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RESEARCH ARTICLE

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Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder

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Abstract

Importance: More than 109,000 Americans died of drug overdose in 2022, with 81,231 overdose deaths involving opioids. Methadone, buprenorphine and naltrexone are the most widely used medications for opioid use disorders (MOUD) and the most effective intervention for preventing overdose deaths. However, there is a concern that methadone results in long QT syndrome, which increases the risk for fatal cardiac arrythmias. Currently few studies have systematically evaluated both the short-term and long-term differences in cardiac and mortality outcomes between MOUD.

Objectives: To compare the risks of cardiac arrythmias, long QT syndrome and overall mortality between patients with opioid use disorders (OUD) who were prescribed methadone, buprenorphine or naltrexone.

Design, Setting, and Participants: Retrospective cohort study based on a multicenter and nationwide database of electronic health records (EHRs) in the United States. The study population was comprised of 144,141 patients who had medical encounters for OUD in 2016-2022, were

prescribed MOUD within 1 month following a medical encounter for OUD diagnosis and had no diagnosis of cardiac arrythmias or long QT syndrome before any MOUD prescription. The study population was divided into three cohorts: (1) Methadone cohort (n = 40,938)—who were only prescribed methadone. (2) Buprenorphine cohort (n = 80,055)—who were only prescribed buprenorphine. (3) Naltrexone cohort (n = 5,738)—who were only prescribed naltrexone.

Exposures: methadone, buprenorphine, or naltrexone.

Main Outcomes and Measures: Cardiac arrythmias, long QT syndrome, and death. Hazard ratio (HR) and 95% confidence interval (CI) of outcomes at six different follow-up time frames (1-month, 3-month, 6-month, 1-year, 3-year, and 5-year) by comparing propensity-score matched cohorts using Kaplan-Meier survival analysis.

Results: Patients with OUD who were prescribed methadone had significantly higher risks of cardiac arrhythmias, long QT syndrome and death compared with propensity-score matched patients with OUD who were prescribed buprenorphine or naltrexone. For the 1-month follow-up, the overall risk for cardiac arrythmias was 1.03% in the Methadone cohort, higher than the 0.87% in the matched Buprenorphine cohort (HR: 1.20, 95% CI: 1.04–1.39); The overall risk for long QT syndrome was 0.35% in the Methadone cohort, higher than the 0.15% in the matched Buprenorphine cohort (HR: 2.40, 95% CI: 1.75–3.28); The overall mortality was 0.59% in the Methadone cohort, higher than the 0.41% in the matched Buprenorphine cohort (HR: 1.48, 95% CI: 1.21–1.81). The increased risk persisted for 5 years: cardiac arrhythmias (HR: 1.31, 95% CI: 1.23–1.38), long QT syndrome (HR: 3.14, 95% CI: 2.76–3.58), death (HR: 1.50, 95% CI: 1.41–1.59).

Conclusions and Relevance: Methadone was associated with a significantly higher risk for cardiac and mortality outcomes than buprenorphine and naltrexone. These findings are relevant to the development of guidelines for medication selection when initiating MOUD treatment and

inform future medication development for OUD that minimizes risks while maximizing benefits.

KEYWORDS
addictions, effectiveness research, substance abuse disorder, substance dependence, treatment evaluation

1 | INTRODUCTION

More than 109,000 Americans died of drug overdose in 2022, with 81,231 overdose deaths involving opioids (The Centers for Disease Control and Prevention—Vital Statistics Rapid Release - Provisional Drug Overdose Data, 2023). Methadone, buprenorphine and naltrexone are the most widely used medications for opioid use disorders (MOUD) and the most effective intervention for preventing overdose deaths (Volkow, 2021; Volkow & Blanco, 2021; Volkow et al., 2014). MOUD target the mu opioid receptor (MOR) but have different properties. Methadone is a full agonist maximally activating intracellular signaling without full MOR occupancy, buprenorphine is a partial agonist that generates limited intracellular signaling even with full MOR occupancy, whereas naltrexone does not result in intracellular signaling but by fully occupying MOR interferes with other drugs doing so (Toce et al., 2018). There is strong evidence for the efficacy of MOUD in improving clinical outcomes including reducing relapse, preventing overdoses and mortality and protecting against infection from drug injection practices (Volkow et al., 2014). Overall, the data indicates that methadone tends to lead to longer retention in treatment than buprenorphine, which in turn leads to longer retention than naltrexone (Timko et al., 2016). However, there is concern that methadone results in long QT syndrome, the prolongation of the time period between the ventricular depolarization and its repolarization, which increases the risk for Torsades de Pointes, a potentially fatal arryhtmia (Alinejad et al., 2015; Bart et al., 2017; Ehret et al., 2006; Klein et al., 2022; Lamont & Hunt, 2006; Martin et al., 2011; Mujtaba et al., 2013; Titus-Lay et al., 2021). Understanding difference in the rate of cardiotoxicity between MOUD is clinically relevant for it can help guide treatment selection on patients with cardiac risks and can help guide future medication developments for opioid use disorder (OUD). Currently, very few studies have systematically evaluated differences in cardiovascular toxicity between MOUD and most have been done on small samples and mostly for methadone and buprenorphine comparisons(Kao et al., 2016; Raji et al., 2022). Here we take advantage of a nation-wide database of patient electronic health records (EHRs) to estimate differences in cardiac arrythmias, QT prolongation and mortality between patients who were prescribed methadone, buprenorphine or naltrexone.

