PRR as our primary metric for evaluating signals of disproportionate reporting, which has been shown to provide results similar to the aforementioned Bayesian methods when >3 adverse events are observed and is used by the FDA, Eudravigilance, and the UK's Yellow Card Scheme. A PRR was considered to be elevated according to standard empirically derived criteria: 1) PRR ≥2.0; 2) chi-square ≥4; and 3) at least 3 unequivocal adjudicated arrhythmia reports.[14-16] Annual opioid-associated deaths expressed as rate per 100,000 was tabulated from National Vital Statistics System Data (Multiple Cause of Death Module: 1999-2020 and U.S. Overdose Deaths, Centers for Disease Control and Prevention). A *P* value of <0.05 was taken to represent statistical significance for all chi-square (categoric) and analysis of variance (continuous) testing.

RESULTS

In total, 9,302,768 FAERS and 514,064 CVAR reports were analyzed (total 10,051,579). In FAERS, 235,403 verbatim drug names were matched to 2,371 Drugs@FDA active ingredients, representing 97.1% of all reports. In CVAR, 17,016 were matched to 1,734 Drugs@FDA active ingredients, representing 96.9% of all reports. The demographic and clinical characteristics of persons with ventricular arrhythmia/cardiac arrest and QTc-prolongation/torsade de pointes in FAERS stratified by opioids of interest are summarized in Table 1. Mitragynine users were significantly younger (34 ± 9 years) whereas diphenoxylate patients were significantly older (60 ± 19 years) compared with other drug groups. Concurrent use of known QTc-prolonging drugs was common, ranging from 33% (naltrexone) to 94% (diphenoxylate).

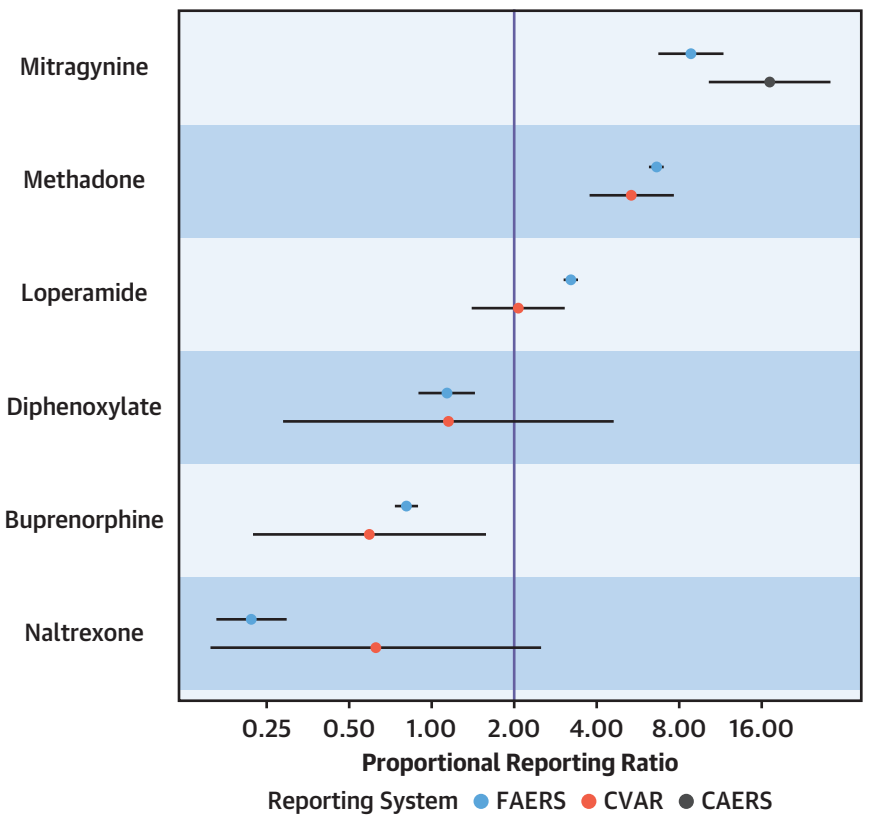
Arrhythmia report frequencies, corresponding PRR and chi-square values for the opioids vs all other drug

TABLE 2 Proportionate Reporting Ratios for Opioid-Associated Ventricular Arrhythmia or Cardiac Arrest in FAERS

