

Original Research Article

Disproportionate Reporting of Sudden Cardiac Death with Methadone in the FDA Adverse Event Reporting System (FAERS): A Case–Non-Case Study

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A B S T R A C T

Background. Methadone can prolong cardiac repolarization, but outcome-specific reporting of sudden cardiac death has not, to our knowledge, been evaluated with contemporary data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

Objective. To quantify disproportionate reporting of sudden cardiac death with methadone in FAERS and to test its stability across exposure definitions, report clustering, and comparators.

Methods. We performed a report-level case–non-case disproportionality analysis of the openFDA Drug Adverse Event API. Methadone exposure was defined by a medicinal-product query and sudden cardiac death by its Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term. Reporting odds ratios (RORs), proportional reporting ratios (PRRs), 95% confidence intervals (CIs), and Fisher exact tests were calculated. Four sensitivity analyses used harmonized and exact exposure definitions, an identical-signature clustering proxy, and exclusive buprenorphine reports as an active comparator.

Results. Among 20,692,690 searchable reports (52,462 mentioning methadone), 89 contained both methadone and sudden cardiac death. The primary ROR was 10.65 (95% CI 8.62–13.14) and the PRR was 10.63 (95% CI 8.61–13.12). Sensitivity RORs ranged from 6.82 to 9.29; every lower 95% CI bound exceeded 1. Fifty-six reports carried duplicate-related metadata, and 57 unique clinical signatures were identified.

Conclusion. Methadone and sudden cardiac death showed a consistent signal of disproportionate reporting in FAERS across exposure, clustering, and comparator assumptions. The signal supports focused pharmacovigilance and case review but does not estimate incidence, establish causality, or determine the cause of an individual death.

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1. Introduction

Methadone is a long-acting opioid agonist with established roles in opioid use disorder and pain management. Longitudinal, randomized, and real-world studies show that methadone can support treatment retention and meaningful health outcomes, although comparative effectiveness varies with population, treatment setting, and outcome definition.^{1–4} Its clinical value must therefore be preserved when safety signals are interpreted. Its long and individually variable elimination can permit delayed accumulation, particularly during initiation, dose escalation, acute illness, altered hepatic function, or exposure to interacting substances, so a serious event cannot be inferred from the prescribed dose alone. Cardiac safety is one component of this benefit–risk balance: a

large electronic-health-record study reported differences in arrhythmia, long-QT, and mortality outcomes among patients prescribed methadone, buprenorphine, or naltrexone, whereas long-term clinical follow-up documented a low absolute frequency of major cardiac complications in treated cohorts.^{5,6} These findings reflect differences in patient selection, comparator groups, exposure duration, dose, comorbidity, and outcome ascertainment, and they show why a relative safety signal must be distinguished from an absolute clinical event rate.

Methadone-related repolarization effects are heterogeneous rather than universal. Switching from racemic methadone to equipotent R-methadone shortened the corrected QT interval (QTc) in a maintenance-treatment study, and acute-poisoning, cardiac-surgical, cancer-pain, pharmacogenetic, and high-risk clinical

cohorts identified varying associations between methadone exposure and QTc or cardiovascular findings.^{7–12} Computational work indicates that methadone can influence more than one cardiac potassium current, and a contemporary case series documents torsades de pointes during methadone therapy.^{13,14} Perioperative, oncologic, population-based, and acute-poisoning studies likewise show that risk expression depends on setting and host factors.^{15–19} Measured QTc reflects methadone concentration but also genetic repolarization reserve, heart rate, electrolyte status, structural disease, organ function, acute toxicity, and concomitant medicines. QTc is therefore an intermediate phenotype and risk marker, not a complete explanation for every sudden death.

The forensic evidence is similarly contextual. Population mortality analyses, forensic-autopsy studies, comparative fatality series, and postmortem concentration research show that methadone-positive deaths occur across heterogeneous exposure and co-intoxicant patterns.^{20–24} Sudden death during methadone exposure may reflect ventricular arrhythmia, respiratory depression, aspiration, polysubstance toxicity, underlying natural disease, or several interacting processes, and postmortem detection alone does not establish mechanism, causal contribution, or manner of death. A community-based evaluation of sudden death associated with therapeutic methadone levels is the closest forensic counterpart of the signal examined here.²⁵ Treatment structure, continuity, and access also affect retention, health outcomes, and mortality in opioid use disorder,^{26–30} so safety communication should support individualized risk reduction rather than abrupt or unsupervised treatment interruption. Co-exposures add further complexity: an experimental signal characterization demonstrated a plausible interaction between methadone and a synthetic cannabinoid receptor agonist,³¹ and sedatives, psychotropics, stimulants, gabapentinoids, or other opioids may change ventilation, repolarization, and metabolism.

