CLINICAL RESEARCH STUDY

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Association of Medication-Assisted Therapy with New Onset of Cardiac Arrhythmia in Patients Diagnosed with Opioid Use Disorders

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ABSTRACT

BACKGROUND: No data exist on comparative risk of cardiac arrhythmias among 3 Medication-Assisted Therapy (MAT) medications in patients with opioid use disorder. Understanding MAT medications with the least risk of arrhythmia can guide clinical decision-making.

METHOD: A multicenter retrospective cohort study was performed of patients 18 years or older diagnosed with opioid use disorder by the International Classification of Diseases, 10th revision, Clinical Modification without baseline arrhythmia in 2018-2019, using Clinformatics Data Mart Database (Optum, Eden Prairie, Minn). Everyone required 1 year of continuous enrollment prior to and after the diagnosis. Patients with MAT were propensity score-matched to those without MAT. Primary outcome was rate of arrhythmia across MAT (methadone, naltrexone, and buprenorphine). A multivariable logistic regression model was built to examine the outcome difference across 3 medications adjusted for patient's demographic and comorbidity.

RESULT: Only 14.1% of the 66,083 patients with opioid use disorder received MAT prescriptions in the 12 months after diagnosis. New-onset arrhythmia diagnoses occur more frequently among MAT vs non-MAT users (4.86% vs 3.92%), with 29% risk of incident arrhythmias among MAT users, even after adjusting relevant confounders (adjusted odds ratio [aOR] 1.29; 95% confidence interval [CI], 1.11-1.52). Incidence of arrhythmia varied by drugs: naltrexone (9.57%), methadone (5.71%), and buprenorphine (3.81%). Difference among the MAT drugs in incidence of arrhythmia remained significant even after adjusting covariates (aOR 2.44; 95% CI, 1.63-3.64 and buprenorphine aOR 0.77; 95% CI, 0.59-1.00, with methadone as reference).

CONCLUSION: MAT users had higher risk of cardiac arrhythmia than non-users. Naltrexone is associated with the highest risk of arrhythmia, suggesting caution with naltrexone use, especially in opioid use disorder patients with pre-existing heart conditions.

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KEYWORDS: Arrhythmias; Buprenorphine; Medication-assisted therapy; Methadone; Naltrexone; Opioid use disorder

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INTRODUCTION

Opioid overdose death—a growing public health problem in the United States—has substantially worsened during the ongoing COVID-19 pandemic.[1,2] A key evidence-based intervention to treat opioid use disorder and mitigate opioid overdose death is Medication-Assisted Therapy (MAT, also called medication for opioid use disorder or Medication-Assisted Treatment).[3,4] MAT medication use is associated with a significant reduction in opioid relapse after recovery and in opioid-related acute care use, overdose, and deaths, compared with no treatment.[3-5] Yet, MAT medications (buprenorphine, naltrexone, and methadone) are underused in opioid use disorder patients, reflecting multiple factors: access, cost, and insurance barriers, stigma, prescriber inertia, policies that restrict MAT prescribing, and concerns about cardiovascular and other side effects.[5-8] An understudied area of cardiovascular toxicity concerns related to the comparative risks of cardiac arrhythmias during treatment with any of the 3 MAT drugs: buprenorphine, naltrexone, and methadone. While the study shows the association of methadone use and increased odds of QT prolongation, few data exist on comparative cardiac toxicity among these 3 medications when used in the setting of opioid use disorder treatment.[8,9] We thus used nationally representative population-based data to examine comparative cardiovascular toxicity of MAT for opioid use disorder and their relative risks for QT prolongations and onset of new arrhythmias. Understanding MAT medications with the least risk of arrhythmia can guide clinical decision-making, especially in opioid use disorder patients with pre-existing cardiovascular conditions.

CLINICAL SIGNIFICANCE

- Patients with opioid use disorder who received medication-assisted therapy had a higher risk of cardiac arrhythmia than those who did not.
- Rates of new-onset arrhythmia varied by medication type: naltrexone 9.57%, methadone 5.71%, and buprenorphine at 3.81%.
- Our findings suggest that in opioid use disorder patients with significant cardiovascular conditions—especially conditions that increase the risk of arrhythmias—clinicians should consider buprenorphine as first-line therapy.

METHODS

Data Source

A retrospective cohort study of patients diagnosed with opioid use disorder in 2018-2019 was performed using administrative claims data extracted from Optum's de-identified Clinformatics Data Mart (CDM) Database (Optum, Eden Prairie, Minn). CDM is one of the nation's largest commercial insurance databases containing patient demographics and clinical information such as prescription drugs dispensed and outpatient and inpatient claims. This study was reviewed and approved by the University of Texas Medical Branch Institutional Review Board.