	Drug	No Drug	PRR	Chi-Square	*P* Value
Ventricular arrhythmia/cardiac arrest					
Mitragynine[a]	46/731 (6.3)	66,048/9,302,037 (0.7)	8.9	315	<0.001
Methadone[a]	1,163/25,199 (4.6)	64,931/9,277,569 (0.7)	6.6	5456	<0.001
Loperamide[a]	1,008/44,394 (2.3)	65,086/9,258,374 (0.7)	3.2	1537	<0.001
Buprenorphine	429/74,184 (0.6)	65,665/9,228,584 (0.7)	0.8	20	1.0
Diphenoxylate	81/11,257 (0.7)	66,482/9,292,511 (0.7)	1.0	0	1.0
Naltrexone	42/26,679 (0.2)	66,052/9,276,089 (0.7)	0.3	115	1.0
QTc-prolongation/torsade de pointes					
Mitragynine	2/731 (0.3)	19,350/9,302,039 (0.2)	1.3	0	-
Methadone[a]	608/25,199 (2.4)	18,793/9,056,828 (0.2)	11.9	5900	<0.001
Loperamide[a]	755/44,394 (1.7)	18,613/9,258,374 (0.2)	8.5	4775	<0.001
Buprenorphine	96/74,211 (0.1)	19,259/9,228,584 (0.2)	0.6	22	1.0
Diphenoxylate	13/11,257 (0.1)	19,339/9,292,511 (0.1)	0.5	4	1.0
Naltrexone	22/26,679 (0.1)	19,346/9,276,089 (0.2)	0.4	20	1.0

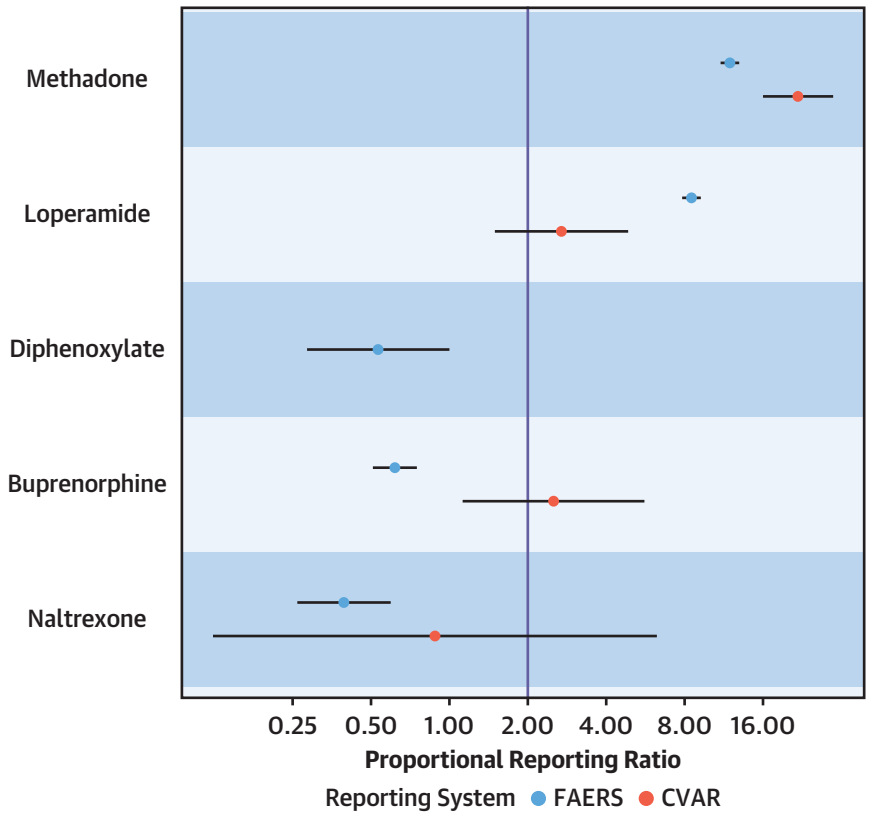
[a]Meets criteria for significant disproportionate reporting (PRR >2, number of events >3, and chi-square >4).
PRR = proportional reporting ratio.

FIGURE 1 Proportional Reporting Ratios for Ventricular Arrhythmia/Cardiac Arrest, 2015-2021



Analysis of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), and Canada Vigilance Adverse Reaction database (CVAR) shows consistent differences between study medications in disproportionate reporting of ventricular arrhythmia or cardiac arrest.