Spontaneous reporting systems offer a complementary lens for rare or serious suspected adverse events. A recent analysis of the FAERS identified clinically important drug-drug interaction patterns among fatal torsades de pointes reports, while an empirical evaluation showed that notoriety bias can alter signal strength in some circumstances.^{32,33} Earlier FAERS analyses examined reporting trends for methadone-associated cardiac arrhythmia and compared arrhythmia reports for methadone and buprenorphine.^{34,35} The openFDA Drug Adverse Event API provides a searchable public representation of FAERS, a repository of spontaneous safety reports from multiple reporter types. A report can contain several drugs and several reactions without a validated one-to-one link, and reporting is incomplete and influenced by publicity, market exposure, treatment setting, and clinical context. The Reporting of A Disproportionality analysis for drUG Safety signal detection using individual case safety reports in Pharmacovigilance (READUS-PV) statement provides a contemporary reporting framework, and comparator-method research demonstrates that the reference group can materially affect the magnitude and interpretation of a signal.^{36,37} A defensible FAERS question therefore concerns disproportionate reporting, not incidence, absolute risk, or individual causality.

Outcome definition is central to that question. Broader composites such as cardiac arrest, ventricular arrhythmia, QT prolongation, and torsades de pointes increase eligible report counts but combine events with different clinical

meanings and levels of diagnostic specificity. The Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term “sudden cardiac death” identifies a narrower reporting concept with particular forensic and medicolegal relevance, while still reflecting the reporter’s terminology rather than independent adjudication. The analytical question is whether this specific term is reported disproportionately with methadone and whether the result remains stable when exposure naming, possible report clustering, and comparator selection change.

To our knowledge, no earlier study has combined an outcome-specific FAERS analysis of the sudden cardiac death Preferred Term with raw, harmonized, and exact methadone definitions, reproducible report-level characterization, a conservative identical-signature stress test, and an exclusive buprenorphine active comparator.

The primary aim was to quantify the disproportionate reporting of sudden cardiac death with methadone in FAERS. The secondary aims were to describe the demographic, temporal, drug-role, co-reported-product, and reaction characteristics of the identified reports; to evaluate stability across exposure definitions and possible report clustering; and to determine whether the reporting signal persisted when exclusive buprenorphine reports replaced the heterogeneous all-other-drug reference.

2. Methods

2.1 Study design and reporting framework

We conducted a retrospective report-level case–non-case disproportionality analysis using individual case safety reports available through the openFDA Drug Adverse Event application programming interface (API). The analysis was planned and reported in accordance with the READUS-PV statement.³⁶ No prospective sample-size calculation was performed because the study used the census of reports returned by prespecified API queries at the frozen snapshot.

The unit of analysis was the safety report, not an exposed person, prescription, treatment episode, or death investigation. In the case–non-case framework, reports containing the outcome term of interest were compared with reports containing other reaction terms, and the relative representation of methadone was evaluated across those report groups. This design is suitable for detecting drug–event pairs reported more frequently than expected from the database margins, but it does not provide an exposure denominator and cannot estimate incidence, absolute risk, mortality rate, or attributable fraction. The target estimand was therefore the report-level odds of the sudden cardiac death term among methadone reports relative to its odds among reference reports.

The study question and analytical interpretation were defined before examination of report characteristics. The primary analysis evaluated the broad searchable methadone token against all other drug reports. Sensitivity analyses then addressed three distinct sources of analytical dependence: variation in medicinal-product naming, repetition of identical report signatures, and the composition of the reference group. This sequence was intended to assess stability rather than to select the largest estimate.

2.2 Data source and snapshot

The primary query was executed on 22 January 2026:

```
patient.drug.medicinalproduct:"methadone" AND
patient.reaction.reactionmeddrapt:"sudden
cardiac death"
```

The API returned 89 reports. The complete JSON response was cached without transformation as a frozen snapshot; its SHA-256 checksum was 188e9d17b22871f51c13aa721765c8f6c809fb8934cefbe33f9ecec139f1ef78. FDA received dates ranged from 1 July 2004 to 21 January 2025. Aggregate counts were obtained through the same endpoint for all searchable drug–event reports and for each exposure or outcome definition; the frozen snapshot applies to the cached report-level JSON, whereas aggregate totals reflect the live API on the retrieval date. Exact query URLs, returned totals, analysis code, derived datasets, and software versions were retained in the study reproducibility archive (hereafter, the reproducibility archive).

FAERS is dynamic: reports can be added, updated, consolidated, or represented differently in later releases, so the analysis should be understood as a reproducible snapshot. The FDA received date was used to describe reporting activity because it was consistently available for the retrieved combination reports; it was not treated as the date of exposure, event onset, or death. Annual counts were therefore descriptive and were not analyzed as person-time rates or secular incidence trends.

2.3 Exposure, outcome, and reference groups

The primary exposure was the raw medicinal-product token query `patient.drug.medicinalproduct:"methadone"`. The outcome was the MedDRA Preferred Term query `patient.reaction.reactionmeddrapt:"sudden cardiac death"`. At report level, cell a contained reports with both methadone and sudden cardiac death; b contained methadone reports with other reactions; c contained sudden cardiac death reports without methadone; and d contained all remaining reports. Because reports can list multiple drugs and reactions, these cells represent co-reporting within a report rather than validated drug–event attribution.

