Real-world Effectiveness of Medications for Opioid Use Disorder (RWE-MOUD)

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Background

The opioid epidemic is a complex public health crisis that disproportionately affects diverse populations across the United States. In 2020, 2.7 million people aged 12 or older in the US has an opioid use disorder (OUD).[6] In Missouri, over 70% of drug overdose deaths in 2022 involved opioids.[1] Effective medications for OUD (MOUD) exist: methadone, buprenorphine, and naltrexone, but they remain highly underutilized in the US. In addition, the regulation of MOUD prescriptions varies: buprenorphine can be prescribed for outpatient treatment, while methadone must be dispensed through a registered opioid treatment program. Thus, treatment retention between methadone and buprenorphine can be different due to difference in regulation.[7] As a result, despite encouraging trial results, a real-world comparative effectiveness study between methadone and buprenorphine is needed to understand their relative effectiveness in reducing the risk of opioid-related acute care use among patients with OUD.

This study aims to quantify the real-world effectiveness of methadone compared to buprenorphine on reducing the risk of opioid-related acute care use among patients with OUD using electronic health records (EHRs).

Methods

Data Source The data are from Barnes Jewish HealthCare (BJC), including EHR databases from 14 hospitals in the St. Louis metro area. The data were standardized to the OMOP common data model v5.3.

Study Design We used a retrospective comparative intent-to-treat cohort design. Patients aged 16 years or above diagnosed with OUD or opioid overdose in an ED or inpatient visit and treated with methadone (target) or buprenorphine (comparator) were included. We define OUD as opioid dependence, opioid abuse, and opioid withdrawal.

The primary outcome was opioid-related acute care use. We define opioid-related acute care use as an ED visit or hospitalization with at least one diagnosis code of OUD or opioid overdose. The secondary outcomes included opioid overdose-related acute care use and OUD-related acute care use (i.e., excluding overdose). Patients were censored if they switched to alternative MOUD or reach the end of observation period. We used Atlas WebAPI to create concept sets and define all cohorts.

Statistical Analyses We used large-scale propensity score (LSPS) and Cox proportional hazards model, as implemented in the CohortMethod R package, to estimate the comparative effectiveness of treatments.[2] To adjust for confounding, patients were matched 1:1 using propensity scores estimated by LSPS with 41,202 pre-treatment covariates. We then fit a Cox proportional hazard outcome model to estimate the hazard ratio for all 3 outcomes. To assess the rigor of study design and method validity, we ran multiple study diagnostics as implemented in the CohortMethod and EmpiricalCalibration R packages.[2,3,4] We assessed the equipoise in propensity score distribution, the standardized difference of means (SDM) between the two treatment groups before and after PS matching, and the minimum detectable relative

risk (MDRR).[8] To systematically assess the residual bias in the study, we included 75 negative control outcomes that were believed not to be affected by the treatments. We used the negative controls to compute the expected absolute systematic error (EASE).[4,9] The negative control outcomes were generated using Atlas WebAPI against a knowledge database in the backend.

Results

The cohort characteristics were summarized in Table 1. The study included 4942 OUD patients treated with methadone and 6258 OUD patients with buprenorphine. The OUD cohort was moderately youn; the three largest age groups were 25-29, 30-34, and 35-40, together accounted for about half of the entire cohort. There were 5870 (52.4%) male patients and 5330 (47.6%) female patients. There were 7450 (66.55%) patients whose race was recorded White and 3286 (29.3%) whose race was recorded as Black or African American. The top 4 most common medical conditions were hypertensive disorder, depressive disorder, heart disease, and viral hepatitis C. The most common medications were psycholeptics, drugs for acid related disorders, anti-inflammatory and antirheumatic products, and antithrombotic agents.

Table 2 summarized the comparative effectiveness of methadone versus buprenorphine on three outcomes. We found that methadone was more effectiveness in reducing the risk of opioid overdose compared to buprenorphine (HR [95% CI]: 0.61 [0.38, 0.98]). However, methadone and buprenorphine had similar effectiveness in preventing OUD-related acute care use (HR [95% CI]: 0.96 [0.81, 1.13]). The study had poor equipoise (Figure 1), but after PS matching, 99.0% of the covariates had SDM<0.1 and only 1% covariates had SDM between 0.1 and 0.22. The MDRR across all outcomes were between 1.09 and 1.24, indicating that our study was reasonably powered and can detect a relative risk of 1.09 or larger (for the primary outcome) as statistically significant. The EASE score was 0.21 for all studies, comparable to other studies where EASE was used and indicating small residual bias in the study.[9]

Discussions

We conducted a retrospective cohort study to compare the effectiveness of methadone versus buprenorphine in reducing the risk of opioid-related acute care use using EHR data. Despite very few studies on real-world effectiveness of MOUD, we were able to find some published studies for comparison. Our study agrees with Heikkinen et al[5], who studied the same treatment pairs, methadone and buprenorphine, but compared them to no MOUD treatment in a Swedish population using drug registry data, and found that methadone and buprenorphine had similar effectiveness at lowering the risk of OUD hospitalization compared to those who did not use any OUD medication[5]. However, they did not compare the effectiveness on reducing opioid overdose. Wakeman et al[1] conducted a similar real-world effectiveness study comparing different treatment pathways for OUD using Optum claims data. In this study, they grouped methadone and buprenorphine into one treatment pathway and found that this treatment pathway was protective against serious opioid-related ED visit or hospitalization compared to no treatment[1]. However, they did not separate the two treatments and thus we were not able to directly compare our results against theirs.