2 | METHODS

2.1 | Database description

We used the TriNetX Analytics network platform ("US Collaborative Network") that contains nation-wide and real-time deidentified EHRs of 95.1 million unique patients from 57 health care organizations, mostly large academic medical institutions with both inpatient and outpatient facilities at multiple locations across 50 states in the US, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types (TriNetX, 2021). Though the data are deidentified, the built-in statistical functions within TriNetX Analytics Platform perform statistical analyses on patient-level data. TriNetX reports population level data and results without including protected health information (PHI) identifiers. MetroHealth System, Cleveland OH, Institutional Review

Board has determined that any research using TriNetX is not Human Subject Research and therefore exempt from review (more details in eMethod). We previously used TriNetX Analytics network platform to conduct retrospective cohort studies in diverse populations (Gao et al., 2023; Wang et al., 2021; Wang et al., 2022a; Wang et al., 2022b; Wang, Berger, et al., 2022; Wang, Davis, Kaelber, Volkow et al., 2022; Wang, Davis et al., 2023; Wang, Volkow, et al., 2023; Wang, Wang, et al., 2022), including patients with OUD and other substance use disorders (Gao et al., 2023; Wang, Volkow, et al., 2023; Wang, Wang, et al., 2022).

2.2 | Study population

TriNetX database includes 746,155 patients with a diagnosis of OUD. The study population comprised 144,141 patients with OUD who had a medical encounter for their OUD diagnosis in 2016-2022, were prescribed any MOUD within 1 months following their medical encounter for OUD diagnosis in 2016–2022 and had no cardiac arrythmias or long QT syndrome before any MOUD prescription. The start date of 2016 was chosen to allow us to examine cardiac and mortality associated with methadone to correspond to the time when fentanyl entered the illicit drug market in the United States and became a main contributor to overdose deaths. The study population was divided into 3 cohorts: (1) Methadone cohort ($n = 40{,}938$)—who were prescribed methadone but never prescribed buprenorphine or naltrexone in 2016–2022. (2) Buprenorphine cohort ($n = 80{,}055$)—who were prescribed buprenorphine but never prescribed naltrexone or methadone in 2016–2022. (3) Naltrexone cohort ($n = 5738$)—who were prescribed naltrexone but never prescribed buprenorphine or methadone in 2016–2022 (Figure 1). The status of OUD was based on the International Classification of Diseases (ICD-10) diagnosis code F11 "Opioid related disorders". Three outcomes were examined: cardiac arrythmias (ICD-10 code I47 "Paroxysmal tachycardia", I48 "Atrial fibrillation and flutter", and I49 "Other cardiac arrhythmias"), long QT syndrome (ICD-10 code I45.81 "Long QT syndrome") and death. The status of death was based on the vital status code "deceased" that TriNetX regularly (on weekly basis) imports from the Social Security Death Index.

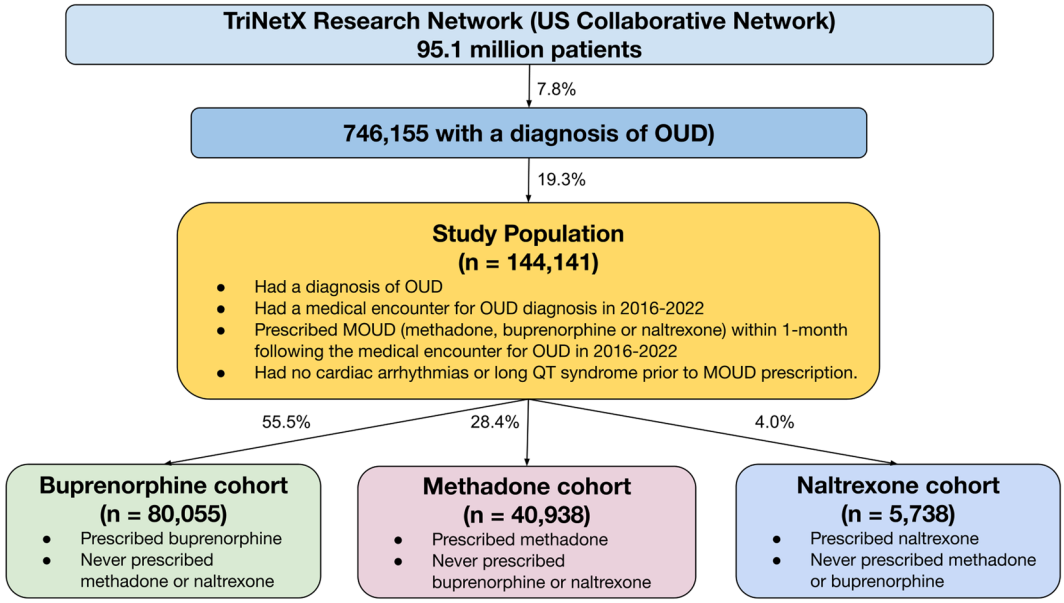

FIGURE 1 Cohort selection from TriNetX database.