Study Cohort

We identified patients aged 18 years and older in the analysis if they had a diagnosis of opioid use disorder in 2018-2019. Eligible individuals were identified using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD−10−CM) based on the Centers for Medicare & Medicaid Services CMS Chronic Condition Data Warehouse (Supplementary Table 1, available online). The index date as defined by the first opioid use disorder diagnosis is 2018-2019. Patients were excluded if they were not continuously enrolled in the 12 months prior to and the 12 months following the index date. Another exclusion criterion was arrhythmia diagnoses in the 12 months prior to the index date, giving a final analytical sample size of 66,083 patients. The control group included those without any MAT in the 12 months after the index date. The Supplementary Figure (available online) details the cohort selection flowchart. For each patient, we identified whether they received MAT in the 12 months after the index date. We used National Drug Codes in pharmacy claims and Common Procedural Terminology codes in medical claims to identify MAT by receiving prescription or injection of methadone, naltrexone, and buprenorphine (Supplementary Table 2, available online). The control group included those without any MAT in the 12 months after the index date.

Study Outcome and Covariates

We assessed whether both groups were diagnosed with arrhythmias, including long QT prolongation, within 1 year after the index date. Diagnosis of cardiac arrhythmias was based on the definition from the Elixhauser Comorbidity Index Supplementary Table 1. shows the ICD-10 codes of the study outcome. Age at the index date was obtained from the CDM database. We examined and adjusted for all conditions 12 months prior to the index date, which was included in the Elixhauser Comorbidity Index. Each condition was examined as a separate covariate. We also adjusted for sex and the geographic region (Midwest, Northeast, South, West) of each patient. To control for differences between the 2 groups, we performed propensity score matching. The propensity score of having MAT was generated using a logistic regression model including age, sex, region, and comorbidity related to MAT use and arrhythmias (congestive heart failure, chronic pulmonary disease, diabetes, fluid and electrolyte disorders, and hyperthyroidism). For each patient with MAT, we performed greedy

Table 1 Descriptive Statistics of Patient Demographics and Comorbidity Related to MAT Use and Arrhythmias Between Patients with and Without MATs in the Matched Cohort (n = 20,765)

Variable	MAT n = 7511 n (%)	No MAT n = 13,254 n (%)	Overall n = 20,765	Standard Difference	*P* Value
Age, mean (SD)	51.11 (15.37)	50.64 (15.34)	50.81 (15.36)	0.0309	.0325
Sex					
Female	6104 (46.05)	3525 (46.93)	9629	−0.0176	.2233
Male	7150 (53.95)	3986 (53.07)	11,136		
Region					
Midwest	2121 (16.0)	1173 (15.62)	3294		
Northeast	1480 (11.17)	899 (11.97)	2379		.1662
South	6280 (47.38)	3479 (46.32)	9759	0.0329	
West	3373 (25.45)	1960 (26.1)	5333		
Elixhauser comorbidities					
Congestive heart failure	348 (2.63)	286 (3.81)	634	0.0670	.0001
Chronic pulmonary disease	3083 (23.26)	1820 (24.23)	4903	0.0228	.1137
Diabetes	2161 (16.3)	1312 (17.47)	3473	0.0311	.0309
Fluid and electrolyte disorders	1188 (8.96)	784 (10.44)	1972	0.0498	.0005
Hyperthyroidism	74 (0.56)	77 (1.03)	151	0.0527	.0001

MAT = Medication-Assisted Therapy.

nearest neighbor matching to select 2 patients without MAT within a caliper equal to 0.2 standard deviations (SD) of the logit of the propensity score. The date of first MAT use from the MAT user was assigned to the 2 matched non-MAT users. Then, we excluded the pairs in which MAT users had arrhythmias that occurred prior to MAT use, the pairs in which both non-MAT users had arrhythmias that occurred prior to their assigned MAT use, and the individual non-MAT user who had arrhythmias that appeared prior to their assigned MAT user. Our final propensity match cohort included 7511 pairs, with 5743 of them having 2 matched non-MAT users and 1768 of them having 1 matched non-MAT user. We regenerated the propensity score model for sensitivity analysis, including all Elixhauser comorbidity, hyperthyroidism, age, sex, and region. Then we repeated the matching process and had 7489 pairs of patients.