Each report contributed once to the 2×2 table created for a given query definition. A report was classified as exposed when any medicinal-product entry satisfied the relevant methadone query and as an outcome report when any reaction entry contained the specified Preferred Term. The principal all-other-drug reference was intentionally broad because it represents conventional database-wide disproportionality screening. Its interpretive limitation is heterogeneity: reference reports include medicines, indications, ages, comorbidity patterns, and reporting channels that may differ substantially from those associated with methadone. This limitation motivated the active-comparator sensitivity analysis rather than a post hoc change to the primary estimand.

2.4 Report characterization and clinical-signature proxy

All 89 combination reports were profiled for `safetyreportid`, FDA received date, primary-source country, patient sex, age, number of listed drugs, methadone role, co-reported drugs and reactions, and the `API duplicate/reportduplicate` metadata. Age was analyzed only when the unit code was 801 (years); other units were not combined. Methadone role was derived from `drugcharacterization` as primary suspect, concomitant, or interacting.

Categorical summaries used the number of reports with available information as the denominator, and the denominator was retained alongside each result. Medicinal-product names were normalized only for descriptive frequency tabulation by standardizing case and punctuation; this did not alter the exposure definitions used for disproportionality calculations. Co-reported products and reactions were counted as report attributes. They were not interpreted as confirmed concomitant administration, verified interactions, independent diagnoses, or causes of death because the API does not establish timing or a validated relationship between each listed drug and each listed event.

A clinical signature was constructed from FDA received date, primary-source country, sex, age and age unit, the sorted reaction terms, and sorted medicinal-product names. Identical signatures were treated as possible clustered reporting patterns. This procedure was not a validated patient-level deduplication algorithm and did not label any reports as confirmed duplicates.

2.5 Statistical analysis

The reporting odds ratio (ROR) was calculated as:

$$\text{ROR} = \frac{a \times d}{b \times c}$$

The proportional reporting ratio (PRR) was calculated as:

$$\text{PRR} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Log-scale standard errors provided two-sided 95% CIs. A two-sided Fisher exact test evaluated departure from independence. The prespecified signal criterion was a lower 95% ROR confidence bound greater than 1; p-values were interpreted as ancillary because the reference set was very large. The conventional screening criteria (PRR ≥2, $\chi^2 \geq 4$, and at least three reports) and the information component (IC) with its lower 95% bound (IC025) were also calculated from the primary cells as supplementary measures. ROR was emphasized over PRR because the case–non-case odds formulation makes the reference-group choice explicit and because recent comparator research demonstrates that the reference construction is part of the estimand.³⁷

ROR and PRR answer closely related but not identical report-level questions. The ROR compares the odds of the specified reaction among exposed and reference reports, whereas the PRR compares the corresponding reporting proportions. Concordance between the measures was used as a descriptive consistency check. Confidence intervals were prioritized over null-hypothesis testing because the very large database can generate extremely small p-values for associations whose scientific meaning still depends on the estimate, reference group, reporting process, and bias structure. No continuity correction was required because all primary and sensitivity cells were non-zero.

Descriptive variables are presented as counts and percentages with available-data denominators, or medians with interquartile ranges (IQRs) and ranges. Missing demographic fields were not imputed because missingness in spontaneous reports cannot be assumed to be random.

Full individual-level covariate data for the approximately 20.7 million reference reports were not available in the reproducibility archive, and the public report structure does not validate linkage between a specific drug and reaction. Adjusted regression across the full reference population was therefore not estimable and was not

forced. Adjustment was also not attempted within the 89 combination reports because such a model would condition on joint drug–event reporting and could not reconstruct the covariate distribution in the full reference population. Demographic fields were frequently missing, indication and dose were not consistently retrievable in a validated form, and the effective number of outcome reports would not support a reliable multi-parameter model. An adjusted estimate could therefore imply a level of confounding control that the source structure does not provide. Stability was instead evaluated through transparent alternative definitions and comparator construction, with all 2×2 cells retained for audit. Analyses were performed with Python 3.12.13; reproducible code generated all tables and figures.

2.6 Sensitivity analyses

Four sensitivity analyses were performed; the first three were prespecified in the archived protocol. First, methadone was defined with the harmonized field `patient.drug.openfda.generic_name: "METHADONE"`. Second, the exact product-name field `patient.drug.medicinalproduct.exact: "METHADONE"` was used. Third, the 57 unique clinical signatures replaced cell a while the other primary cells were retained; this deliberately conservative stress test estimated how the signal behaved if all reports sharing a signature represented one cluster.