FIGURE 2 **Proportional Reporting Ratios for QTc-Prolongation/Torsade de Pointes, 2015-2021**

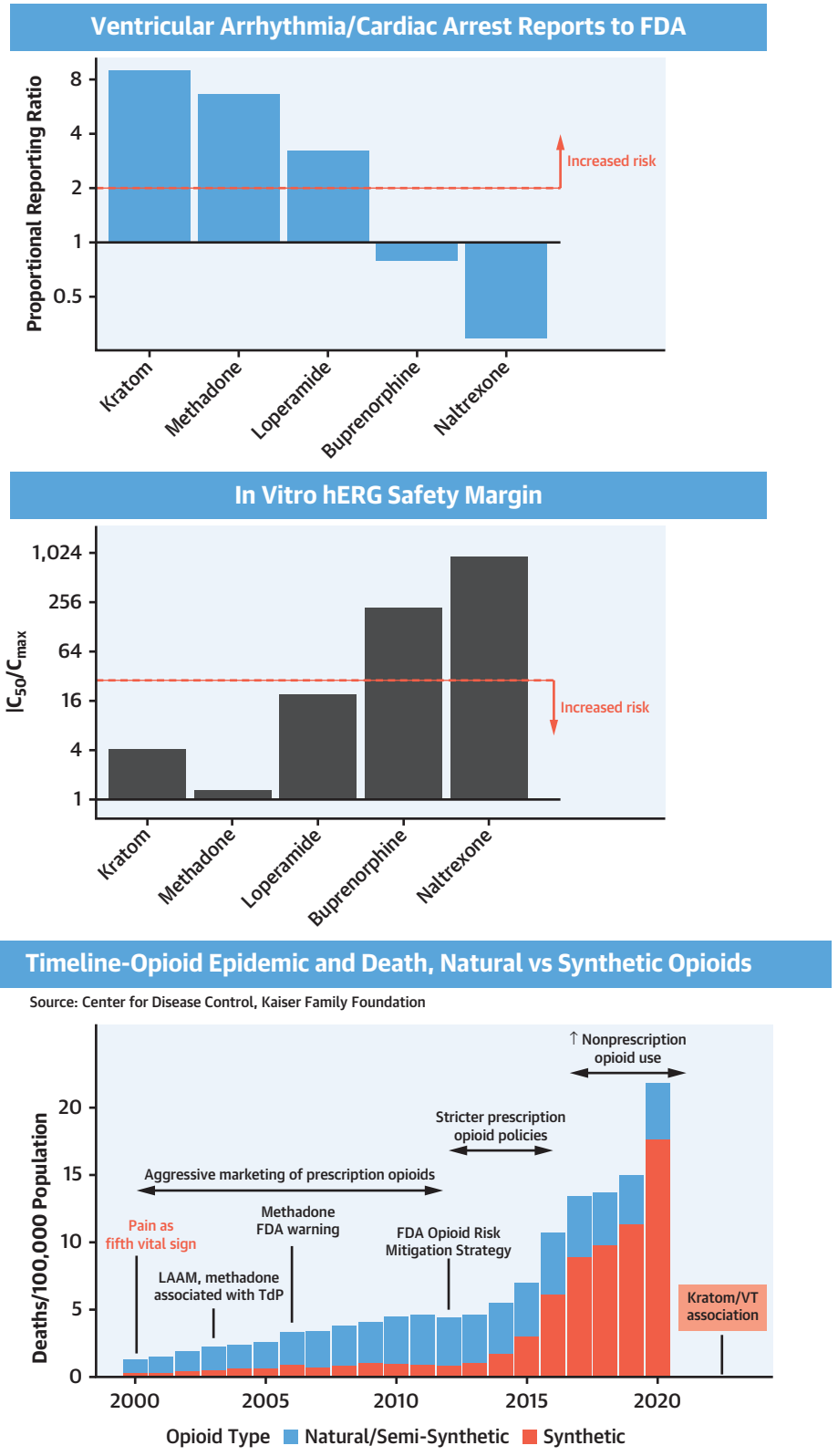


Analysis of FAERS and CVAR show consistent differences between study medications in disproportionate reporting of QTc-prolongation or torsade de pointes. Abbreviations as in Figure 1.

