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Cardiovascular Risk of Opioids: A Real-World Study Based on FAERS

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Abstract: *Objective*: This research utilizes the FAERS for data mining to identify heart-related side effects caused by opioids, ensuring the safe use of these medications. *Methods*: Data from 79 quarters (Q1 2004 to Q3 2023) involving adverse event (AE) reports for opioids like morphine and oxycodone was reviewed. We applied the MedDRA system to categorize events and used statistical tools, ROR and BCPNN, for signal detection. These findings were cross-checked with drug labels and SIDER 4.1 for accuracy. Identified risks were then categorized by severity using DME and IME classifications. *Results*: Analysis of adverse events (AEs) for the five examined drugs (35359, 14367, 144441, 10592, and 28848) identified 33, 6, 12, 37, and 34 cardiovascular AEs, and 16, 5, 7, 25, and 21 instances of important medical events (IMEs) respectively. Each drug was linked to cases of cardiac and cardiopulmonary arrest. The cardiovascular AEs varied widely in occurrence and severity, with methadone notably presenting diverse and potent risks, including sudden cardiac death as a distinct medical event (DME). A comparison with SIDER 4.1 showed 11 opioid-related cardiovascular AEs in line with our findings. Standardized MedDRA Queries (SMQs) confirmed these results, indicating stronger signals for methadone and tramadol, while morphine, hydromorphone, and oxycodone exhibited fewer and weaker signals. *Conclusion*: The study revealed numerous heart-related adverse effects (AEs) not listed on drug labels and identified new AE patterns. Recognizing these differences in AE profiles and risks across different opioids is crucial for safer prescription practices to minimize cardiac complications.

Keywords: Opioids; FAERS; Cardiovascular adverse events; Morphine; Hydromorphone; Oxycodone; Methadone; Tramadol

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1. Introduction

Opioids may induce or exacerbate cardiovascular adverse events (CVAEs) through various mechanisms [1], including arrhythmias [2], cardiac arrest [3], myocardial infarction [4], and heart failure [4], among others. Though the association between opioids and CVAEs has been reported in the existing literature, most studies are retrospective cohort studies, case reports, and small-scale prospective controlled studies, which are limited to the use

of specific drugs or populations. These studies lack a comprehensive risk assessment under real-world clinical medication scenarios. This study, leveraging over 16 million real-world medication records from the FAERS database, identifies CVAEs associated with specific opioids, systematically evaluates the CVAE risks of commonly used opioids, and compares the risk differences between various drugs, aiming to provide a reference for clinical medication practices.

2. Data processing and statistical methods

(1) Source of Data: FDA official website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html)

(2) Statistical analysis and plotting software: SAS9.4 for statistical analysis and WPS, Chiplot (online version) [5], and Bioinformatics (online version) [6] for graphing.

(3) Data cleansing: DEMO table's PRIMARYID, CASEID, and FDA_DT fields were selected, retaining reports with the same CASEID but the greatest FDA_DT value; and for identical CASEID and FDA_DT, the highest PRIMARYID value was preserved.

(4) Adverse event name encoding: MedDRA 26.1 (Medical Dictionary for Regulatory Activities, MedDRA) was adopted for encoding and correcting the nomenclature of adverse events in the database.

(5) Signal detection method and calculation: The disproportionality method was employed for drug adverse event signal detection. The reporting odds ratio (ROR; $ROR = a \times (c + d) / c \times (a + b)$, where a is the number of cases where both the specific drug and specific adverse reaction are reported; b is the number of cases where the drug is reported but not the adverse reaction; c is the number of cases where the adverse reaction is reported but not the drug; and d is the number of cases where neither the drug nor the adverse reaction is reported) method was used to generate signals, with a threshold of $a \geq 3$ and 95% CI (lower limit) > 1 indicating the production of a signal [7]. The Bayesian Confidence Propagation Neural Network (BCPNN) method was used to evaluate the intensity of signals [8], with thresholds defined as follows: IC-2SD ≤ 0 indicating no signal, 0 < IC-2SD ≤ 1.5 indicating a weak signal, 1.5 < IC-2SD ≤ 3.0 indicating a moderate signal, and > 3.0 IC-2SD indicating a strong signal.

(6) Target drugs: Target drug screening was conducted through the DRUGNAME and PROD_AI fields. The aim is to furnish a reference for clinical medication use.