The fourth, active-comparator analysis used buprenorphine, an alternative medication for opioid use disorder with a related reporting context. Reports mentioning both medicines were excluded from both arms so that the exposure categories were mutually exclusive. The resulting 2×2 table compared sudden cardiac death with other reactions in exclusive methadone reports versus exclusive buprenorphine reports. This analysis addressed the dependence of disproportionality estimates on comparator composition. An active comparator may improve clinical interpretability and reduce some indication- and channel-related differences, but it cannot eliminate differences in treatment selection, dose, comorbidity, co-exposure, market history, or reporting behavior.³⁷

2.7 Ethics

The study used publicly available, de-identified report-level data and involved no participant recruitment, clinical intervention, or access to medical records. Ethical approval was granted by the CMHC Research Center Ethics Committee Indonesia (No. 2026/011). Individual informed consent was not applicable to this secondary analysis.

3. Results

3.1 Primary disproportionality analysis

The snapshot contained 20,692,690 searchable reports, including 52,462 reports mentioning methadone and 3,383 mentioning sudden cardiac death. Eighty-nine reports contained both terms. Under independence, approximately 8.6 joint reports would have been expected from the marginal totals. All 89 `safetyreportid` values were unique.

The primary ROR was 10.65 (95% CI 8.62–13.14), and the PRR was 10.63 (95% CI 8.61–13.12). The two-sided Fisher exact test p-value was 5.32×10^{-58} . The supplementary criteria were also met: $\chi^2 = 756.1$, 89 reports, and an IC of 3.30 (IC025 2.95). These estimates indicate that sudden cardiac death occupied a larger share of methadone reports than of other-drug reports; they do not indicate a 10.65-fold patient risk.

In absolute reporting-proportion terms, sudden cardiac death appeared in 0.170% of reports mentioning methadone (89/52,462) and in 0.016% of reports not mentioning methadone (3,294/20,640,228). Expressed per 100,000 reports, these values corresponded to approximately 169.6 and 16.0 reports, respectively. These are database reporting proportions rather than clinical event rates because neither group represents a defined population of treated individuals or a measured duration of exposure. The close agreement between the ROR and PRR reflected the rarity of the outcome term within both report groups. The mutually exclusive 2×2 cell counts and primary estimates are shown in Table 1.

Table 1. Primary report-level disproportionality analysis.

Item	Report category or estimate	Value
a	Methadone + sudden cardiac death	89
b	Methadone + other reactions	52,373
c	Other drugs + sudden cardiac death	3,294
d	Other drugs + other reactions	20,636,934
ROR	Reporting odds ratio (95% CI)	10.65 (8.62–13.14)
PRR	Proportional reporting ratio (95% CI)	10.63 (8.61–13.12)
Fisher exact test	Two-sided p-value	5.32×10^{-58}

Notes: CI, confidence interval; PRR, proportional reporting ratio; ROR, reporting odds ratio. Cells are mutually exclusive at report level within the frozen searchable corpus.

3.2 Sensitivity to exposure, clustering, and comparator

The harmonized generic-name query identified 63 methadone–sudden cardiac death reports and yielded an ROR of 8.53 (95% CI 6.65–10.95). The exact product-name query identified 40 reports and yielded an ROR of 6.89 (95% CI 5.05–9.41). Collapsing identical clinical signatures in cell a produced an ROR of 6.82 (95% CI 5.25–8.86). In

the exclusive active-comparator analysis, there were 89 sudden cardiac death reports among methadone-only reports and eight among buprenorphine-only reports; the ROR was 9.29 (95% CI 4.51–19.16). Every sensitivity lower 95% CI bound exceeded 1. The numerical estimates are shown in Table 2, and their direction and uncertainty are shown graphically in Figure 1.

Narrower name definitions reduced both the number of joint reports and the magnitude of the estimate, as expected when a broad token search is replaced by more restrictive field matching. The signature-collapse proxy produced the lowest point estimate, but its lower confidence bound remained above the null. The active-

comparator estimate was closer to the primary estimate than the exposure-definition sensitivities, although its interval was wider because the comparator-event cell contained eight reports. Across the complete set of analyses, point estimates ranged from 6.82 to 10.65 and did not change direction.

Table 2. Sensitivity analyses of methadone–sudden cardiac death disproportionality.

Analysis	Cells a / b / c / d	Joint reports (a)	ROR (95% CI)	PRR (95% CI)
Raw medicinal-product query	89 / 52,373 / 3,294 / 20,636,934	89	10.65 (8.62–13.14)	10.63 (8.61–13.12)
Harmonized generic name	63	63	8.53 (6.65–10.95)	8.52 (6.64–10.93)
Exact product name	40	40	6.89 (5.05–9.41)	6.89 (5.04–9.40)
Identical-signature collapse proxy	57 / 52,373 / 3,294 / 20,636,934	57	6.82 (5.25–8.86)	6.81 (5.24–8.85)
Exclusive buprenorphine comparator	89 / 49,928 / 8 / 41,707	89	9.29 (4.51–19.16)	9.28 (4.50–19.13)

Notes: CI, confidence interval; PRR, proportional reporting ratio; ROR, reporting odds ratio. The signature proxy collapses identical clinical signatures only in cell a and is not validated patient-level deduplication. The active-comparator row uses a different reference construction from the database-wide analyses: a = methadone-only reports with sudden cardiac death, b = methadone-only reports with other reactions, c = buprenorphine-only reports with sudden cardiac death, and d = buprenorphine-only reports with other reactions, after excluding reports mentioning both medicines.