There are several limitations in this study. First, the study had poor equipoise. Potential causes were instrumental variables in the covariate set and unstable propensity score model in high-dimensional setting. We will leverage domain knowledge and data-driven approaches to refine the cohort definitions and leverage other dimension reduction techniques other than regularized regression to handle the high dimensionality. Second, the negative control outcomes were not reviewed by domain experts and many of them had too few events for calculating a relative risk. Third, the study was conducted using a single

database. Results may not be generalizable to other data sources. Our next step is to coordinate with other data partners in the OHDSI community to conduct a network study and use meta-analysis to obtain more generalizable findings.

Conclusion

This study found that methadone was more effective in reducing acute care use due to opioid overdose compared to buprenorphine, but no significant difference was found in reducing the risk of opioid-related acute care use.

References

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Table 1. Cohort characteristics.

	Before matching			After matching		
Characteristic	Target %	Comparator %	Std. diff	Target %	Comparator %	Std. diff
Age group						
15 - 19	1	1.1	-0.02	0.2	1.1	-0.11
20 - 24	7.6	7.5	0.01	7.4	5.4	0.08
25 - 29	16.5	15.9	0.02	14.8	13.6	0.04
30 - 34	17.3	18	-0.02	17.6	16.6	0.03
35 - 39	14.1	15.5	-0.04	15.6	14.7	0.02
40 - 44	9.8	12.9	-0.1	12.4	12.5	0
45 - 49	8.3	9.0	-0.02	8.5	7.8	0.03
50 - 54	7.3	6.2	0.04	6.7	7.3	-0.02
55 - 59	7.2	5.3	0.08	6.4	7.8	-0.05
60 - 64	5.6	4.7	0.04	4.8	7.0	-0.09
65 - 69	3	2.6	0.03	3	4.1	-0.06
70 - 74	1.4	0.8	0.07	1.9	1.1	0.06
75 - 79	0.5	0.3	0.03	0.4	0.5	-0.02
80 - 84	0.3	0.1	0.03	0.4	0.4	0
85 - 89	0.1	0	0.03	0	0.1	0
90 - 94	0	0	0	0	0	0
120 - 124	0	0	0	0	0	0
Gender: female	52	44.1	0.16	50.6	51.5	-0.02
Race						
race = Asian	0.2	0.2	0	0.5	0	NA
race = Black or African American	28.4	30	-0.04	27.1	26.6	0.01
race = White	65.9	67	-0.02	69.6	69	0.01
race = American Indian or Alaska Native	0.2	0.3	0	0.2	0	NA
race = Black	0.9	0	0.13	0	0.1	NA
race = Other Pacific Islander	0	0.1	-0.04	0.1	0	NA
Ethnicity						
ethnicity = Hispanic or Latino	0.9	1.1	-0.02	1.6	1.7	-0.01
ethnicity = Not Hispanic or Latino	72.9	90.5	-0.47	89.1	85.5	0.11
Medical history: General						
Acute respiratory disease	15.6	14.3	0.04	15.6	15.2	0.01
Attention deficit hyperactivity disorder	1.7	3.7	-0.12	2.6	3.3	-0.04
Chronic liver disease	10.2	8.2	0.07	12.0	11.7	0.01