reports in FAERS are summarized in Table 2. Mitragynine, methadone, and loperamide were associated with a significant ventricular arrhythmia risk signal (PRRs 8.9 [95% CI: 6.7-11.7], 6.6 [95% CI: 6.2-7.0], and 3.2 [95% CI: 3.0-3.4], respectively). Methadone and loperamide were also associated with an analogous signal for QTc-prolongation/torsade de pointes (PRRs 11.9 [95% CI: 11.0-12.9] and 8.5 [95% CI: 7.9-9.1], respectively), whereas mitragynine did not, given only 2 total reports. The number of reports in CVAR (n = 514,064) was substantially lower than in FAERS. Descriptive statistics for patient reports (Supplemental Table 1) and risk signals (Supplemental Table 2) in CVAR demonstrated that loperamide and methadone had notably more reports of both ventricular arrhythmia/cardiac arrest and QTc-prolongation/torsade de pointes vs buprenorphine, naltrexone, and diphenoxylate, confirmatory of FAERS. All findings were similar with the use of GPS and BCPNN signal detection algorithms.

There were 34,971 specific product reports submitted to CAERS during the study period. Of the 375 reports involving mitragynine, 17 (4.5%) reported ventricular arrhythmia or cardiac arrest. In comparison, ventricular arrhythmia/cardiac arrest were reported in only 92/34,596 (0.3%) of all other identified products and only 125/55,870 (0.2%) of all other cases. This corresponded to a substantially elevated PRR of 17.1 (chi-square = 204; $P < 0.001$); death occurred in 13/17 cases (76%) of mitragynine-associated ventricular arrhythmia/cardiac arrest. Notably, despite representing only 1% of all CAERS reports, mitragynine accounted for 30% of ventricular arrhythmia/cardiac arrest deaths. There was only 1 report of mitragynine-related QTc-prolongation/torsade de pointes, although only 5 reports for all drugs were observed during the study period. Arrhythmia reporting for all 3 databases are compared in Figures 1 and 2. Disproportionate reporting of ventricular arrhythmia/cardiac arrest were consistently noted for

CENTRAL ILLUSTRATION **Opioid Arrhythmia Reports and Safety Margins During Rising Opioid Mortality**



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mitragynine, methadone, and loperamide, while signals of QTc-prolongation/torsade de pointes were limited to methadone and loperamide.

DISCUSSION

From 2015 to 2021, a substantial number of ventricular arrhythmia reports associated with prescription, over-the-counter, and unregulated recreational opioids were recorded in North America. These reports surfaced during evolution of the opioid epidemic, as addicted individuals moved from prescription narcotics to repurposed medications (loperamide) and poorly understood traditional remedies (kratom), inadvertently unmasking heretofore unrecognized arrhythmia hazards (**Central Illustration**). This shift to novel opioids raises public health and regulatory challenges regarding variable scheduling classifications and widespread drug availability. In the present study, the risk signal for ventricular arrhythmia/cardiac arrest was most pronounced for mitragynine, a pharmacologically complex opioid-stimulant that is nonscheduled. Notably, 91% of reports in FAERS and 76% in CAERS resulted in death. Similarly, the over-the-counter antidiarrheal agent loperamide was associated with both ventricular arrhythmia/cardiac arrest and QTc-prolongation/torsade de pointes, with fatalities in more than one-third of reports. This suggests that a shift toward over-the-counter and recreational opioids poses novel cardiovascular hazards.

In **Table 3**, the relationships between hERG safety margins and QTc-prolongation/torsade de pointes reports of over-the-counter and recreational opioids are compared with synthetic opioids known to cause ventricular arrhythmia. There was expected alignment for methadone, with clear signals for both ventricular arrhythmia and QTc-prolongation/torsade de pointes along with pronounced hERG liability. Loperamide exhibited alignment with methadone owing to a similar dual aromatic ring structure that intercalates within the hERG channel. This relationship, however, was dissociated for 2 mechanistically complex opioids: buprenorphine, a mixed μ-opioid agonist/antagonist, and kratom, a multicomponent herbal compound including the active alkaloid mitragynine. Both are pharmacologically distinct from methadone, the archetype for hERG-blocking opioids.[3] Finally, no arrhythmia signal was observed with the pure antagonist naltrexone or the prescription antidiarrheal diphenoxylate, both devoid of hERG blockade.