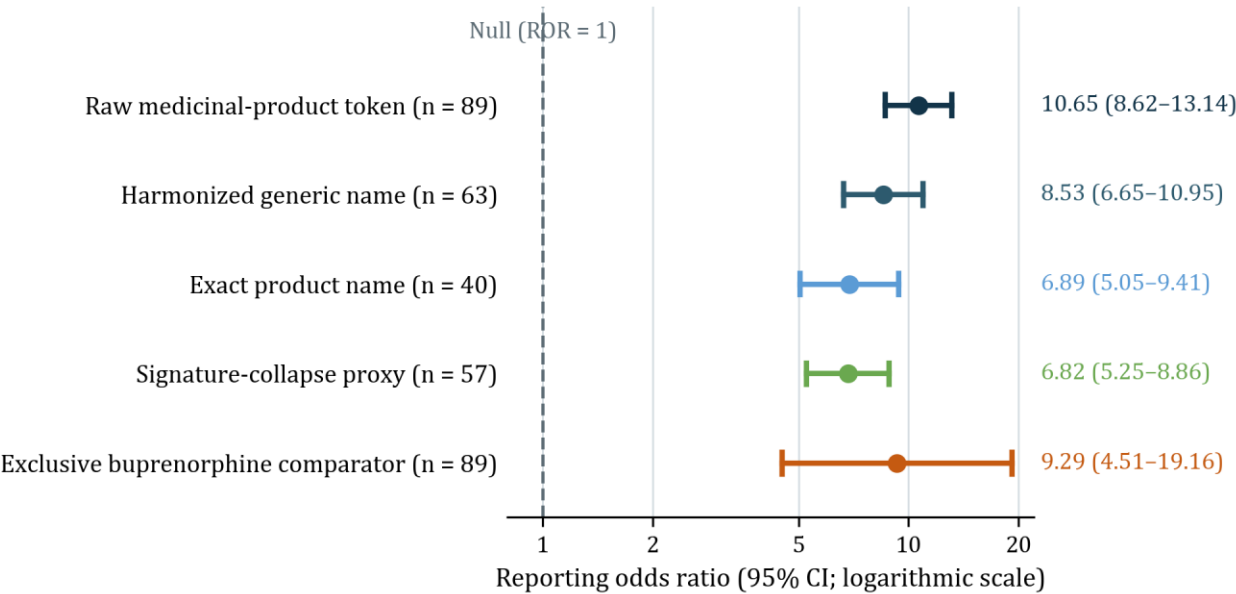


Figure 1. Reporting odds ratios across the primary and sensitivity analyses. Points indicate RORs and horizontal lines indicate 95% confidence intervals on a logarithmic scale; the dashed line marks the null value (ROR = 1). Values in parentheses after each label give the number of joint reports.

3.3 Temporal and report-level characteristics

Reports were unevenly distributed over time. The annual distribution is shown in Figure 2. The years 2008 and 2018 each contained 24 reports, together accounting for 53.9% of the 89-report set. The pattern is compatible with batch

submission, literature reporting, or administrative updating. The FDA received year may differ from the exposure or event year, and no validated denominator of annual methadone use was available, so the distribution describes reporting activity and cannot show that sudden cardiac death became more common in particular years.