2.3 | Statistical analysis

We examined whether the Methadone cohort had higher risk for cardiac arrythmias, long QT syndrome and mortality compared with the propensity-score matched Buprenorphine cohort and Naltrexone cohort. Cohorts were propensity-score matched (1:1 using a nearest neighbor greedy matching with a caliper of 0.25 times the standard deviation) for covariates including demographics (age, gender, and race/ethnicity); adverse socioeconomic determinants of health (education, employment, occupational exposure, physical, social, and psychosocial environment, and housing), substance use disorder comorbidities (alcohol, cannabis, cocaine, tobacco, and other stimulants), psychiatric comorbidities (mood disorders, anxiety disorders, schizophrenia and other psychoses, eating disorders), pain (chronic pain and lower back pain), cardiovascular diseases (hypertension, coronary artery disease, chronic heart diseases, congenital heart diseases), metabolic disorders (type 2 diabetes, hyperthyroidism, hypothyroidism), sleep disorders including sleep apnea, disorders of fluid, electrolyte, and acid–base balance (e.g., hypernatremia, hyponatremia, acidosis, hyperkalemia, fluid overload) (Table 1 and described in detail in Supporting Information). Three outcomes (death, cardiac arrythmias and long QT syndrome) were followed for 6 different time frames (1-month, 3-month, 6-month, 1-year, 3-year, and 5-year) starting from the index event (prescription of MOUD) and compared between matched Methadone and Buprenorphine cohorts, between matched Methadone and Naltrexone cohorts. and between matched Buprenorphine and Naltrexone cohorts. Kaplan-Meier analysis was used to estimate the probability of outcomes. Cox's proportional hazards model was used to compare the two matched cohorts with the proportional hazard assumption being tested with the generalized Schoenfeld approach. Hazard ratio (HR) and 95% confidence intervals (CI) was used to describe the relative hazard of cardiac arrythmias, long QT syndrome and death based on comparison of time to event rates.

The study was conducted during June 26 to 27, 2023. All statistical tests were conducted within the TriNetX Advanced Analytics Platform. The TriNetX platform calculates HRs and associated CIs using R's Survival package, version 4.0.2. P-values were calculated from a *t*-test for continuous variable and *Z*-test for categorical variables at significance set at $p < .05$ (two-sided). Details of the TriNetX database, covariates, propensity-score matching are in Supporting Information.

3 | RESULTS

3.1 | Patient characteristics

Compared to the Buprenorphine cohort, the Methadone cohort was older, comprised more black patients, had significantly lower prevalence of adverse socioeconomic determinants of health and comorbidities including other substance use disorders and mental disorders. After propensity-score matching, the two cohorts (38,178 in each cohort) were balanced (Table 1). Characteristics of Methadone versus Naltrexone cohorts and Naltrexone versus Buprenorphine cohorts before and after propensity-score matching are in Supporting Information.

3.2 | Prescription of methadone is associated with increased risk for cardiac and mortality outcomes among patients with OUD

The Methadone cohort had significantly higher risks of cardiac arrhythmias, long QT syndrome and death compared with propensity-score matched Buprenorphine cohort. Increased risks were observed for all 6 follow-up times (1 month, 3-month, 6-month, 1-year, 3-year, and 5-year). For the 1-month follow-up, the overall risk for cardiac arrythmias was 1.03% in the Methadone cohort, higher than the 0.87% in the matched Buprenorphine cohort (HR: 1.20, 95% CI: 1.04–1.39); The overall risk for long QT syndrome was 0.35% in the Methadone cohort, higher than

TABLE 1 Characteristics of the Methadone and the Buprenorphine cohorts before and after propensity-score matching that was performed on all listed variables with the status of these variables based on anytime to 1 day before the index event (MOUD prescription).

	Before propensity-score matching			After propensity-score matching		
	Methadone cohort	Buprenorphine cohort	SMD	Methadone cohort	Buprenorphine cohort	SMD
Total number	40,938	80,055		38,178	38,178	
Age at index (years, mean ± SD)	41.5 ± 15.2	38.7 ± 12.1	0.20[a]	40.8 ± 14.9	41.1 ± 13.0	0.02
Sex (%)						
Female	47.4	44.8	0.05	47.0	48.8	0.04
Male	52.5	55.2	0.05	53.0	51.2	0.04
Ethnicity (%)						
Hispanic/Latinx	7.4	5.9	0.06	7.4	7.3	0.003
Not Hispanic/Latinx	57.3	73.1	0.34[a]	60.4	59.8	0.01
Unknown	35.2	21.0	0.32[a]	32.2	32.9	0.01
Race (%)						
Asian	0.6	0.4	0.03	0.5	0.5	0.001
Black	15.0	11.6	0.10[a]	13.5	13.4	0.005
White	68.5	73.4	0.11[a]	69.5	69.9	0.008
Unknown	15.4	13.7	0.05	15.8	15.6	0.006
Adverse socioeconomic determinants of health (%)	6.5	10.2	0.13[a]	6.9	7.1	0.01
Comorbidities (%)						
Alcohol use disorders	10.3	14.2	0.12[a]	10.7	11.6	0.03
Cannabis use disorders	7.3	11.6	0.15[a]	7.7	8.3	0.02
Cocaine use disorders	10.7	11.4	0.02	10.8	11.6	0.02
Other stimulant disorders	5.8	10.1	0.16[a]	6.1	6.6	0.02
Tobacco use disorders	35.5	41.3	0.12[a]	36.2	38.4	0.05
Chronic pain	16.8	15.9	0.02	16.5	17.1	0.02
Low back pain	12.7	15.5	0.08	12.9	13.6	0.02
Mood disorders	27.0	34.7	0.17[a]	27.8	29.9	0.05
Anxiety	27.2	33.7	0.14[a]	27.9	29.9	0.05
Schizophrenia and other psychotic disorders	3.2	5.1	0.09	3.4	3.7	0.02
Behavioral disorders	2.1	3.2	0.06	2.3	2.5	0.01
Hypertension	19.9	16.9	0.08	19.3	20.1	0.02
Heart diseases	4.5	3.5	0.05	4.2	4.3	0.005
Coronary artery diseases	2.9	2.1	0.05	2.7	2.7	0.001