The most commonly recognized mechanism of opioid-associated mortality is ventilatory depression. Nevertheless, malignant arrhythmias are also well documented, and these mechanisms are not mutually exclusive. Indeed, methadone causes a dose-dependent reduction in oxygen saturation during sleep, correlating with increased QT interval variability and ventricular ectopy.[22] In contrast, mitragynine departs from this paradigm in that respiratory and central nervous system depression are uncommonly reported.[23] Mitragynine is a partial μ-opioid agonist and δ-opioid antagonist that does not recruit β-arrestin-2 activity,[24,25] the pathway associated with tolerance and sympathetic nervous system activation.[26] In an observational study, no evidence of an increased incidence of QTc-prolongation was noted,[27] though an 8-fold increase in sinus tachycardia occurred, suggestive of increased sympathomimetic activity. These properties have led some to describe mitragynine as a safer alternative to conventional opioids.[28] This opinion, however, is undermined by the present study, which suggests that mitragynine possessed the strongest signal of disproportionate ventricular arrhythmia reporting.

Mitragynine exhibits modest hERG blockade with an estimated mean IC_{50} of 0.62 μmol/L.[29,30] Maximum total plasma levels are approximately 0.15 μmol/L,[31,32] yielding an hERG safety margin of 4.1, approaching that of methadone. Although this indicates a theoretic arrhythmia propensity, no disproportionate reporting was detected (3 total reports). This sparsity comports with the literature, where only 1 published case of polymorphic ventricular tachycardia associated with kratom was noted in a systematic review through 2021.[33] Two potential

CENTRAL ILLUSTRATION Continued

(Top) Opioid arrhythmia reporting to the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). Risk is conveyed as a proportional reporting ratio (PRR), akin to an OR, for ventricular arrhythmia/cardiac arrest among the various opioids in descending order of risk from left to right. PRR >2 **(dashed line)** suggests increased risk. **(Middle)** panel shows the hERG safety margin, a pharmacologic metric to determine risk for drug-induced QTc-prolongation/torsade de pointes (TdP). A margin <30 **(dashed line)** connotes increased risk. **(Bottom)** Timeline from 1999 to 2020 with Centers for Disease Control and Prevention statistics showing a substantial rise in opioid deaths per 100,000 population (y-axis). Synthetic opioid deaths **(red)** predominate over natural/semisynthetic drugs **(blue)** during the past several years. Sentinel events during the opioid epidemic and emergence of opioid-associated TdP and ventricular tachycardia (VT) are presented sequentially, starting with the Joint Commission endorsing pain as the fifth vital sign. LAAM = levacetylmethadol.

TABLE 3 Comparative Electrophysiologic Properties of Opioid Analogs

Drug	ΔQTc Magnitude[a]	I_{kr} IC_{50}, μmol/L	C_{max},[b] μmol/L, Total (Free)	hERG Safety Margin,[c] Total (Free)	Plasma Protein Binding	Intrinsic Arrhythmia Risk Factors	Extrinsic Arrhythmia Risk Factors	Torsade de Pointes[d]
Mitragynine	+	0.62	0.15 (0.008)	4.1 (88)	95%	Stimulant properties, multiple alkaloids	Addiction patients, polypharmacy	No
Methadone	++	3	3.6 (0.36)	0.83 (6.4)	90%	Na^+, Ca^{2+}, I_{K1} blockade, CYP3A4, long $T_{1/2}$	Addiction and pain patients, psychotropic and ARV potentiate QTc-prolongation	Yes
Loperamide (labeled)	–	0.04	0.001 (<0.001)	40 (80)	95%	-	-	No
Loperamide (abuse/OD)	++	0.04	0.05 (0.003)	0.8 (13.3)	95%	Na^+ blockade, PGP + CYP3A4 inhibitor	Addiction patients, polypharmacy	Yes
Buprenorphinee	+	75	0.36 (0.014)	208 (>500)	96%	Mixed μ-agonist/antagonist	Addiction patients, polypharmacy	No
Diphenoxylate	–	-	-	-	75%-95%	Combined with atropine[e]	-	No
Naltrexone	–	31	0.035 (0.028)	>500 (>500)	20%	Pure antagonist	Addiction patients	No

[a]–) no QTc-liability; +) >10 ms increase; ++) >20 ms increase. [b]C_{max} given as total and (free) plasma concentration, the latter calculated based on listed plasma protein binding percentage (FDA ICH E14/S7B). [c]hERG safety margin = IC_{50} divided by C_{Max} (total [free]), where lower ratios connote reduced arrhythmia safety margin. [d]Reports from CredibleMeds.[19] [e]Atropine may alter autonomic factors involved in repolarization (eg, ↑ heart rate).