Statistics Analysis

Mean (SD) and frequency of patient characteristics and comorbidity were calculated for both groups prior to propensity match and compared by *t* test for continuous variables and chi-squared test for categorical variables. After the propensity score match, we used the standardized difference to assess the balance of covariates between 2 groups. A conditional logistic regression model was built to examine the association between MAT use and arrhythmia in the propensity match cohort. We further compared the rate of arrhythmia across 3 medications (methadone, naltrexone, and buprenorphine). In these analyses, we excluded 29 patients with more than one type of medication in the 12 months after the index date. A multivariable logistic regression model was built to examine the outcome difference across 3 medications adjusted for patient's demographic and comorbidity. All tests of statistical significance were 2-sided, and analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Among 66,083 opioid use disorder patients who met selection criteria, 14.1% received MATs in the 12 months after diagnosis (Supplementary Table 3, available online). Patients who received MATs were younger, more likely to be male, residing in Northeast and Midwest regions, and have alcohol use disorder, depression, and liver disease, but less likely to have other chronic conditions. To account for these differences, we conduct propensity matching. After matching, patient demographics and comorbidity related to MAT and arrhythmia between MAT and non-MAT groups were very similar. The SD was <0.1, which shows these characteristics were well balanced between the 2 groups after matching (Table 1). However, the comorbidity not included in the propensity score model was different between the 2 groups (Table 2). Alcohol abuse was less common in the MAT group (9.77%) than in the non-MAT group (13.73%). Depression was less prevalent (39.66%) in the MAT group than in the non-MAT group (45.84%). On the contrary, 20.59% were obese in the MAT group, compared with 16.39% in the non-MAT group. The rate of arrhythmias was 4.86% and 3.92% among MAT and non-MAT groups, respectively. After adjusting for comorbidity, which was significantly different between the 2 groups, the risk of arrhythmias was 29% higher among MAT users (adjusted odds ratio [aOR] 1.29; 95% confidence interval [CI], 1.11-1.52) (Table 3). Other comorbidity associated with arrhythmias included valvular disease (aOR 2.55; 95% CI, 1.65-3.93), peripheral vascular disorders (aOR 1.51; 95% CI, 1.14-2.00), renal failure (aOR 1.40; 95% CI, 1.03-1.92), and liver disease (aOR 1.43; 95% CI, 1.06-1.92).

Among MAT users, we found that the rate of arrhythmia with the use of naltrexone was higher (9.57%) compared with methadone (5.71%), and the rate of arrhythmia was the least with the help of buprenorphine (3.81%). There were significant age differences among patients in different MAT groups. Patients in the methadone group were older (mean age 56.96 years) compared with buprenorphine (mean age 51.11) and naltrexone (mean age 37.93). Alcohol abuse was highest in naltrexone (50.76%) compared with buprenorphine and methadone group (Table 4). This finding can be explained because naltrexone is also used to treat patients with alcohol use disorder. After adjusting for demographics and comorbidity, the use of naltrexone was associated with a more than 2 times higher risk of arrhythmias than methadone (aOR 2.43; 95% CI, 1.61-3.65) (Table 5). In contrast, the use of buprenorphine was associated with a lower risk of arrhythmias than the use of methadone; however, this difference was marginally significant (aOR 0.78; 95% CI, 0.60-1.02).

Our sensitivity analyses with the matching propensity score including all comorbidity were well balanced between MAT and non-MAT groups (Supplementary Table 4, available online). The association between MAT use and arrhythmias was robust (aOR 1.30; 95% CI, 1.13-1.50). Also, the association between type of medication and arrhythmias remained similar for naltrexone (aOR 2.44; 95% CI, 1.63-3.64) and buprenorphine (aOR 0.77; 95% CI, 0.59-1.00) in comparison with methadone.

Table 3 Results from the Unadjusted and Adjusted Conditional Logistic Regression Models Examining Associations Between MAT and Arrhythmias

Variables	OR	95% CI	*P* Value
Unadjusted			
MAT	1.354	1.166-1.572	< .0001
Adjusted			
MAT	1.294	1.105-1.516	.0014
Alcohol	1.219	0.93-1.598	.1523
Deficiency anemia	1.182	0.839-1.666	.3388
Depression	1.198	0.98-1.465	.0771
Hypothyroidism	1.137	0.873-1.48	.3399
Liver disease	1.426	1.056-1.924	.0204
Cancer	1.414	0.969-2.063	.0724
Obesity	1.006	0.797-1.27	.9611
Peptic ulcer disease excluding bleeding	1.45	0.767-2.744	.2529
Peripheral vascular disorders	1.51	1.137-2.004	.0044
Renal failure	1.401	1.023-1.918	.0357
Rheumatoid arthritis/collagen	1.056	0.813-1.372	.6826
Valvular disease	2.547	1.652-3.927	< .0001

CI = confidence interval; MAT = Medication-Assisted Therapy; OR = odds ratio.

