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Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment Is Associated With Decreased Mortality

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Objective: Buprenorphine is a medication for opioid use disorder that reduces mortality. This study aims to investigate the less well-understood relationship between the dose in the early stages of treatment and the subsequent risk of death.

Methods: We used Kentucky prescription monitoring data to identify adult Kentucky residents initiating transmucosal buprenorphine medication for opioid use disorder (January 2017 to November 2019). Average daily buprenorphine dose for days covered in the first 30 days of treatment was categorized as 8 mg, >8 to 16 mg, and >16 mg. Patients were followed for 365 days after the first 30 days of buprenorphine treatment. Endpoints were opioid-involved overdose death and death from other causes. Causes and dates of death were obtained using Kentucky death certificate records. Associations were evaluated using multivariable Fine and Gray models adjusting for patient baseline characteristics.

Results: In the cohort of 49,857 patients, there were 227 opioid-involved overdose deaths and 459 deaths from other causes. Compared with 8 mg, the adjusted subdistribution hazard ratio (aSHR) of opioid-involved overdose death decreased by 55% (aSHR, 0.45; 95% confidence interval [CI], 0.34–0.60) and 64% (aSHR, 0.36; 95% CI, 0.25–0.52) for patients receiving doses of >8 to 16 mg and >16 mg, respectively. The incidence of death from other causes was lower in patients receiving >8 to 16 mg (aSHR, 0.78; 95% CI, 0.62–0.98) and >16 mg (aSHR, 0.62; 95% CI, 0.47–0.80) versus 8 mg dose.

Conclusions: Higher first 30-day buprenorphine doses were associated with reduced opioid-involved overdose death and death from other causes, supporting benefit of higher dosing in reducing mortality.

Key Words: opioid use disorder, buprenorphine, prescription drug monitoring program, opioid-involved overdose deaths

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The United States (US) is amid an opioid crisis. More than 2.7 million Americans had opioid use disorder (OUD) in 2020.[1] Opioid-involved overdose deaths have surged in the past decade, with more than 80,000 deaths in 2021, increased by nine times since 1999.[2,3] Fentanyl has been the most frequently involved opioid in US opioid-involved overdose deaths in recent years.[4]

US Food and Drug Administration (FDA)–approved medications for opioid use disorder (MOUDs) treatment, particularly buprenorphine and methadone, significantly improve treatment retention and reduce HIV risk, illicit opioid use, and mortality.[5-7] Buprenorphine is considered safer than methadone because of its ceiling effect on respiratory depression.[8] Unlike methadone, which requires administration in federally licensed Opioid Treatment Programs, buprenorphine can be prescribed by office-based practitioners and dispensed through community pharmacies. Consequently, buprenorphine plays a critical role in expanding access to treatment of OUD.[9]

The first 30 days of transmucosal buprenorphine treatment for OUD (TMbup) represent a critical period in the initiation and stabilization of the treatment. The first 30-day period, encompassing the induction and stabilization phases of TMbup, is vital for establishing therapeutic efficacy. Dose adjustments aim to optimize positive outcomes while minimizing adverse

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effects and are often more frequent in the first month compared with subsequent months for persons on maintenance treatment. Furthermore, the highest risk of discontinuation occurs within the first 30 days (~20%–30% discontinuation rate).[10-12] Among patients initiating buprenorphine MOUD, a lower-dose (4 mg) initial prescription has been associated with increased risk of treatment discontinuation.[11,13]

Clinical guidelines vary on TMbup's target dose and how quickly it should be reached, but it is agreed that most patients reach stable maintenance daily doses between 4 mg and 24 mg, with 16 mg being a common target.[7,14] Despite prior findings suggesting that higher doses of buprenorphine (eg, >16 mg daily) may provide better treatment outcomes, such as decreased discontinuation and return to opioid use,[10,11,15] limited information is available about the associations between TMbup doses and subsequent risk of death.

The dose recommendations were established before the emergence of illicitly manufactured fentanyl. In Kentucky, fentanyl was identified in 29% and 69% of overdose deaths in 2016 and 2020, respectively.[16] Kentucky has historically ranked among the top 5 states with the highest age-adjusted drug overdose mortality and the highest opioid analgesics dispensing in the United States in recent years.[17] Using real-world data representative of patients receiving outpatient TMbup in Kentucky, we conducted the study to examine the associations between the average daily dose of TMbup for days covered within the first 30 days of treatment (hereinafter "first 30-day TMbup dose") and the incidence of opioid-involved overdose deaths in the following 365 days. In addition, we evaluated the association of the average dose with deaths from causes other than opioid-involved overdose and with all-cause mortality. Our study is aimed to gather data from real-world settings to inform the design of further studies to test hypotheses about these associations.