TABLE 1 (Continued)

	Before propensity-score matching			After propensity-score matching		
	Methadone cohort	Buprenorphine cohort	SMD	Methadone cohort	Buprenorphine cohort	SMD
Congenital heart diseases	1.7	0.7	0.09	1.3	1.3	0.002
Type 2 diabetes	7.9	5.6	0.10[a]	7.4	7.5	0.005
Thyroid disorders	5.6	4.9	0.03	5.3	5.6	0.01
Sleep apnea	3.9	2.9	0.05	3.6	3.7	0.007
Disorders of fluid, electrolyte and acid-base balance	15.2	10.7	0.14[a]	13.9	14.1	0.006

Note: Self-reported sex, race and ethnicity data in TriNetX comes from the underlying clinical EHR systems of the contributing health care systems. TriNetX maps race and ethnicity data from the contributing health care systems to the following categories: (1) Race: Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race; and (2) Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity. The status of adverse socioeconomic determinants of health was based on the ICD-10 code "Persons with potential health hazards related to socioeconomic and psychosocial circumstances" (Z55-Z65), which includes codes "Problems related to housing and economic circumstances" (Z59), "Problems related to upbringing" (Z62), among others.

Abbreviation: SMD, standardized mean differences.

[a]SMD greater than 0.1, a threshold indicating imbalance.

the 0.15% in the matched Buprenorphine cohort (HR: 2.40, 95% CI: 1.75–3.28); The overall mortality was 0.59% in the Methadone cohort, higher than the 0.41% in the matched Buprenorphine cohort (HR: 1.48, 95% CI: 1.21–1.81). The increased risk persisted for 5 years: cardiac arrhythmias (HR: 1.31, 95% CI: 1.23–1.38), long QT syndrome (HR: 3.14, 95% CI: 2.76–3.58), death (HR: 1.50, 95% CI: 1.41–1.59) (Figure 2a).

Compared with the propensity-score matched Naltrexone cohort, the Methadone cohort had higher risks for cardiac arrhythmias, long QT syndrome and death for all 6 follow-up times (1 month, 3-month, 6-month, 1-year, 3-year, and 5-year), except that the risk for death at 1-, 3- and 6-month follow-up time was higher but not significant (Figure 2b). The matched Naltrexone and Buprenorphine cohorts had similar cardiac and mortality outcomes except for lower risk of cardiac arrythmia in the Naltrexone cohort at 1-, 3-, and 6-month follow-up times (Figure 2c).

4 | DISCUSSION

Our study shows that mortality is significantly higher for patients who were prescribed methadone than those prescribed buprenorphine or naltrexone. Though the risk for cardiac arrythmias and long QT syndrome were also higher for methadone than for buprenorphine and naltrexone, this is unlikely to be the only mechanism responsible for the higher death rate since estimates of death (5 years: Methadone: 7.02%, Buprenorphine 4.51%) were higher than for the prevalence of arrythmias (5 years: Methadone: 5.65%, Buprenorphine 3.68%) and of long QT syndrome (5 years Methadone: 2.47%, Buprenorphine 0.78%). This suggests that other factors contribute to the greater death rates from methadone than that observed for buprenorphine and naltrexone. We hypothesize that misuse of opioid drugs while on methadone treatment is more likely to result in a fatal overdose than with buprenorphine or naltrexone treatment. We reasoned that because methadone treatment results in a relatively low occupancy of MOR (Kling et al., 2000; Melichar et al., 2005) compared with buprenorphine or naltrexone treatment, which result in almost complete MOR occupancy (Greenwald et al., 2014; Zubieta, 2000), this allows for the remaining unoccupied MOR to be activated when the person misuses opioid drugs triggering an overdose. Also methadone by itself results in respiratory depression to a much greater extent than buprenorphine (Whelan & Remski, 2012),

(a) **Cardiac and mortality outcomes in patients with opioid use disorders comparison between propensity–score matched cohorts: methadone vs. buprenorphine**