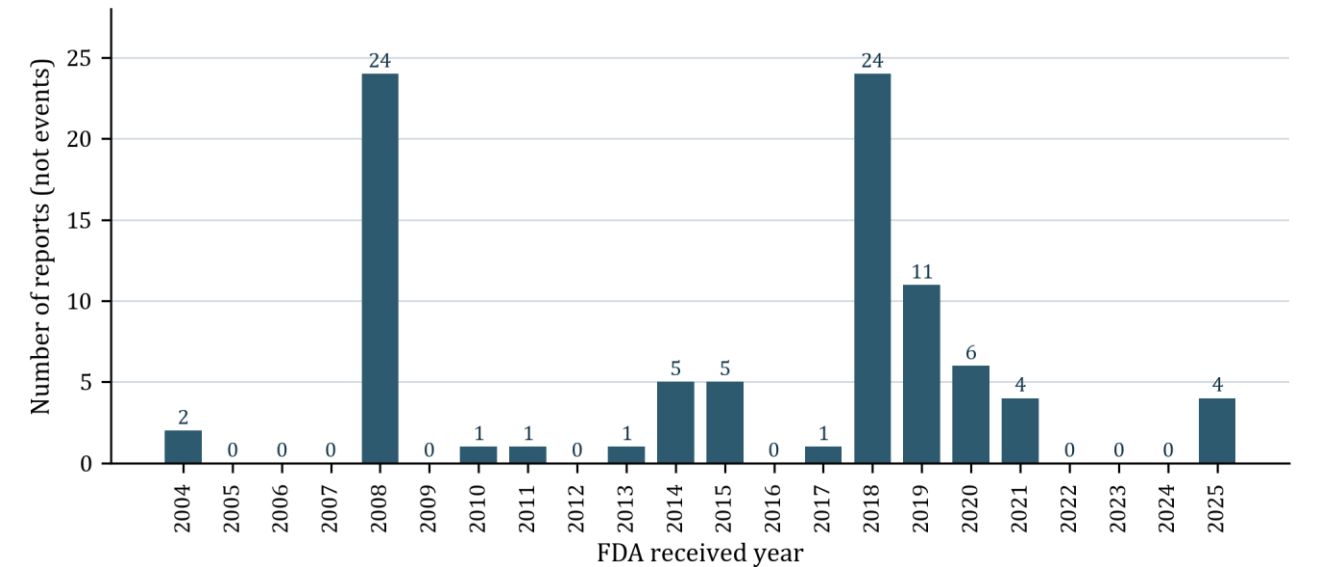


Figure 2. Number of methadone–sudden cardiac death reports by FDA received year. Counts describe reporting activity (reports, not events) and are not an incidence time series.

Age in years was available in 38 reports (42.7%); the median was 33 years (IQR 25–43; range 20–55). Sex was available in 41 reports (46.1%): 37 were male and four female. Primary-source country was available in 61 reports (68.5%), most often the United States (37), the United Kingdom (10), and Canada (10). Methadone was coded as primary suspect in 77 reports, interacting in nine, and concomitant in three.

Age was unavailable in more than half of the set and could not be treated as representative of all methadone-exposed individuals; likewise, the predominance of male reports describes the available subset rather than a sex-specific reporting rate. The primary-suspect designation in 77 reports indicates the reporter’s attribution category within the case safety report; it does not independently verify that methadone initiated the fatal sequence.

The median number of listed drugs was two (IQR 1–5; range 1–46). After normalization of punctuation and case, the most frequent non-methadone products were quetiapine (21 reports), clonazepam (15), pregabalin (12), amitriptyline (11), and gabapentin, etizolam, and naproxen (10 each). The most frequent additional reaction terms

were drug interaction (14 reports), withdrawal arrhythmia (13), left ventricular enlargement (10), and toxicity to various agents (9); “electrocardiogram QT prolonged” appeared in three reports.

Fifty-six reports carried the API `duplicate/reportduplicate` metadata. This field was described rather than used as proof of duplicate patients. The clinical-signature algorithm identified 57 unique signatures; 32 reports (89 – 57) were therefore redundant under the signature rule. Data availability, demographics, source country, methadone role, listed-drug burden, duplicate metadata, and signature counts are shown in Table 3.

The coexistence of 89 unique safety-report identifiers, 56 reports with duplicate-related API metadata, and 57 unique clinical signatures illustrates that report identity, regulatory duplication metadata, and clinical-pattern similarity are different constructs. None alone established the number of distinct patients. For that reason, the full report set was retained in the primary analysis, while the signature-collapse result was presented as a deliberately conservative stress test.

Table 3. Characteristics of the 89 methadone–sudden cardiac death reports.

Characteristic	Available n	Summary
FDA received-date range	89	1 July 2004–21 January 2025
Unique safetyreportid	89	89 (100%)
Age, years	38	Median 33; IQR 25–43; range 20–55
Sex	41	Male 37 (90.2%); female 4 (9.8%)
Primary-source country	61	United States 37; United Kingdom 10; Canada 10; Switzerland 3; Italy 1; not reported 28
Methadone role	89	Primary suspect 77; interacting 9; concomitant 3
Number of listed drugs	89	Median 2; IQR 1–5; range 1–46
API duplicate/reportduplicate metadata present	89	56 (62.9%)
Unique clinical signatures	89	57 (64.0%)

Notes: FDA, United States Food and Drug Administration; IQR, interquartile range. Percentages use the number of reports with available data (column “Available n”). API metadata do not establish duplicate patients.

4. Discussion

4.1 Principal findings

This analysis identified a strong report-level signal for methadone and sudden cardiac death. The primary ROR was 10.65, and its lower 95% confidence bound remained well above 1 after progressively narrower drug-name definitions and a conservative collapse of identical clinical signatures. The direction also persisted when the broad all-other-drug reference was replaced with exclusive buprenorphine reports, although the active-comparator interval was wider because only eight comparator-event reports were available. The direction of the signal therefore did not depend on a single analytical representation, but the numerical magnitude did: the lower 95% confidence bounds of all sensitivity RORs exceeded 1, whereas the point estimates fell from 10.65 to between 6.82 and 9.29 as definitions narrowed. The identical-signature stress test was intentionally stringent because it reduced only the joint cell while leaving the other primary cells unchanged.