3. Results

3.1. Data filtering outcomes and patient

The information about the patient demographics and filtered results are shown in **Table 1**. Female patients more commonly used morphine, hydromorphone, and tramadol, while oxycodone and methadone were prevalent among males. Medical professionals primarily reported on morphine, methadone, and tramadol (60%–70%); in contrast to oxycodone and hydromorphone, which were mainly reported by patients and non-medical individuals like lawyers (over 70%). Reports of oxycodone spiked in 2020–2022, possibly linked to U.S. lawsuits. Methadone-related deaths were disturbingly high at 41.52%.

Table 1. Summary of basic information categories

	Morphine (%)	Hydromorphone (%)	Oxycodone (%)	Methadone (%)	Tramadol (%)
Sex					
Female (%)	17659 (49.94)	7158 (49.82)	56090 (38.83)	3260 (30.78)	14325 (49.66)
Male (%)	13957 (39.47)	6485 (45.14)	80302 (55.60)	4093 (38.64)	10744 (37.24)
Not specified (%)	3743 (10.59)	724 (5.04)	8049 (5.57)	3239 (30.58)	3779 (13.10)
Age					
< 18(%)	1095 (3.10)	202 (1.41)	1559 (1.08)	1329 (12.55)	1228 (4.26)
≥ 18, < 45(%)	5547 (15.69)	1549 (10.78)	10793 (7.47)	3036 (28.66)	6870 (23.81)
≥ 45, < 65(%)	8369 (23.67)	2007 (13.97)	10196 (7.06)	2043 (19.29)	5711 (19.80)
≥ 65, < 75(%)	3360 (9.50)	700 (4.87)	2811 (1.95)	417 (3.94)	2280 (7.90)
≥ 75(%)	2551 (7.21)	641 (4.46)	2295 (1.59)	137 (1.29)	2964 (10.27)
Not specified (%)	14437 (40.83)	9268 (64.51)	116787 (80.85)	3630 (34.27)	9795 (33.95)
Reporting year					
2004 (%)	1122 (3.17)	91 (0.63)	3727 (2.58)	302 (2.85)	396 (1.37)
2005 (%)	1143 (3.23)	173 (1.20)	2775 (1.92)	372 (3.51)	483 (1.67)
2006 (%)	792 (2.24)	190 (1.32)	739 (0.51)	264 (2.49)	391 (1.36)
2007 (%)	458 (1.30)	170 (1.18)	2004 (1.39)	218 (2.06)	653 (2.26)
2008 (%)	883 (2.50)	131 (0.91)	800 (0.55)	341 (3.22)	484 (1.68)
2009 (%)	600 (1.70)	190 (1.32)	662 (0.46)	362 (3.42)	497 (1.72)
2010 (%)	933 (2.64)	211 (1.47)	1255 (0.87)	318 (3.00)	641 (2.22)
2011 (%)	790 (2.23)	250 (1.74)	1057 (0.73)	486 (4.59)	774 (2.68)
2012 (%)	1058 (2.99)	336 (2.34)	987 (0.68)	1676 (15.82)	816 (2.83)
2013 (%)	1873 (5.30)	617 (4.29)	5485 (3.80)	594 (5.61)	1216 (4.22)
2014 (%)	1999 (5.65)	318 (2.21)	2382 (1.65)	392 (3.70)	1221 (4.23)
2015 (%)	2156 (6.10)	398 (2.77)	2283 (1.58)	422 (3.98)	1925 (6.67)
2016 (%)	1964 (5.55)	466 (3.24)	2583 (1.79)	467 (4.41)	1508 (5.23)
2017 (%)	1681 (4.75)	472 (3.29)	2927 (2.03)	572 (5.40)	1803 (6.25)
2018 (%)	4154 (11.75)	490 (3.41)	4136 (2.86)	746 (7.04)	2414 (8.37)
2019 (%)	3698 (10.46)	936 (6.51)	3451 (2.39)	643 (6.07)	3259 (11.30)
2020 (%)	2541 (7.19)	1470 (10.23)	19132 (13.25)	948 (8.95)	3496 (12.12)
2021 (%)	4546 (12.86)	1141 (7.94)	56049 (38.80)	627 (5.92)	2555 (8.86)
2022 (%)	1592 (4.50)	5878 (40.91)	30132 (20.86)	448 (4.23)	2786 (9.66)
2023 (%)	1376 (3.89)	439(3.06)	1875 (1.30)	394 (3.72)	1530 (5.30)
Occupation/Role					
Consumer (%)	8528 (24.12)	4623 (32.18)	51923 (35.95)	2323 (21.93)	6840 (23.71)
Lawyer (%)	3225 (9.12)	5328 (37.08)	68320 (47.30)	53 (0.50)	765 (2.65)
Not specified (%)	2154 (6.09)	344 (2.39)	2178 (1.51)	798 (7.53)	1194 (4.14)
Other health professionals (%)	6015 (17.01)	861 (5.99)	4582 (3.17)	3081 (29.09)	5500 (19.07)