Outcome	Overall risk (# of cases) Methadone cohort (n = 38,178)	Overall risk (# of cases) Buprenorphine cohort (n = 38,178)	HR (95% CI)
	1–month follow–up		
Cardiac arrhythmias	1.03% (394)	0.87% (331)	1.20 (1.04–1.39)
Long QT syndrome	0.35% (133)	0.15% (56)	2.40 (1.75–3.28)
Death	0.59% (226)	0.41% (155)	1.48 (1.21–1.81)
	3–month follow–up		
Cardiac arrhythmias	1.77% (677)	1.36% (518)	1.33 (1.18–1.49)
Long QT syndrome	0.66% (253)	0.21% (81)	3.18 (2.47–4.08)
Death	1.33% (509)	0.78% (298)	1.74 (1.51–2.01)
	6–month follow–up		
Cardiac arrhythmias	2.35% (898)	1.89% (723)	1.27 (1.15–1.40)
Long QT syndrome	0.97% (370)	0.34% (131)	2.89 (2.37–3.52)
Death	2.14% (816)	1.27% (483)	1.73 (1.54–1.93)
	1–year follow–up		
Cardiac arrhythmias	3.30% (1,258)	2.67% (1,019)	1.26 (1.16–1.37)
Long QT syndrome	1.44% (548)	0.45% (173)	3.25 (2.73–3.85)
Death	3.27% (1,250)	1.96% (747)	1.71 (1.56–1.87)
	3–year follow–up		
Cardiac arrhythmias	5.97% (2,280)	4.47% (1,707)	1.34 (1.25–1.42)
Long QT syndrome	2.22% (849)	0.69% (263)	3.26 (2.84–3.74)
Death	5.65% (2,158)	3.68% (1,404)	1.53 (1.43–1.64)
	5–year follow–up		
Cardiac arrhythmias	7.10% (2,712)	5.30% (2,022)	1.31 (1.23–1.38)
Long QT syndrome	2.47% (942)	0.78% (297)	3.14 (2.76–3.58)
Death	7.02% (2,681)	4.51% (1,720)	1.50 (1.41–1.59)

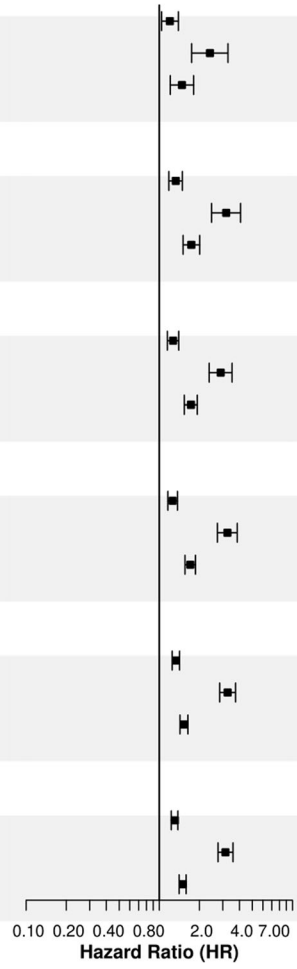

FIGURE 2 Comparing cardiac and mortality outcomes in patients with OUD following MOUD prescription (a) between propensity-score matched Methadone and Buprenorphine cohorts, (b) between propensity-score matched Methadone and Naltrexone cohorts, and (c) between propensity-score matched Naltrexone and Buprenorphine cohorts. Three outcomes (cardiac arrythmias, long QT syndrome, death) were followed for 6 different time frames (1-month, 3-month, 6-month, 1-year, 3-year, and 5-year) following the prescription of methadone, buprenorphine, or naltrexone. MOUD, medications for opioid use disorders; OUD, opioid use disorders.

which requires very high doses to slow down breathing whereas naltrexone is devoid of respiratory depressant effects. Nonetheless, it is also likely that the higher risk for long QT syndrome and cardiac arrythmias associated with methadone than with buprenorphine are likely to contribute to greater lethality following an opioid overdose.

Methadone was associated with higher risks of cardiac outcomes than buprenorphine or naltrexone for both short term (1-month, 3-month, and 6-month) and longer-term (1-year, 3-year, and 5-year) follow-up time. hERG potassium channels are essential for normal electrical activity in the heart. Blockage of hERG channels by drugs may