ARV = antiretroviral medications; C_{max} = maximum serum concentration; CYP = cytochrome P; IC_{50} = 50% in vitro inhibitory concentration; OD = overdose; PGP = P-glycoprotein; $T_{1/2}$ = half-life.

explanations for the absence of torsade de pointes warrant consideration. First, mitragynine is highly protein bound, with variable binding to plasma proteins. Applying the proposed free plasma concentration rather than total results in a substantially greater safety margin (Table 3). A second possibility is that mitragynine's arrhythmia mechanism might not solely involve QTc-prolongation. This might be analogous to that of propoxyphene (Darvon), which was removed from the market for ventricular arrhythmia despite only 1 case of torsade de pointes in the literature. Propoxyphene is a potent inhibitor of voltage-gated sodium channels, which can promote monomorphic rather than polymorphic ventricular tachycardia.[3] The importance of looking beyond hERG blockade when evaluating opioid proarrhythmic potential has been recently investigated: in addition to inhibiting hERG, methadone equipotently blocked I_{K1}, the ion channel responsible for terminal repolarization and U-waves on surface electrocardiography, likely amplifying its risk.[34] Finally, the cardiac ion-channel effects of kratom are likely complex because the available product represents an admixture of >50 bioactive alkaloids rather than a single pharmacologic entity.[35]

Similar to kratom, the nonprescription opioid loperamide remains widely accessible and inexpensive despite commendable efforts by the FDA to limit quantities for purchase of this antidiarrheal agent. Given this landscape of addiction-driven experimentation, ongoing pharmacovigilance is needed to identify newly emerging threats. These efforts must be coupled with methodologically robust prospective, dose-controlled, clinical studies assessing the impact of these over-the-counter and recreational opioids on both cardiac repolarization and cardiac rhythm.

STUDY LIMITATIONS. We acknowledge several limitations to interpreting arrhythmia risk signals. First, pharmacovigilance data, though providing large numbers of reports, cannot measure incidence, and causal determinations cannot be made. Redundant counting was minimized, but the same adverse event could be reported in the FAERS and CAERS databases. Additional risky behaviors, including unmeasured illicit drug ingestion, may have played a role in case fatalities but not captured in voluntary reporting. This confounding may be particularly relevant for mitragynine, given discordance in lines of evidence: few cases of torsade de pointes despite concerning hERG inhibition and electrocardiographic data, albeit limited, that is not indicative of QTc liability. Although the number of arrhythmia reports for loperamide was large, the overall number was quite low for mitragynine, limiting robustness of the estimate. Third, though typical for all proarrhythmic drugs, concomitant QTc-prolonging agents were reported. Notwithstanding these limitations, signal confirmation in 2 North American databases (U.S. and Canada) increases causal likelihood. Overall, biological plausibility, confirmed case reports, and substantial signals of disproportionate reporting raise public health concern regarding the proarrhythmic potential for both the over-the-counter drug loperamide and the recreational opioid kratom.

CONCLUSIONS

Certain prescription opioid analogs have been shown to be proarrhythmic, particularly the long-acting synthetic opioid methadone. With increasingly stringent opioid prescribing practices, opioid-dependent patients are turning toward alternative drugs, including over-the-counter and nonscheduled opioids as substitutes. The data from multiple adverse event reporting systems suggest that mitragynine and loperamide may represent underappreciated triggers for malignant arrhythmias. Although a convincing mechanistic link between mitragynine and ventricular arrhythmia is lacking, our pharmacovigilance findings suggest that additional in vitro and clinical research, quantifying the arrhythmia liability of this novel compound, is needed. This is essential to inform regulatory decisions in the ever-changing landscape of opioid use and abuse.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients presenting with malignant ventricular arrhythmia, both prescription and nonprescription opioids should be considered as potential causes.

TRANSLATIONAL OUTLOOK: Prospective studies of nonprescription drugs with potential arrhythmia liability along with targeted collaboration between industry, regulatory, and academic stakeholders are needed to address emerging public health threats.

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KEY WORDS arrhythmia, kratom, loperamide, methadone, mitragynine, QTc-prolongation

APPENDIX For supplemental tables, please see the online version of this paper.