Table 1 (Continued)

	Morphine (%)	Hydromorphone (%)	Oxycodone (%)	Methadone (%)	Tramadol (%)
Pharmacist (%)	5382 (15.22)	1600 (11.14)	5392 (3.73)	2058 (19.43)	6251 (21.67)
Physician (%)	10055 (28.44)	1611 (11.21)	12046 (8.34)	2279 (21.52)	8298 (28.76)
Outcome					
Life-threatening (%)	1397 (3.95)	476 (3.31)	1252 (0.87)	528 (4.98)	1866 (6.47)
Hospitalization - initial or prolonged (%)	5851 (16.55)	2084 (14.51)	11546 (7.99)	1996 (18.84)	9571 (33.18)
Disability (%)	958 (2.71)	1734 (12.07)	22080 (15.29)	113 (1.07)	808 (2.80)
Death (%)	8217 (23.24)	1980 (13.78)	25903 (17.93)	4398 (41.52)	5120 (17.75)
Congenital anomaly (%)	59 (0.17)	82 (0.57)	645 (0.45)	177 (1.67)	114 (0.40)
Required intervention to prevent permanent impairment/damage (%)	598 (1.69)	223 (1.55)	340 (0.24)	81 (0.76)	120 (0.42)
Others (%)	13680 (38.69)	10001 (69.61)	116769 (80.84)	4885 (46.12)	14057 (48.73)

3.2. Distribution of CVAE signals

Across five medications, a total of 76 CVAE-positive signals were detected (**Figure 1C**). Morphine, hydromorphone, oxycodone, methadone, and tramadol accounted for 33, 6, 12, 37, and 34 signals respectively (**Figure 1B**). All five drugs exhibited signals of cardiac arrest and cardiorespiratory arrest (**Figure 1A**).

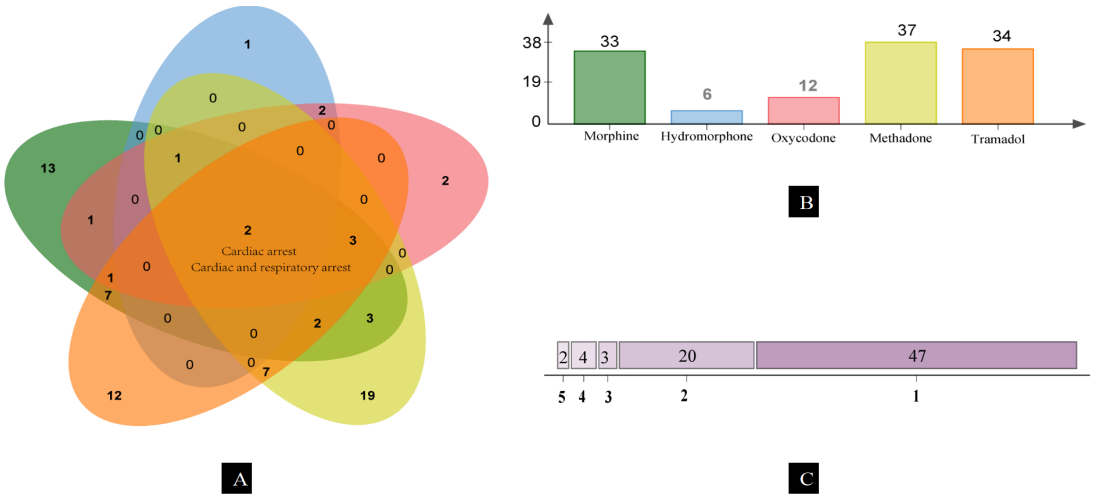

Figure 1. CVAE signal distribution

3.3. Comparison between CVAE signal frequency and IME/DME

Morphine was mentioned in 2,427 reports (6.8% of the total), primarily involving sudden cardiac arrest (513 cases). It was associated with 16 IMEs and 17 unlisted adverse events (AEs) (**Figure 2A**). Hydromorphone had 370 reports (2.5%), with heart anomalies as the leading issue (129 cases), and 5 IMEs noted (**Figure 2B**). Oxycodone was cited in 4,299 reports (2.9%), mainly for heart anomalies (1,659 cases), and included 7 IMEs (**Figure 2C**). Methadone appeared in 1,734 reports (1.6%), mostly for sudden cardiac arrest (448 cases), with one DME and 25 IMEs (**Figure 2D**). Tramadol was reported 2,258 times (7.8%), with tachycardia being the most frequent event (455 cases), and 21 IMEs were recorded (**Figure 2E**).