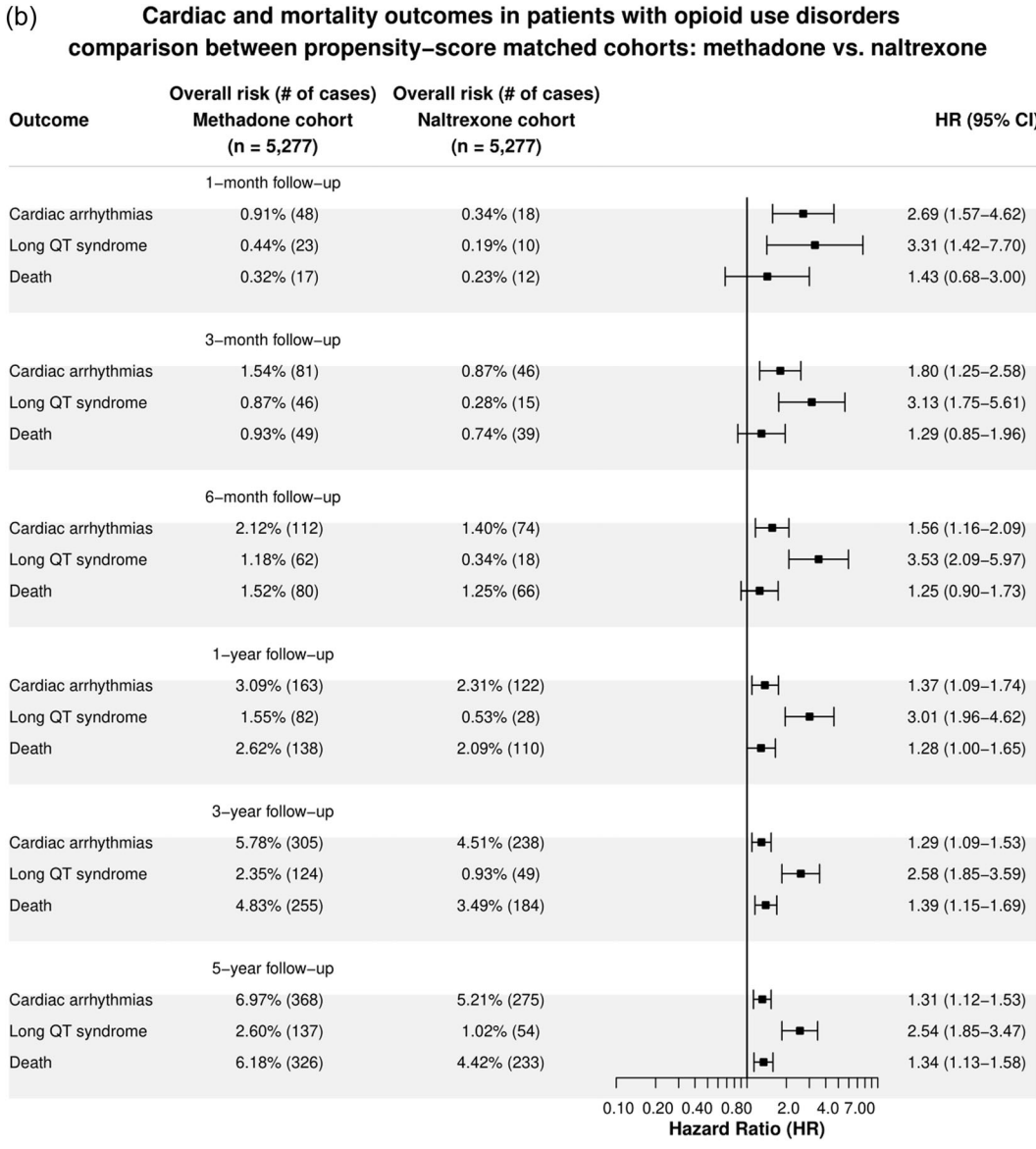

FIGURE 2 (Continued).

lead to long QT syndrome and fatal arrhythmias(Sanguinetti & Tristani-Firouzi, 2006). Methadone's acute inhibition of hERG may be responsible for long QT syndrome (Katchman et al., 2002). Indeed, multiple reports of methadone-associated long QT syndrome in patients with OUD undergoing methadone treatment have been published with prevalence estimates ranging from 15% after 2 weeks of initiation (Titus-Lay et al., 2021) to up to 62% over a 5-year period(Fareed et al., 2013). Differences in the methadone doses taken as well as the time QTc interval (>440 to >480 ms) used for diagnoses of long QT syndrome contribute to the different prevalence estimates (Titus-Lay et al., 2021). Buprenorphine does not inhibit the hERG channel (Tran et al., 2020) nor is there clinical evidence of its association with Torsade de Pointes, though at high doses it can lead to long QT syndrome through an unknown mechanism (Harris et al., 2017). Naltrexone does not inhibit hERG and there is no clinical evidence of QT prolongation with naltrexone treatment (Tran et al., 2020). Our findings comparing methadone, buprenorphine and