DISCUSSION

Our findings can be summarized as follows. Only 14.1% of the 66,083 patients with opioid use disorder received MAT

Table 2 Descriptive Statistics of Comorbidity Not Included in the Propensity Score Model Between MAT and Non-MAT Users in the Match Cohort

Variables	MAT n = 7511 n (%)	No MAT n = 13,254 n (%)	Overall n = 20,765	*P* Value
Elixhauser comorbidities				
Alcohol abuse	1295 (9.77)	1031 (13.73)	2326	.0001
Blood loss anemia	114 (0.86)	69 (0.92)	183	.6645
Coagulopathy	380 (2.87)	215 (2.86)	595	.9848
Deficiency anemia	696 (5.25)	443 (5.9)	1139	.0492
Depression	5257 (39.66)	3443 (45.84)	8,700	.0001
AIDS/HIV	80 (0.6)	47 (0.63)	127	.844
Hypertension complicated	833 (6.28)	451 (6)	1284	.4202
Hypertension uncomplicated	5914 (44.62)	3293 (43.84)	9207	.2781
Hypothyroidism	1735 (13.09)	1097 (14.61)	2832	.0022
Liver disease	988 (7.45)	743 (9.89)	1731	.0001
Cancer	648 (4.89)	303 (4.03)	951	.0046
Obesity	2729 (20.59)	1231 (16.39)	3960	.0001
Other neurological disorders	980 (7.39)	593 (7.9)	1573	.1898
Pulmonary circulation disorders	211 (1.59)	143 (1.9)	354	.0953
Peptic ulcer disease excluding bleeding	156 (1.18)	116 (1.54)	272	.0253
Peripheral vascular disorders	1465 (11.05)	637 (8.48)	2102	.0001
Paralysis	167 (1.26)	81 (1.08)	248	.2471
Psychoses	449 (3.39)	275 (3.66)	724	.3017
Renal failure	1029 (7.76)	486 (6.47)	1515	.0006
Rheumatoid arthritis/collagen	1976 (14.91)	945 (12.58)	2921	.0001
Valvular disease	357 (2.69)	244 (3.25)	601	.0219
Weight loss	558 (4.21)	324 (4.31)	882	.722

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; MAT = Medication-Assisted Therapy.

Table 4 Descriptive Statistics of Patient Demographics and Comorbidity Across Patients Received Methadone, Naltrexone, and Buprenorphine (n = 7482)

Variables	Methadone n = 1612 n (%)	Naltrexone n = 721 n (%)	Buprenorphine n = 5149 n (%)	Overall n = 7482*	*P* Value
Age, mean (SD)	56.96 (13.62)	37.93 (14.66)	51.11 (14.84)	51.18 (15.35)	.0001
Sex					
Female	777 (48.2)	323 (44.8)	2410 (46.81)	3510	.3024
Male	835 (51.8)	398 (55.2)	2739 (53.19)	3972	
Region					
Midwest	246 (15.26)	164 (22.75)	752 (14.6)	1162	.0001
Northeast	171 (10.61)	97 (13.45)	628 (12.2)	896	
South	647 (40.14)	284 (39.39)	2538 (49.29)	3469	
West	548 (34)	176 (24.41)	1231 (23.91)	1955	
Elixhauser comorbidities					
Alcohol abuse	96 (5.96)	366 (50.76)	563 (10.93)	1025	.0001
Blood loss anemia	15 (0.93)	6 (0.83)	48 (0.93)	69	.9652
Congestive heart failure	79 (4.9)	9 (1.25)	198 (3.85)	286	.0001
Chronic pulmonary disease	445 (27.61)	116 (16.09)	1253 (24.33)	1814	.0001
Coagulopathy	78 (4.84)	13 (1.8)	124 (2.41)	215	.0001
Deficiency anemia	116 (7.2)	30 (4.16)	297 (5.77)	443	.0115
Depression	666 (41.32)	429 (59.5)	2331 (45.27)	3426	.0001
Diabetes	407 (25.25)	52 (7.21)	851 (16.53)	1310	.0001
Fluid and electrolyte disorders	192 (11.91)	87 (12.07)	502 (9.75)	781	.015
AIDS/HIV	12 (0.74)	7 (0.97)	28 (0.54)	47	.3178
Hypertension complicated	145 (9)	18 (2.5)	287 (5.57)	450	.0001
Hypertension uncomplicated	847 (52.54)	178 (24.69)	2261 (43.91)	3286	.0001
Hypothyroidism	289 (17.93)	72 (9.99)	736 (14.29)	1097	.0001
Hyperthyroidism	12 (0.74)	5 (0.69)	60 (1.17)	77	.2212
Liver disease	170 (10.55)	60 (8.32)	509 (9.89)	739	.2503
Cancer	115 (7.13)	15 (2.08)	173 (3.36)	303	.0001
Obesity	347 (21.53)	94 (13.04)	786 (15.27)	1227	.0001
Other neurological disorders	150 (9.31)	51 (7.07)	391 (7.59)	592	.0577
Pulmonary circulation disorders	48 (2.98)	7 (0.97)	88 (1.71)	143	.0008
Peptic ulcer disease excluding bleeding	23 (1.43)	NA	90 (1.75)	116	.0229
Peripheral vascular disorders	232 (14.39)	19 (2.64)	386 (7.5)	637	.0001
Paralysis	30 (1.86)	4 (0.55)	46 (0.89)	80	.0016
Psychoses	35 (2.17)	45 (6.24)	193 (3.75)	273	.0001
Renal failure	183 (11.35)	14 (1.94)	288 (5.59)	485	.0001
Rheumatoid arthritis/ collagen	269 (16.69)	32 (4.44)	643 (12.49)	944	.0001
Valvular disease	71 (4.4)	11 (1.53)	161 (3.13)	243	.001
Weight loss	78 (4.84)	25 (3.47)	221 (4.29)	324	.3135