Consistency across definitions reduces the likelihood that the finding is solely a technical consequence of one product-name field or one reference construction, and the sensitivity analyses are correlated rather than independent replications. The signal does not establish incidence, an individual causal probability, or a therapeutic ranking. Because the outcome term is assigned by the reporter, it also cannot discriminate arrhythmic from respiratory or toxic mechanisms. The most defensible interpretation is that the methadone–sudden cardiac death pair deserves sustained pharmacovigilance and case-level examination.

4.2 Relation to prior pharmacovigilance and clinical evidence

The findings extend contemporary pharmacovigilance evidence rather than simply repeating it. Earlier FAERS analyses addressed composite arrhythmia outcomes and compared methadone with buprenorphine,^{34,35} and recent FAERS research on fatal torsades de pointes identified drug–drug interaction patterns, but the endpoint and exposure structure differ from the present analysis.³² The present study isolates the specific Preferred Term “sudden cardiac death” and adds three methadone name representations, report-level characterization, and a clustering stress test. That narrower endpoint matters because QT prolongation is an electrophysiological observation, torsades de pointes is a particular ventricular tachyarrhythmia, cardiac arrest is a physiological state with many causes, and sudden cardiac death is a fatal clinical classification; a signal for one cannot be assumed from a signal for another.

Observational cohorts provide clinically anchored but still non-randomized context. A national electronic-health-record analysis reported higher arrhythmia, long-QT, and mortality outcomes with methadone than with propensity-matched buprenorphine or naltrexone cohorts, whereas another long-term cohort reported a low absolute frequency of cardiac complications.^{5,6} A ten-fold reporting disproportion is compatible with a low absolute frequency because the outcome is rare, reporting is selective and may be stimulated, the reference group is heterogeneous, and treated cohorts differ from the FAERS reporting pool. Clinical cohorts estimate outcomes among defined treated populations but may lack power for rare adjudicated deaths; spontaneous reports reveal uncommon drug–

event combinations across diverse reporters but lack systematic ascertainment and denominators; and forensic series provide detailed toxicology but commonly lack a comparable population of living exposed patients.

4.3 Biological interpretation and co-reported medicines

Cardiac repolarization provides a plausible pathway. Contemporary computational and clinical research indicates that methadone can alter cardiac potassium currents, prolong QTc in susceptible settings, and create a substrate for torsades de pointes, while the magnitude varies across maintenance treatment, acute poisoning, perioperative care, cancer pain, and genetically susceptible populations.^{7–19} Only three reports contained a co-reported prolonged-QT term, but absent documentation in a spontaneous report cannot exclude an arrhythmic pathway: sudden death may occur before diagnostic electrocardiography, reporters may prioritize the fatal outcome over intermediate findings, and related concepts may be coded under other terms. Conversely, a reported sudden cardiac death term may not have been supported by rhythm documentation or forensic adjudication.

Other sequences may equally lead from methadone exposure to an abrupt fatal event. Opioid-induced hypoventilation may produce hypoxemia and acidosis that precipitate terminal rhythm disturbance, and sedatives may amplify respiratory depression while psychotropic medicines add electrophysiological burden. The median age of 33 years and the prominence of sedatives, gabapentinoids, and interacting products are consistent with overdose or polysubstance toxicity as well as arrhythmic death during stable maintenance; attention to initiation, titration, co-prescribed sedatives and QT-active drugs, and overdose prevention therefore belongs alongside QTc assessment.

The co-reported products, chiefly quetiapine, clonazepam, pregabalin, amitriptyline, and gabapentin, indicate case complexity rather than confirmed interactions. They may bear on repolarization burden, metabolic interaction, sedation or respiratory depression, or broader polysubstance context, but the API does not show whether they were taken concurrently, at what dose, or in what temporal relation to the event. Long drug lists may reflect true co-exposure, background medication history, emergency treatment, or reporting practice. Identical reaction descriptors recurring in 10–14 reports suggest shared source narratives, which reinforces the need to verify whether a small number of cases account for much of the signal. These frequencies should generate case-review questions, not causal assertions.

4.4 Reporting processes, comparator choice, and alternative explanations

Several alternative explanations may increase or decrease the observed signal. Methadone is a recognized QT-prolonging drug, so reporters may preferentially connect it with cardiac outcomes; notoriety bias is plausible for an individual drug–event pair, although an empirical evaluation of selected FDA safety alerts did not find a consistent database-wide increase in signal strength after warnings.³³ The concentration of reports in 2008 and 2018 and the repeated clinical signatures are compatible with batch or literature effects, and the conservative signature-collapse analysis reduced the ROR without removing the signal. Confounding by indication, overdose, opioid-use severity, chronic pain, comorbidity, and co-medication

cannot be controlled with the available aggregate reference data.