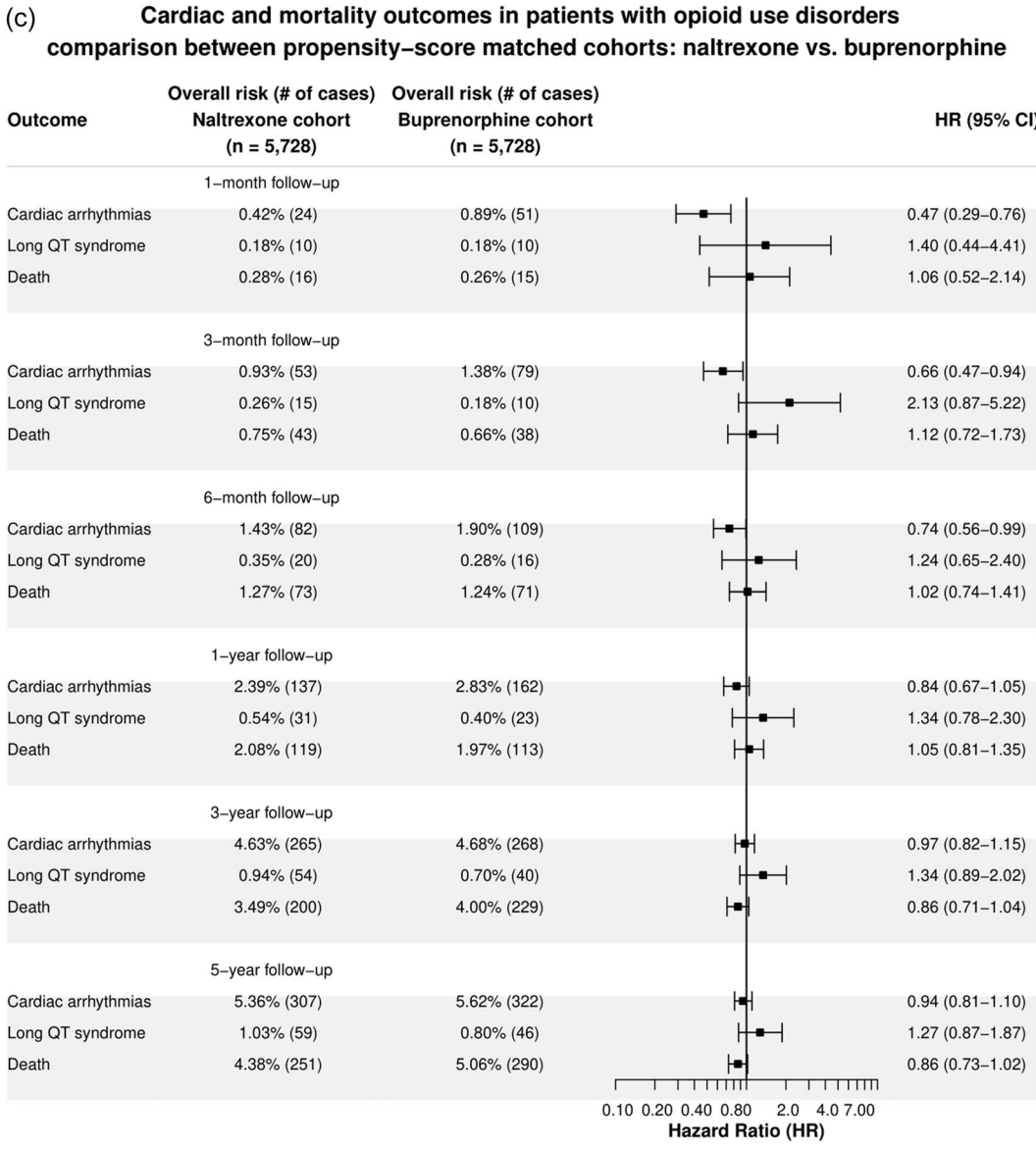

FIGURE 2 (Continued).

naltrexone in matched patients with OUD provide further real-world evidence of cardiac outcome difference between MOUDs. Methadone is dispensed as a racemic mixture of (*R*)-methadone, which is primarily responsible for MOR agonism and its therapeutic effects (Olsen et al., 1977) and of (*S*)-methadone, which has much lower affinity for MOR but inhibits hERG channels to a greater extent than (*R*)-methadone (Titus-Lay et al., 2021). As such development of a pure R-methadone for the treatment of OUD might help decrease some of the cardiotoxic risks from methadone (McCance-Katz, 2011).

Our findings showing lower risk of cardiac arrythmias in OUD patients who were prescribed naltrexone compared to those prescribed methadone differs from the findings of higher incidence of cardiac arrythmias with naltrexone compared to buprenorphine and methadone reported by Raji et al. (2022) using administrative claims data (Raji et al., 2022). There are various factors that likely contributed to these discrepant results. To start with this

could reflect the distinct characteristics of clinical populations in the TriNetX and in the Optum's deidentified Clinformatics Data Mart (CDM) databases and the different purpose for the data captured in claims data from that in EHRs (Maeng et al., 2014). There were also differences in the methodologies used in both analyses including the co-variates used to adjust for differences between the original unadjusted cohorts. This is important as patients with OUD who were prescribed these 3 medications differed significantly. Our analyses included alcohol use disorder (AUD) (as well as other substance use disorders) as covariate whereas Raji et al did not. This is relevant since for both databases the prevalence of alcohol abuse(Raji et al., 2022) and AUD in our unadjusted sample were at least 4–5 five times higher than in patients who were prescribed methadone and buprenorphine. Similarly the prevalence estimate for alcohol abuse in the CDM database for the naltrexone cohort was significantly higher than for the other two medications and comprised 50% of cases compared to 6% for methadone and 11% for buprenorphine (Raji et al., 2022). The higher rates for alcohol abuse/AUD in patients who were prescribed naltrexone was not unexpected, for patients with comorbid OUD and alcohol abuse/AUD are more likely to be prescribed naltrexone since it is also an effective treatment for AUD(Kranzler & Soyka, 2018). Inasmuch as alcohol is an arrhythmogenic drug (Day & Rudd, 2019), the higher incidence in arrythmias with naltrexone reported by Raji et al is therefore likely to reflect in part the arrhythmogenic effects of alcohol in this cohort of patients. In addition, in our study population patients with OUD prescribed naltrexone had significantly higher prevalence of adverse socioeconomic determinants of health (problems with education, employment, occupational exposure, physical, social and psychosocial environment, and housing) than those prescribed methadone or buprenorphine (22.6%, 8.2%, and 10.3%, respectively) (Table 1). Since socioeconomic determinants of health have a significant effect on cardiovascular health and in mortality (Clark et al., 2009; Schultz et al., 2018; Zhang et al., 2021), it is important to control for them when comparing cardiac and mortality outcomes between MOUDs.