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

prescriptions in the 12 months after diagnosis. New-onset arrhythmia diagnoses occur more frequently among MAT vs non-MAT users (4.86% vs 3.92%), with a 29% risk of incident arrhythmias among MAT users, even after adjusting for relevant confounders. The incidence of arrhythmia varied by drugs: naltrexone (9.57%), methadone (5.71%), and buprenorphine (3.81%). The difference among the MAT drugs in arrhythmia risks remained significant even after adjustment for covariates: naltrexone is about 2.44 times, and buprenorphine is 0.77 times as likely as methadone to be linked to new-onset arrhythmia.

The overall low rate of MAT prescribing for opioid use disorder patients is consistent with prior research that showed a low rate of MAT use, ranging from 10% to 40% of opioid use disorder patients receiving MAT.[10-13] Kuo et al[13] found that <10% of the 6932 Medicare enrollees

Table 5 Results from Unadjusted and Adjusted Logistic Regression Examining the Association on Type of MAT Medications and Arrhythmias

Variables	OR	95% CI	*P* Value
Unadjusted			
Drug (reference = Methadone)			
Naltrexone	1.749	1.264-2.422	.0008
Buprenorphine	0.654	0.507-0.843	.0011
Adjusted			
Drug (reference = methadone)			
Naltrexone	2.425	1.612-3.648	< .0001
Buprenorphine	0.781	0.595-1.024	.0733
Age	1.000	0.991-1.01	.9967
Males vs females	0.901	0.712-1.141	.3872
Region (reference = South)			
Midwest	0.866	0.602-1.246	.4386
North	1.361	0.964-1.922	.0803
West	1.145	0.876-1.496	.3224
Alcohol	1.318	0.965-1.799	.0823
Congestive heart failure	1.649	1.081-2.518	.0204
Chronic pulmonary disease	1.113	0.866-1.432	.4032
Coagulopathy	1.038	0.62-1.739	.8859
Deficiency anemia	1.616	1.136-2.297	.0076
Depression	1.182	0.934-1.498	.1647
Diabetes	1.042	0.786-1.382	.7755
Fluid and electrolyte disorders	1.89	1.427-2.503	< .0001
Hypertension complicated	1.633	1.085-2.458	.0188
Hypertension uncomplicated	1.534	1.158-2.032	.0029
Hypothyroidism	0.938	0.695-1.267	.6787
Cancer	1.154	0.729-1.827	.542
Obesity	0.975	0.736-1.29	.8575
Pulmonary circulation disorders	1.574	0.921-2.688	.0969
Peptic ulcer disease excluding bleeding	1.329	0.686-2.574	.399
Peripheral vascular disorders	1.812	1.327-2.475	.0002
Paralysis	1.034	0.459-2.329	.9361
Psychoses	1.229	0.747-2.023	.4169
Renal failure	1.215	0.819-1.802	.3322
Rheumatoid arthritis/ collagen	1.149	0.847-1.557	.3719
Valvular disease	1.67	1.096-2.545	.0171

CI = confidence interval; MAT = Medication-Assisted Therapy; OR = odds ratio.

who died from opioid overdose in 2012-2016 had any prescription for MAT. The persistently low adoption of MAT intervention for the opioid use disorder population is concerning, considering the proven effectiveness of MAT in saving lives and treating opioid use disorder.[10] The low rate of MAT use underscores the urgent need for the development and implementation of practical policy and practice guidelines by state and federal agencies, insurance payers, and health systems to lessen barriers to MAT prescribing for the growing population of opioid use disorder patients.[14] This is particularly critical at this moment of the COVID-19 pandemic, with its associated social isolation and limited access to medical care. For example, state and federal policies should consider allowing all clinicians who already prescribe opioid analgesics to have automatic approval to prescribe MAT drugs for individuals living with opioid use disorder. Government policies should also consider the elimination of the limit on opioid use disorder patient census in the clinicians' patient panels. Finally, decision-makers in insurance companies and health systems should consider removal of the onerous preauthorization process for MAT prescribing.[14,15]

Our finding of the highest rate of incident arrhythmia in naltrexone users is unexpected, given the large body of literature on the arrhythmogenic risk of methadone. The reason for this finding is unclear. One possibility for the higher arrhythmia rate in naltrexone than methadone is that MAT prescribers might avoid methadone in opioid use disorder patients with any history of cardiac conditions or abnormal electrocardiography (ECG) findings. This possibility is plausible given that prescribing guidelines recommend ECG to rule out arrhythmias and measure QTc prior to initiating methadone. In this scenario,[8,9] high arrhythmia risk patients are screened out when prescribers are considering methadone for opioid use disorder, thus giving the higher rate for naltrexone. Although we excluded participants with prior diagnoses of cardiac arrhythmias, we found that the naltrexone group had a baseline lower rate of heart failure, hypertension, and valve disease than the methadone group. We do not, however, have detailed information on ECG to explore the possibility of differences in the rate of ECG abnormalities in methadone users vs users of other MATs.