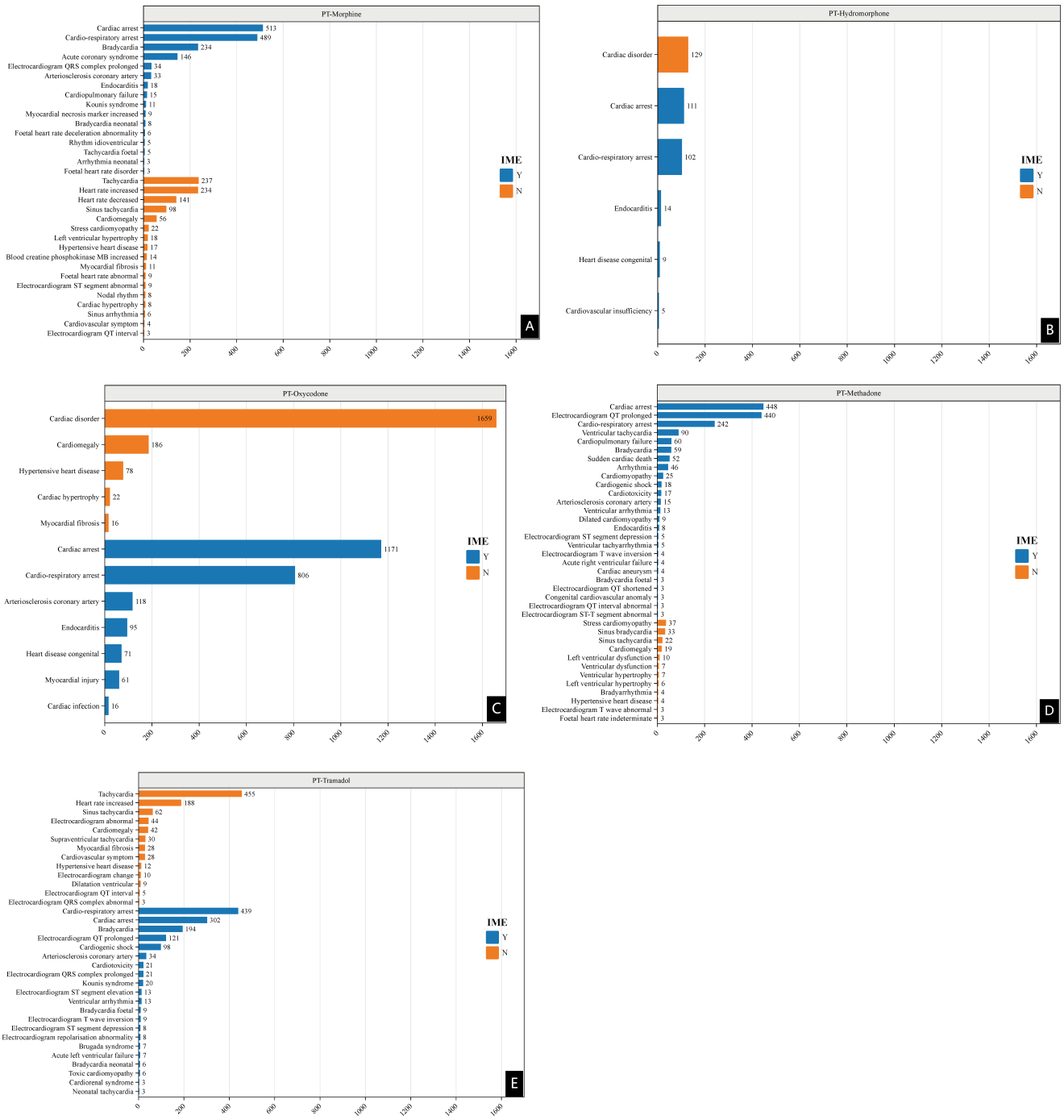

Figure 2. Comparison of PT signal frequency and IME, DME

3.4. CVAE signal intensity outcomes

Figure 3D shows that the methadone group was associated with five significant issues: cardiac arrest, prolonged QT on ECGs, cardiopulmonary arrest, heart failure, and sudden death due to heart problems, with the latter posing a high safety concern. Tramadol use was linked to two notable effects: heart tissue scarring and heart-related issues, as seen in **Figure 3E**, which may be a new finding not reported previously. Morphine users experienced three concerning effects: cardiac arrest, cardiopulmonary arrest, and acute heart blockages (**Figure 3A**). Hydrocodone was connected to one issue of moderate concern: heart disease related to high blood pressure (**Figure 3C**). Meanwhile, the hydromorphone group showed only minor issues (**Figure 3B**).