Chronic obstructive lung disease	10.1	8.6	0.05	9.3	10.1	-0.03
Crohn's disease	1.1	0.8	0.03	0.5	1.1	-0.07
Dementia	0.5	0.5	0.01	0.5	0.7	-0.03
Depressive disorder	27.1	31.6	-0.1	29.3	31.1	-0.04
Diabetes mellitus	9.7	7.8	0.07	8.9	11.4	-0.08
Gastroesophageal reflux disease	12.3	9.8	0.08	10.9	13.6	-0.08
Gastrointestinal hemorrhage	3.2	2.6	0.04	2.7	3.8	-0.06
Human immunodeficiency virus infection	1.6	1.3	0.02	1.7	1.1	0.05
Hyperlipidemia	10.6	7.9	0.1	10.9	12.9	-0.06
Lesion of liver	3.5	2.3	0.07	3.2	3.5	-0.01
Obesity	7.9	6.8	0.04	9.4	8	0.05
Osteoarthritis	14.4	10.7	0.11	11.1	15.7	-0.13
Pneumonia	10.3	7.3	0.11	11.5	12	-0.02
Psoriasis	0.4	0.6	-0.03	0.2	0.9	-0.08
Renal impairment	12.6	10.9	0.05	14.8	14.1	0.02
Rheumatoid arthritis	1.9	1.4	0.04	1.9	1.6	0.02
Schizophrenia	2.4	5.6	-0.16	4.1	3.6	0.03
Ulcerative colitis	0.3	0.3	0.01		0.9	
Urinary tract infectious disease	12.2	7.8	0.15	9	10.1	-0.04
Viral hepatitis C	19.4	20	-0.01	22.9	24.4	-0.03
Medical history: Cardiovascular disease						
Atrial fibrillation	2.6	2	0.04	2.6	3.3	-0.04
Cerebrovascular disease	2.8	1.3	0.11	1.9	2.6	-0.05
Coronary arteriosclerosis	5.9	3.8	0.1	4.1	6.6	-0.11
Heart disease	24.9	16.7	0.2	24	24.7	-0.02
Heart failure	7.1	5	0.09	7.9	8	0
Ischemic heart disease	5.8	4.1	0.08	5.3	6.8	-0.06
Peripheral vascular disease	2.8	1.9	0.06	2.2	3.2	-0.06
Pulmonary embolism	3.1	2	0.07	4.2	4.3	-0.01
Venous thrombosis	3.5	2.2	0.08	3.2	3.8	-0.03
Medical history: Neoplasms						
Malignant lymphoma	0.6	0.3	0.04	0.2	0.6	-0.06
Malignant neoplasm of anorectum	0.4	0.1	0.08	0.2	0.1	0.03

Malignant neoplastic disease	6.7	2.6	0.2	4.3	5.7	-0.06
Malignant tumor of breast	0.6	0.3	0.06	0.1	0.5	-0.07
Malignant tumor of colon	0.4	0.1	0.07	0.2	0.4	-0.02
Malignant tumor of lung	0.6	0.1	0.11	0.2	0.2	0
Malignant tumor of urinary bladder	0.2	0	0.06	0.1	0.1	0
Primary malignant neoplasm of prostate	0.2	0.1	0.02	0.1	0.1	0
Medication use						
Agents acting on the renin-angiotensin system	13.8	10.6	0.1	13.2	14.5	-0.04
Antibacterials for systemic use	53.8	44.1	0.19	53.4	55.4	-0.04
Antidepressants	38.2	46.3	-0.16	38.2	37.8	0.01
Antiepileptics	47.7	36	0.24	28.9	34.7	-0.12
Antiinflammatory and antirheumatic products	67.2	64	0.07	63	63.5	-0.01
Antineoplastic agents	5.2	2.6	0.14	3.8	4.6	-0.04
Antipsoriatics	1.2	1.4	-0.02	1.5	1.7	-0.02
Antithrombotic agents	58.1	36.7	0.43	53.8	59.1	-0.11
Beta blocking agents	17.2	13.3	0.11	15.9	18.8	-0.08
Calcium channel blockers	11.5	10	0.05	11.7	12.9	-0.03
Diuretics	16.3	11.3	0.15	14.3	16.8	-0.07
Drugs for acid related disorders	77.7	63.9	0.3	66	69.3	-0.07
Drugs for obstructive airway diseases	36.5	29.1	0.16	35.2	38.7	-0.07
Drugs used in diabetes	14.5	8.9	0.18	11.5	14.2	-0.08
Immunosuppressants	2.1	1.5	0.05	1.9	2.5	-0.04
Lipid modifying agents	10.2	9	0.04	10.3	13.2	-0.09
Opioids	54.1	36.2	0.36	49.1	54	-0.1
Psycholeptics	79.4	75.1	0.1	73.4	73.9	-0.01
Psychostimulants, agents used for adhd and nootropics	3	4	-0.05	3.8	3.3	0.03

Table 2. Hazard ratios and study diagnostics.

Target	Comparator	Outcome	Max SDM	Equipoise	MDRR	EASE
Methadone	Buprenorphine	OUD or opioid overdose (primary outcome)	0.22	13.8%	1.09	0.21
Methadone	Buprenorphine	OUD	0.19	13.8%	1.10	0.21
Methadone	Buprenorphine	Opioid overdose	0.19	13.8%	1.24	0.21

Figure 1. PS distribution.

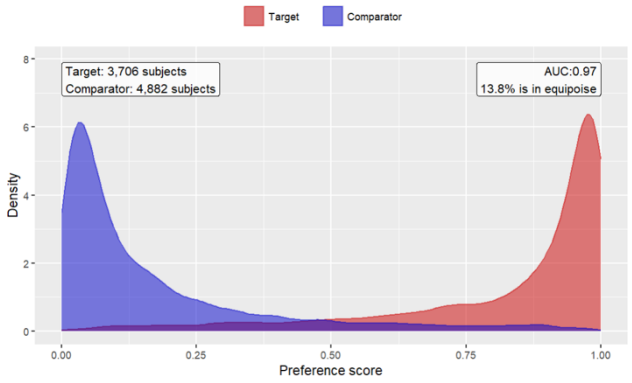

Figure 2. Covariate balance distribution.