CONCLUSION

Our study showed that the rate of arrhythmia with the use of naltrexone was higher (9.57%) compared with methadone (5.71%), and the rate of arrhythmia was the least with the use of buprenorphine (3.81%). We also found that the rate of arrhythmia was significantly higher (27.59%) when 2 or more MAT medications were used in combination.

Limitations

Our findings must be interpreted in view of several limitations. First, information on outcomes and comorbidities is based on diagnosis codes included in charges for outpatient and hospitalization services. Such diagnoses are not always accurate or complete. Second, given the retrospective nature of this study, undetected selection bias may have affected the findings. For example, patients who received MATs may have been more likely than their counterparts to have had subsequent diagnoses. However, we attempted to address this potential bias by propensity matching for a broad range of demographics and comorbidity. Third, our database lacked information on several important factors, such as race/ethnicity and socioeconomic status. Fourth, prescription claims data do not capture data on drugs obtained outside the plan. Given the various stigmas and restrictions associated with MATs, some patients may have accessed these drugs outside their health care setting.

CLINICAL IMPLICATIONS

Our findings suggest that in opioid use disorder patients with significant cardiovascular conditions—especially conditions that increase the risk of arrhythmias—clinicians should consider buprenorphine as first-line therapy. Of course, the final clinical decision for MAT prescribing is made on a case-by-case basis, with consideration by the prescriber of the overall clinical profile of the individual patient with opioid use disorder and with the health care preferences of the patient.

References

1. Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021. Available at: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed February 28, 2022.
2. Becker WC, Fiellin DA. When epidemics collide: Coronavirus disease 2019 (COVID-19) and the opioid crisis. *Ann Intern Med.* 2020;173(1):59–60.
3. Larochelle MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med* 2018;169(3):137–45.
4. Wakeman SE, Larochelle MR, Ameli O, et al. Comparative effectiveness of different treatment pathways for opioid use disorder. *JAMA Netw Open* 2020;3(2):e1920622.
5. Joudrey PJ, Edelman EJ, Wang EA. Methadone for opioid use disorder—decades of effectiveness but still miles away in the US. *JAMA Psychiatry* 2020;77(11):1105–6.
6. Patrick SW, Buntin MB, Martin PR, et al. Barriers to accessing treatment for pregnant women with opioid use disorder in Appalachian states. *Subst Abus* 2019;40(3):356–62.
7. Beetham T, Saloner B, Wakeman SE, Gaye M, Barnett ML. Access to office-based buprenorphine treatment in areas with high rates of opioid-related mortality: an audit study. *Ann Intern Med.* 2019;171(1):1–9.
8. Pani PP, Trogu E, Maremmani I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. *Cochrane Database Syst Rev* 2013(6):CD008939.
9. Krantz MJ, Palmer RB, Haigney MCP. Cardiovascular complications of opioid use: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021;77(2):205–23.
10. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med.* 2014;370(22):2063–6.
11. Haffajee RL, Bohnert ASB, Lagisetty PA. Policy pathways to address provider workforce barriers to buprenorphine treatment. *Am J Prev Med.* 2018;54(6 suppl 3):S230–42.
12. Saloner B, Karthikeyan S. Changes in substance abuse treatment use among individuals with opioid use disorders in the United States, 2004–2013. *JAMA* 2015;314(14):1515–7.
13. Kuo YF, Baillargeon J, Raji MA. Overdose deaths from nonprescribed prescription opioids, heroin, and other synthetic opioids in Medicare beneficiaries. *J Subst Abuse Treat* 2021;124:108282.
14. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Medication-Assisted Treatment for Opioid Use Disorder. In: Mancher M, Leshner AI, eds. *Medications for Opioid Use Disorder Save Lives*, Washington, DC: National Academies Press (US); 2019.
15. Ferries E, Racsa P, Bizzell B, Rhodes C, Suehs B. Removal of prior authorization for medication-assisted treatment: impact on opioid use and policy implications in a Medicare Advantage population. *J Manag Care Spec Pharm* 2021;27(5):596–606.