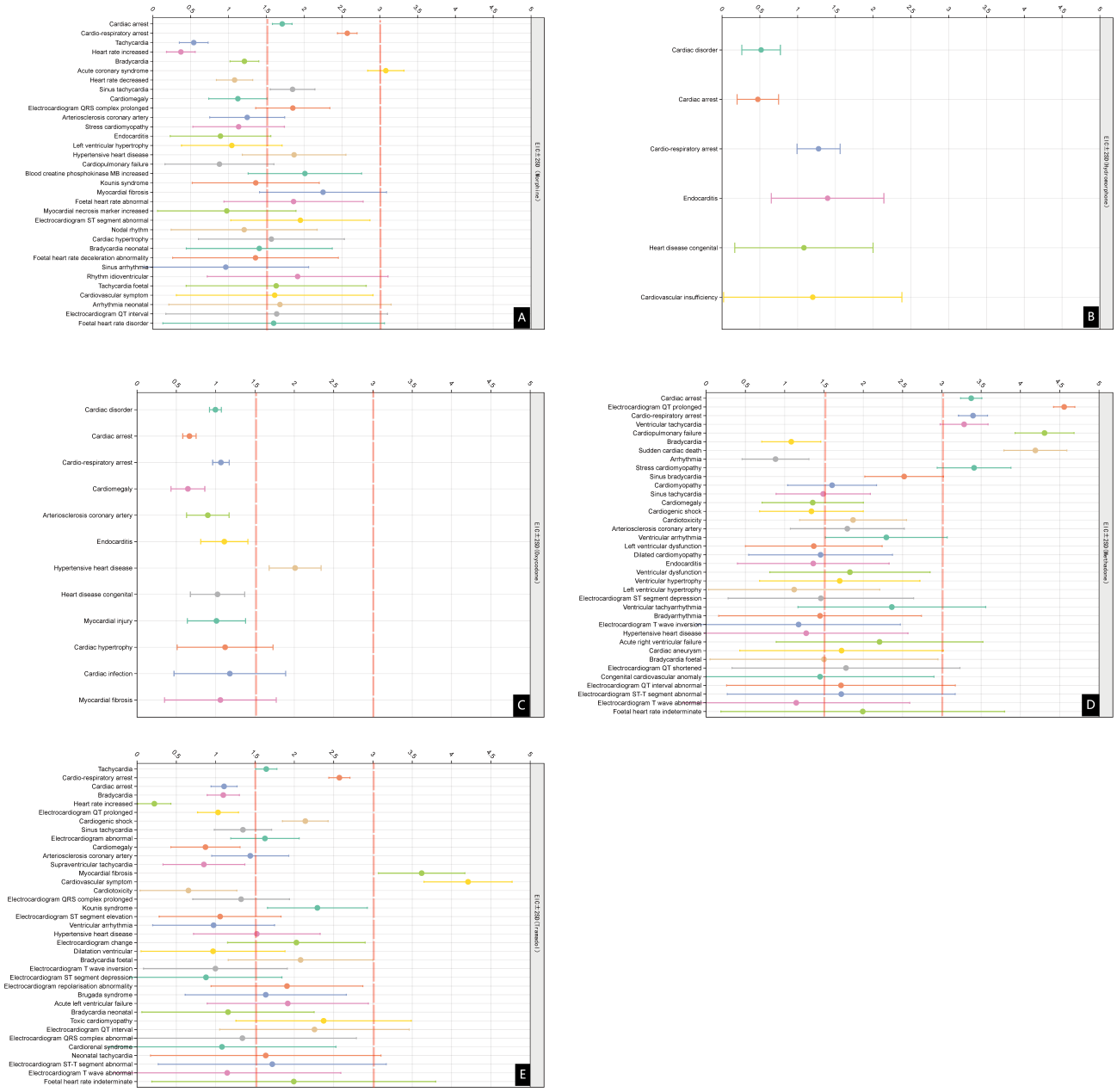

Figure 3. PT signal strength distribution map

3.4. SMQ analysis

Methadone is associated with the highest number of CVAEs, with 11 signals identified in the SMQ analysis, including 5 strong signals and 1 moderate signal, characterized by a high frequency of occurrence and robust signal strength. Tramadol exhibited a moderate intensity signal in shock-related circulatory or cardiac conditions, excluding torsade de pointes type ventricular tachycardia. Morphine, hydromorphone, and oxycodone displayed weak signals (**Table 2**).

Table 2. SMQ calculation results

	SMQs	*n*	ROR (95% CI)	IC_{25} (EIC ± 2SD)	Strength
Morphine	Shock-associated circulatory or cardiac conditions (excl. torsade de pointes)	1,255	2.91 (2.76–3.08)	1.53 (1.44–1.61)	+
Hydromorphone	Shock-associated circulatory or cardiac conditions (excl. torsade de pointes)	293	1.32 (1.18–1.48)	0.4 (0.23–0.57)	+
Oxycodone	Shock-associated circulatory or cardiac conditions (excl. torsade de pointes)	2,243	1.09 (1.05–1.14)	0.13 (0.07–0.19)	+
Methadone	Shock-associated circulatory or cardiac conditions (excl. torsade de pointes)	934	8.18 (7.66–8.73)	2.99 (2.88–3.07)	++
Morphine, Hydromorphone, Oxycodone, Methadone, Tramadol	Torsade de pointes, shock-associated conditions	791	20.23 (18.85–21.72)	4.29 (4.15–4.36)	+++
	Torsade de pointes/QT prolongation	779	25.73 (23.95–27.64)	4.63 (4.48–4.69)	+++