Comparator selection deserves particular attention because disproportionality is intrinsically relative. A medicine can appear strongly disproportionate against a reference dominated by products rarely linked to the event, yet less so against another medicine used in similar patients, and an active comparator with a distinct safety profile or reporting intensity can introduce its own bias.³⁷ The persistence of the signal against buprenorphine makes the result less dependent on the heterogeneous all-other-drug reference but does not create exchangeable treatment groups: methadone and buprenorphine users may differ in opioid-use severity, pain indications, comorbidity, treatment setting, dose, co-exposures, market history, and reporting behavior. The wide interval reflects genuine uncertainty from only eight comparator-event reports.

4.5 Forensic, clinical, and pharmacovigilance implications

Forensic application requires restraint. Mortality, autopsy, comparative fatality, postmortem concentration, and toxicology-surveillance studies show heterogeneous methadone-positive deaths and substantial dependence on tolerance, disease, co-intoxicants, survival interval, and sampling context.^{20–24} Sampling site and postmortem redistribution influence measured concentrations, and numerical overlap means that no single concentration can serve as a universal fatal threshold. This FAERS signal cannot replace circumstances and tempo of collapse, treatment and prescription history (stable maintenance versus initiation, re-induction, or recent dose escalation), tolerance assessment, autopsy and histopathology, quantitative peripheral-blood toxicology, co-intoxicant evaluation, postmortem interval, or formal cause-and-manner-of-death adjudication. Depending on the complete evidence, methadone may be the principal toxic agent, one component of combined toxicity, a contributor through arrhythmic susceptibility, or an incidental therapeutic finding.

Clinically, the result supports attention to established risk factors, medication reconciliation, electrolytes, cardiac history, interacting drugs, and individualized electrocardiographic assessment. It does not support abrupt discontinuation or automatic switching based on FAERS alone, because continuity, access, and treatment structure have clinically important consequences.^{1–4,26–30} For pharmacovigilance programs, the findings justify targeted retrieval of source narratives, with priority variables including indication, daily dose, duration and recent dose change, serum or postmortem concentration, QTc history, documented rhythm, electrolytes, organ function, co-medication timing, and the reporter's basis for using the sudden cardiac death term. Future denominator-based cohorts linking prescribing, dispensing, electrocardiography, and mortality data could compare methadone with active alternatives, and forensic studies using standardized peripheral sampling and structured scene and treatment histories could adjudicate cardiac versus respiratory pathways.

4.6 Strengths and limitations

Strengths include preservation of the raw snapshot and checksum, reproducible report-level characterization, explicit separation of report identifiers from duplicate-related metadata and clinical signatures, retention of available-data denominators, presentation of both ROR and PRR with confidence intervals, mutually exclusive

comparator arms, and reporting according to READUS-PV.³⁶

The principal constraints arise from the spontaneous-reporting design: under-reporting and selective reporting, absent exposure denominators, incomplete demographic and clinical fields, unvalidated drug-reaction linkage, reporter-assigned and unvalidated outcome coding, and inability to adjust the full reference population. The raw token query may retrieve different product representations than the harmonized and exact fields, so the estimates should be read as a range of plausible database representations rather than replications. The clinical-signature proxy is not a validated deduplication method and may collapse distinct cases or miss related follow-up reports; duplicate-related API metadata are likewise not confirmed duplicate patients, and duplicates in the reference cells were not addressed. A small number of literature-derived series may account for much of the signal. Analyses restricted to primary-suspect reports, excluding 2008 and 2018 or literature-sourced reports, stratified by reporter type, using positive and negative control drugs or additional opioid comparators, or computed with case-version de-duplication of the quarterly FAERS files were not performed. Dose, indication, electrocardiographic findings, event chronology, and toxicological concentrations were not available in a sufficiently complete structure for inferential modeling. These limitations define the appropriate boundary of inference without negating the value of the study as a reproducible signal-detection analysis.

5. Conclusion

Methadone and sudden cardiac death were reported disproportionately in the frozen openFDA/FAERS snapshot, with a primary ROR of 10.65 (95% CI 8.62–13.14), and the signal persisted under raw, harmonized, exact, identical-signature, and exclusive buprenorphine definitions. The finding supports focused pharmacovigilance, structured retrieval of case narratives, and verification with de-duplicated data, additional comparators, and denominator-based studies. It does not establish incidence, rank absolute treatment safety, alter the benefit-risk balance of methadone treatment on its own, or support the attribution of any individual death.

Declarations

Use of generative artificial intelligence. None. The authors declare that no generative artificial intelligence (AI) tools were used in the preparation, drafting, analysis, or editing of this manuscript.

Author contributions. SS: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Project administration. IS: Investigation, Validation, Writing – review & editing. EMP: Validation, Visualization, Writing – review & editing. MF: Resources, Supervision, Writing – review & editing.

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Ethical approval. Ethical approval was granted by the CMHC Ethics Committee Indonesia (No. 2026/011).

Consent to participate. Not applicable. The analysis used publicly available, de-identified report-level data.

Data availability. The exact primary query, raw-snapshot SHA-256 checksum, executable analysis code, derived tables, and figure sources are retained in the reproducibility archive and are available from the corresponding author.

Reporting guideline. READUS-PV.

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