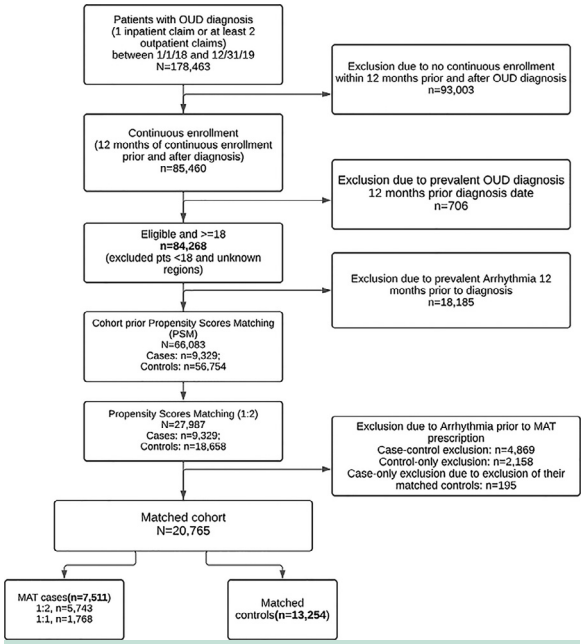
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.01.032.

Supplementary Table 1 International Classification of Diseases, 10th Revision, Clinical Modification (ICD−10−CM) Based on the CMS Chronic Condition Data Warehouse for OUD, Arrhythmia, and Long QT Syndrome

Disease	ICD-10 Diagnosis
OUD	F1110, F11120, F11121, F11122, F11129, F1114, F11150, F11151, F11159, F11181, F11182, F11188, F1119, F1120, F11220, F11221, F11222, F11229, F1123, F1124, F11250, F11251, F11259, F11281, F11282, F11288, F1129, F1190, F11920, F11921, F11922, F11929, F1193, F1194, F11950, F11951, F11959, F11981, F11982, F11988, F1199, T400X1A, T400X2A, T400X3A, T400X4A, T401X1A, T401X2A, T401X3A, T401X4A, T402X1A, T402X2A, T402X3A, T402X4A, T403X1A, T403X2A, T403X3A, T403X4A, T403X5A, T404X1A, T404X2A, T404X3A, T404X4A, T40411A, T40412A, T40413A, T40414A, T40415A, T40421A, T40422A, T40423A, T40424A, T40425A, T40491A, T40492A, T40493A, T40494A, T40495A, T40601A, T40602A, T40603A, T40604A, T40691A, T40692A, T40693A, T40694A
Arrhythmia	I441, I443, I456, I459, I47, I470, I471, I472, I479, I48, I480, I481, I4811, I4819, I482, I4820, I4821, I483, I484, I489, I4891, I4892, I49, I490, I4901, I4902, I491, I492, I493, I494, I4940, I4949, I495, I498, I499, R000, R001, R008, T821, Z450, Z950
Long QT syndrome	I4581, R9431

CMS = Centers for Medicare & Medicaid Services; OUD = opioid use disorder.



Supplementary Figure Diagram for selection of opioid use disorder (OUD) patients with and without Medication-Assisted Therapy (MAT).

Supplementary Table 2 CPT/HCPCS Codes for MAT Use Prescription (Methadone, Buprenorphine, and Naltrexone)

Procedure	CPT/HCPCS Codes	NDC Codes
MAT	G2067, G2068, G2069, G2070, G2071, G2072, G2073, G2078, G2079, H0020, J0571, J0572, J0573, J0574, J0575, J0592, S0109, J1230, J2315	2810010070, 2808120005, 2808080040

CPT = Common Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; MAT = Medication-Assisted Therapy; NDC = National Drug Codes.

Supplementary Table 3 Patient Demographics and Comorbidity Between Patients with and Without MATs