	Conduction defects	491	12.07 (11.04–13.20)	3.56 (3.4–3.66)	+++
	Ventricular tachyarrhythmias	398	15.29 (13.84–16.88)	3.9 (3.71–4.00)	+++
	Cardiac failure	220	1.57 (1.38–1.80)	0.65 (0.45–0.84)	+
	Cardiomyopathy	97	3.19 (2.61–3.90)	1.67 (1.35–1.93)	+
	Cardiac arrhythmia terms, nonspecific	62	1.59 (1.24–2.04)	0.67 (0.29–1.02)	+
	Arrhythmia-related investigations, signs, and symptoms	55	22.52 (17.25–29.39)	4.47 (3.62–4.40)	+++
	Disorders of sinus node function	38	4.12 (3.00–5.67)	2.04 (1.47–2.39)	+
	Tachyarrhythmia terms, nonspecific	4	4.35 (1.63–11.62)	2.12 (0.09–2.67)	+
Tramadol	Bradyarrhythmia terms, nonspecific	1,173	3.05 (2.88–3.23)	1.59 (1.5–1.67)	++
	Shock-associated circulatory or cardiac conditions (excl. torsade de pointes)	297	2.23 (1.99–2.5)	1.15 (0.98–1.31)	+
	Torsade de pointes, shock-associated conditions	167	1.61 (1.38–1.87)	0.68 (0.45–0.90)	+
	Torsade de pointes/QT prolongation	115	1.31 (1.09–1.57)	0.39 (0.12–0.65)	+
	Ventricular tachyarrhythmias	19	2.33 (1.48–3.65)	1.21 (0.48–1.77)	+
	Arrhythmia-related investigations, signs, and symptoms	8	2.55 (1.28–5.12)	1.35 (0.15–2.08)	+

3.5. Comparison between CVAE signals and SIDER4.1

In SIDER4.1, 14 CVAEs associated with the target drug were identified, of which eleven showed relevant signals in the analysis. No related signals were detected for the three AEs: arrhythmia, heart failure, and ventricular fibrillation.