Our study has several limitations: First, this is a retrospective observational study, so no causal inferences can be drawn. Second, there are inherent limitations in studies based on patient EHRs including over/mis/under-diagnosis and unmeasured confounders. However, we compared the risks for three outcomes between the three cohort populations both drawn from the TriNetX data set, therefore these issues should not substantially affect the relative risk analyses. Third, patients in the TriNetX database represented those who had medical encounters with health care systems contributing to the TriNetX Platform. Even though this platform includes 28% of US population, it does not necessarily represent the entire US population. Therefore, results from the TriNetX platform need to be validated in other populations. Fourth in our study we were unable to compare treatment retention lengths, which have been reported to differ between MOUD with longer retention reported for methadone than for buprenorphine or naltrexone (Timko et al., 2016). Additionally OUD patients who consume fentanyl which is associated with higher lethality than heroin but also with more severe physical dependence might have been more likely to receive methadone since in these patients buprenorphine and naltrexone might trigger withdrawal (Volkow, 2021). We showed the risk for both cardiac and mortality outcomes was higher within 30-day of methadone prescription compared with 30-day buprenorphine or naltrexone prescription. Effects of difference in drug retention length on the outcome should be mitigated for such short-term follow-up time period. In addition, our study controlled for main factors that could influence drug adherence including social and economic, demographics, health care system and health conditions (Burkhart & Sabaté, 2003). Fifth, a potential confounder from our findings is that both ASAM and SAMHSA recommend performing electrocardiogram (ECG) in methadone maintenance treatment for individuals at higher risk before induction and for periodic monitoring (Martin et al., 2011) whereas such guidelines do not apply to buprenorphine or naltrexone, thus patients on methadone were more likely to have received ECG increasing the probabilities of detection of arrythmias. Even though our inclusion selection criteria were prescription of MOUD within 1 months of an OUD diagnoses we cannot rule out the possibility that methadone and buprenorphine were prescribed for pain management or whether naltrexone was prescribed for alcohol use disorders. To mitigate these potential limitations, we matched cohorts for pain, alcohol use disorders and other comorbidities that may confound the findings. Also in our study the dosage information for MOUDs including methadone is largely incomplete. Future studies should evaluate how different

doses of MOUD influence cardiac and mortality outcomes for inadequate doses of methadone, buprenorphine or naltrexone could lead to higher risks of relapse and overdoses.

In considering the clinical implications of our findings on the relative higher risk for cardia arrythmias from methadone than from buprenorphine and naltrexone, one needs to place it in the context of the very high risks of overdose mortality associated with fentanyl and analogs dominating the illicit drugs and the large protective effects that methadone and other MOUD offer in preventing overdoses and mortality. In particular, consideration should be given to the strong physical dependence and tolerance observed in patients chronically exposed to fentanyl in whom methadone might offer a better initial intervention to prevent withdrawal and to initiate treatment than buprenorphine or naltrexone and it might also improve retention. In this respect it might be particularly hard to initiate patients with OUD into naltrexone treatment. Research studies to compare retention on treatment for methadone versus buprenorphine or naltrexone for individuals with a fentanyl use disorder are needed to help clarify the risk and benefits uniquely associated with these three medications. Because fentanyl did not become a main driver of the overdose epidemic until 2016, we focused our analyses on the 2016–2022 period to assess differences between methadone and buprenorphine and naltrexone at a time when most overdoses deaths were ascribed to fentanyl.

In summary, patients with OUD who were prescribed methadone were at significantly increased risk for death, cardiac arrythmias and long QT syndrome compared to matched patients prescribed buprenorphine or naltrexone. Studies are necessary to compare the risk and benefits of treatments with methadone, buprenorphine and naltrexone among patients with OUD to help develop guidelines for optimizing medication selection when initiating MOUD treatment. Such data is also relevant to inform future medication development for OUD that can minimize risk while maximizing benefits.

AUTHOR CONTRIBUTIONS

Nora D. Volkow conceived the study and Rong Xu designed the study. Nora D. Volkow and Rong Xu drafted the manuscript. Lindsey Wang performed data analysis and prepared tables and figures and participated in manuscript preparation. Pamela B. Davis, Nathan A. Berger, David C. Kaelber critically contributed to study design, result interpretation and manuscript preparation. We confirm the originality of content. Rong Xu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

We do not collect or generate original data ourselves, but rather analyzed population-level and deidentified data collected, stored and maintained by TriNetX. All the data related to the characteristics of study populations, clinical codes to define study populations, statistics, and statistical methods are in the accompanying Supplemental file.

ETHICS STATEMENT

MetroHealth System, Cleveland OH, Institutional Review Board has determined that any research using TriNetX is not Human Subject Research and therefore exempt from review.

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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