Variables	MAT n = 9329 n (%)	No MAT n = 56,754 n (%)	Overall n = 66,083	*P* Value
Age, mean (SD)	52.20 (15.54)	62.11 (14.7)	60.71 (15.23)	.0001
Sex				
Female	4412 (47.29)	32,580 (57.41)	36,992	.0001
Male	4917 (52.71)	24,174 (42.59)	29,091	
Region				
Midwest	1445 (15.49)	7478 (13.18)	8923	.0001
Northeast	1121 (12.02)	3649 (6.43)	4770	
South	4288 (45.96)	28,385 (50.01)	32,673	
West	2475 (26.53)	17,242 (30.38)	19,717	
Elixhauser comorbidities				
Alcohol abuse	1331 (14.27)	4223 (7.44)	5554	.0001
Blood loss anemia	102 (1.9)	908 (1.6)	1010	.0002
Congestive heart failure	560 (6)	6016 (10.6)	6576	.0001
Chronic pulmonary disease	2567 (27.52)	19,226 (33.88)	21,793	.0001
Coagulopathy	326 (3.49)	2896 (5.1)	3222	.0001
Deficiency anemia	638 (6.84)	5145 (9.07)	5783	.0001
Depression	4466 (47.87)	24,767 (43.64)	29,233	.0001
Diabetes	1834 (19.66)	17,607 (31.02)	19,441	.0001
Fluid and electrolyte disorders	1352 (14.49)	10,077 (17.76)	11,429	.0001
AIDS/HIV	64 (0.69)	308 (0.54)	372	.0854
Hypertension complicated	743 (7.96)	9153 (16.13)	9896	.0001
Hypertension uncomplicated	4438 (47.57)	36,721 (64.7)	41,159	.0001
Hypothyroidism	1445 (15.49)	11,671 (20.56)	13,116	.0001
Hyperthyroidism	109 (1.17)	689 (1.21)	798	.7086
Liver disease	1051 (11.27)	5391 (9.5)	6442	.0001
Cancer	440 (4.72)	4520 (7.96)	4960	.0001
Obesity	1668 (17.88)	14,476 (25.51)	16,144	.0001
Other neurological disorders	910 (9.75)	6244 (11)	7154	.0003
Pulmonary circulation disorders	242 (2.59)	2372 (4.18)	2614	.0001
Peptic ulcer disease excluding bleeding	160 (1.72)	1091 (1.92)	1251	.1734
Peripheral vascular disorders	963 (10.32)	12,773 (22.51)	13,736	.0001
Paralysis	120 (1.29)	159 (1.87)	1179	.0001
Psychoses	390 (4.18)	1754 (3.09)	2144	.0001
Renal failure	733 (7.86)	10,350 (18.24)	11,083	.0001
Rheumatoid arthritis/collagen	1252 (13.42)	11,020 (19.42)	12,272	.0001
Valvular disease	424 (4.54)	3,814 (6.72)	4238	.0001
Weight loss	461 (4.94)	3,769 (6.64)	4230	.0001

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; MAT = Medication-Assisted Therapy.

Supplementary Table 4 Descriptive Statistics of Patient Demographics and Comorbidity Between Patients with and Without MATs in the Matched Cohort from Sensitivity Analyses

Variables	Any MAT n = 7489 n (%)	No MAT n = 13,092 n (%)	Overall n = 20,581	Standard Difference	*P* Value
Age, mean (SD)	51.15 (15.36)	50.65 (15.74)	50.83 (15.60)	0.0325	.0242
Sex					
Female	3497 (46.7)	5990 (45.75)	9487	−0.0189	.1921
Male	3992 (53.3)	7102 (54.25)	11,094		
Region					
Midwest	1173 (15.66)	2086 (15.93)	3259	0.0329	.1784
Northeast	904 (12.07)	1460 (11.15)	2364		
South	3457 (46.16)	6172 (47.14)	9629		
West	1955 (26.1)	3374 (25.77)	5329		
Elixhauser comorbidities					
Alcohol abuse	1029 (13.74)	1514 (11.56)	2543	0.0655	.0001
Blood loss anemia	62 (0.83)	90 (0.69)	152	0.0162	.2576
Congestive heart failure	304 (4.06)	468 (3.57)	772	0.0253	.0784
Chronic pulmonary disease	1836 (24.52)	3013 (23.01)	4849	0.0353	.0146
Coagulopathy	215 (2.87)	315 (2.41)	530	0.0290	.0428
Deficiency anemia	443 (5.92)	709 (5.42)	1152	0.0216	.1334
Depression	3440 (45.93)	5681 (43.39)	9121	0.0511	.0004
Diabetes	1321 (17.64)	2087 (15.94)	3408	0.0454	.0016
Fluid and electrolyte disorders	821 (10.96)	1342 (10.25)	2163	0.0231	.109
Hypertension complicated	459 (6.13)	673 (5.14)	1132	0.0429	.0028
Hypertension uncomplicated	3300 (44.06)	5421 (41.41)	8721	0.0537	.0002
Hypothyroidism	1111 (14.84)	1754 (13.4)	2865	0.0537	.0042
Liver Disease	750 (10.01)	1209 (9.23)	1959	0.0265	.0666
Cancer	293 (3.91)	442 (3.38)	735	0.0286	.0461
Obesity	1225 (16.36)	2011 (15.36)	3236	0.0273	.0588
Other neurological disorders	590 (7.88)	933 (7.13)	1523	0.0285	.0475
Pulmonary circulation disorders	141 (1.88)	194 (1.48)	335	0.0312	.0287
Peripheral vascular disorders	647 (8.64)	958 (7.32)	1605	0.0488	.0007
Paralysis	81 (1.08)	128 (0.98)	209	0.0103	.4745
Psychoses	272 (3.63)	445 (3.4)	717	0.0126	.3805
Renal failure	487 (6.5)	679 (5.19)	1166	0.0561	.0001
Rheumatoid arthritis/collagen	942 (12.58)	1495 (11.42)	2437	0.0357	.0133
Valvular disease	246 (3.28)	383 (2.93)	629	0.0207	.1496
Weight loss	323 (4.31)	503 (3.84)	826	0.0238	.0977

MAT = Medication-Assisted Therapy.