4. Discussion

The increasing cardiovascular dangers of opioids are concerning, with studies linking them to a rise in heart disease and fatalities [9]. Research including nearly 40,000 subjects found a higher chance of cardiac arrest outside hospitals with opioid use [10], and reviews cite connections to arrhythmias [11]. Most opioids can lead to heart attacks, heart failure, and strokes [12-14]. Particularly, methadone is known for causing QT interval prolongation at low doses, risking deadly arrhythmias like torsades de pointes [9,15]. However, morphine and hydromorphone at standard doses generally do not significantly prolong QT [16]. Yet, high doses of synthetic opioids such as fentanyl and tramadol may carry similar dangers [16]. The cardiovascular risk varies depending on individual health factors, drug interactions, and usage patterns [12,15,17]. Higher-risk populations include heart patients, the elderly, and infants exposed to opioids before birth [18,19]. Women may also experience different cardiovascular risks from opioids [20]. Opioids can harm the cardiovascular system through several pathways:

(1) Methadone blocks the hERG potassium channel, causing QT prolongation and possibly torsades de pointes due to its strong hERG inhibition, unlike the weaker effect of hydromorphone [21]. Tramadol's sodium channel blockade may also lead to ECG changes and arrhythmias [22].

(2) Opioids can disrupt autonomic cardiovascular control, affecting heart rate [14].

(3) Respiratory suppression from opioids can cause hypoxia, which is particularly dangerous for those with pre-existing heart conditions [10,16].

(4) Using opioids with benzodiazepines and antidepressants can heighten arrhythmia risks [22].

(5) Long-term opioid misuse can disrupt hormone levels, impacting cardiovascular health [21].

After extensive analysis of CVAE signals linked to five common opioids, several strategies were suggested to help healthcare providers lessen the risks of opioid-induced CVAEs:

(1) Drugs and dosages should be selected with care, avoiding opioids like methadone that significantly increase the QT interval, preferring safer options such as morphine and hydromorphone, and applying strict dosage regulations [11,15].

(2) ECG and electrolytes should be monitored regularly, particularly for patients on long-term or high-dose opioid therapy or those using QT-prolonging drugs, to prevent QT prolongation and dangerous arrhythmias [4,16].

(3) Patients should be educated, and initial screenings for cardiovascular conditions should be conducted before starting opioid treatment [12,18].

(4) Drug combinations should be optimized, avoiding combinations with other medications that might affect the QT interval or increase cardiovascular burden, with treatments adjusted as necessary [4].

(5) Increased monitoring and support should be provided for high-risk patients, including those with cardiac issues, the elderly, and those recovering from surgery, with intensive vital sign monitoring and preparations for immediate cardiovascular interventions [10,18].

(6) Comorbidities such as hypertension, diabetes, and renal insufficiency should be managed diligently to reduce cardiovascular stress from opioid use [18].

Future research should explore the molecular mechanisms behind opioids' cardiovascular effects [9,11], develop prevention and treatment strategies for early identification and reduction of opioid-related cardiovascular events, and boost data exchange and cross-disciplinary teamwork to improve cohort study and database analysis quality. Despite the FAERS database's variable reports causing reliability issues, the approach — thorough signal analysis involving data review, cleansing, normalization, and literature evaluation — ensures more reliable results than basic disproportionality methods. SIDER4.1 provides strong evidence for confirming cardiovascular adverse event signals with its drug-event pairing data, including placebo-controlled comparisons. Incident

Management Events (IMEs) and Drug Monitoring Events (DMEs) play a crucial role in drug safety and regulation, with IMEs covering non-severe medical events and DMEs involving serious, potentially drug-related AEs. In MedDRA, Standardized MedDRA Queries (SMQs) [19] offer wide-ranging symptom searches for consistency, and Preferred Terms (PTs) [21] ensure accurate recording of medical events. Analyzing both SMQs and PTs enhances signal detection and comprehension of drug safety.

5. Conclusion

Opioid medications often cause CVAEs, with varying effects depending on the drug. Methadone has many severe side effects, while hydromorphone has fewer and milder issues. Oxycodone leads in the number of adverse events reported. This research evaluates the CVAE risks of five widely used opioids to guide safer clinical use.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Golibkhon A, Ugli B, Ugli M, 2023, Opioid Agents and Cardiac Arrhythmia: A Literature Review. Cureus Journal of Medical Science, 15(4): e38007.

[2] Behzadi M, Joukar S, Beik A, 2018, Opioids and Cardiac Arrhythmia: A Literature Review. Medical Principles and Practice, 27(5): 401–414.

[3] Doshi R, Majmundar M, Kansara T, et al., 2019, Frequency of Cardiovascular Events and In-hospital Mortality with Opioid Overdose Hospitalizations. Am J Cardiol, 124(10):1528–1533.

[4] Krantz MJ, Palmer RB, Haigney MCP, 2021, Cardiovascular Complications of Opioid Use: JACC State-of-the-Art Review. Journal of the American College of Cardiology, 77(2): 205–223.

[5] Ji X, Tang J, Zhang J, 2022, Effects of Salt Stress on the Morphology, Growth and Physiological Parameters of Juglansmicrocarpa L. Seedlings. Plants, 11(18): 2381.

[6] Bardou P, Mariette J, Escudié F, et al. jvenn: An Interactive Venn Diagram Viewer. BMC Bioinformatics, 2014, 15(1): 293.

[7] Sakaeda T, Tamon A, Kadoyama K, et al., 2013, Data Mining of the Public Version of the FDA Adverse Event Reporting System. International Journal of Medical Sciences, 10(7): 796–803.

[8] Bate A, Lindquist M, Edwards IR, et al., 1998, A Bayesian Neural Network Method for Adverse Drug Reaction Signal Generation. Eur J Clin Pharmacol, 54(4): 315–321.

[9] Mann J, Samieegohar M, Chaturbedi A, et al., 2022, Development of a Translational Model to Assess the Impact of Opioid Overdose and Naloxone Dosing on Respiratory Depression and Cardiac Arrest. Clinical Pharmacology and Therapeutics, 112(5): 1020–1032.

[10] Eroglu TE, Barcella CA, Blom MT, et al., 2022, Opioid Use is Associated with Increased Out-Of-Hospital Cardiac Arrest Risk Among 40 000-Cases Across Two Countries. British Journal of Clinical Pharmacology, 88(5): 2256–2266.

[11] Golibkhon A, Akbar Gafur Ugli B, Makhamadjonov Farkhod Ugli M, 2023, Opioid Agents and Cardiac Arrhythmia: A Literature Review. Cureus, 15(4): e38007.

[12] Chow SL, Sasson C, Benjamin IJ, et al., 2021, Opioid Use and Its Relationship to Cardiovascular Disease and Brain Health: A Presidential Advisory from the American Heart Association. Circulation, 144(13): e218–e232.

[13] Krantz MJ, Rudo TJ, Haigney MCP, et al., 2023, Ventricular Arrhythmias Associated with Over-the-Counter and Recreational Opioids. Journal of the American College of Cardiology, American College of Cardiology Foundation, 81(23): 2258–2268.

[14] Toska E, Mayrovitz HN, 2023, Opioid Impacts on Cardiovascular Health. Cureus, 15(9): e46224.

[15] Liew SM, Chowdhury EK, Ernst ME, et al., 2022, Prescribed Opioid Use is Associated with Adverse Cardiovascular Outcomes in Community-Dwelling Older Persons. ESC Heart Failure, 9(6): 3973–3984.

[16] Lovell AG, Protus BM, Saphire ML, et al., 2019, Evaluation of QTc Interval Prolongation Among Patients with Cancer Using Enteral Methadone. The American Journal of Hospice & Palliative Care, 36(3): 177–184.

[17] Rosenfeld LE, Jain S, Amabile A, et al., 2023, Multidisciplinary Management of Opioid Use-Related Infective Endocarditis: Treatment, QTc Values, and Cardiac Arrests due to Ventricular Fibrillation. Journal of Clinical Medicine, 12(3): 882.

[18] Gupta R, Gupta N, Meghrajani V, et al., 2019, Cardiac Arrhythmia and Opioids: Be Watchful. International Journal of Cardiology, 286(1): 83–84.

[19] Bloch-Salisbury E, Rodriguez N, Bruch T, et al., 2022, Physiologic Dysregulation in Newborns with Prenatal Opioid Exposure: Cardiac, Respiratory and Movement Activity. Neurotoxicology and Teratology, 92(1): 107105.

[20] Khodneva Y, Richman J, Kertesz S, et al., 2021, Gender Differences in Association of Prescription Opioid Use and Mortality: A Propensity-Matched Analysis from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Prospective Cohort. Substance Abuse, 42(1): 94–103.

[21] Sessler N E, Walker E, Chickballapur H, et al., 2017, Disproportionality Analysis of Buprenorphine Transdermal System and Cardiac Arrhythmia Using FDA and WHO Postmarketing Reporting System Data. Postgraduate Medicine, 129(1): 62–68.

[22] Wilson J, Bass A, Pixton GC, et al., 2019, Safety and Tolerability of ALO-02 (Oxycodone Hydrochloride and Sequestered Naltrexone Hydrochloride) Extended-Release Capsules in Older Patients: A Pooled Analysis of Two Clinical Trials. Current Medical Research and Opinion, 36(1): 91–99.