METHODS

Data Sources

This study used Kentucky All Schedule Prescription Electronic Reporting (KASPER) and Kentucky Office of Vital Statistics data, 2016 to 2020. Kentucky Office of Vital Statistics death certificate records include 1 underlying cause-of-death and up to 20 multiple cause-of-death codes from the *International Classification of Diseases and Related Health Problems Tenth Revision*.[18] KASPER includes all dispensed Schedule II-V prescriptions from Kentucky retail pharmacies, and internet or mail-order prescriptions dispensed to Kentucky addresses. KASPER and death certificate data were linked, using first name, last name, social security number, birth date, sex, and resident ZIP code, using Link King software.[19] This study was approved by the University of Kentucky Institutional Review Board.

Study Design and Sample

We identified 49,921 adult Kentucky residents who initiated TMbup between January 1 2017, November 30, 2019. Initiation was defined as a minimum of 180 days without TMbup prescriptions, consistent with previous studies.[11,13] Patients on TMbup were identified by dispensed prescriptions with listed National Drug Codes indicating FDA-approved TMbup products (Supplementary Table 1, http://links.lww.com/JAM/A500). TMbup initiation day was defined as the day of the first TMbup prescription dispensed during the study period. The 30-day window starting from the initiation day was defined as the first 30 days of treatment. The subsequent 365-day period was defined as the follow-up (patients were not necessarily retained in treatment during the period). The first day of the follow-up was called the index day (Fig. 1). We excluded 42 patients who died and 17 who switched to long-acting injectable (LAI) buprenorphine during the first 30 days of treatment. Five patients were excluded because of the days' supply for the TMbup prescription being recorded as zero. The final cohort consisted of 49,857 patients, and each patient contributed 1 treatment initiation episode to the analysis.

First 30 Day TMbup Dose

The patient's first 30-day TMbup dose was calculated by dividing the cumulative dose (per unit strength number of units) by the number of calendar days covered during the first

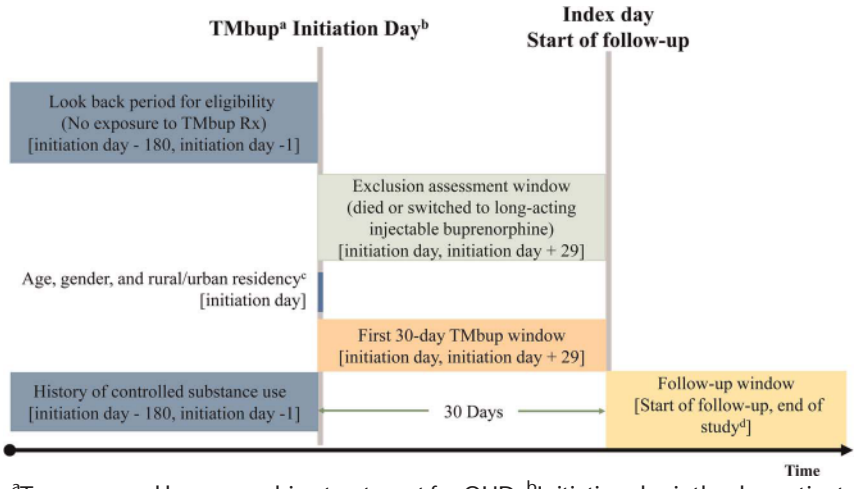

FIGURE 1. Study design. [a]Transmucosal buprenorphine treatment for OUD. [b]Initiation day is the day patients received the first TMbup prescription, preceded by at least 180 days with no records of TMbup prescription. [c]Patients under the age of 18 years and non-Kentucky residents were removed. [d]Earliest outcome of interest deaths), switching to LAI buprenorphine, or 365 days of follow-up.

30 days of treatment (eg, if a patient's supply covers 12 calendar days, the measure denominator will be 12). We categorized the first 30-day TMbup dose as " 8 mg," ">8 to 16 mg," and ">16 mg," based on the current FDA-approved labeling, which indicates a maximum of 8 mg on the first day of initiating TMbup and a maximum of 16 mg on the second day, with the understanding that dosing must always be individualized, and medication treatment should be accompanied by counseling and psychosocial support.[7,20]

Death During Follow up

The primary outcome was opioid-involved overdose death captured with an underlying cause-of-death for drug overdose (X40–X44, X60–X64, X85, Y10–Y14) and multiple cause-of-death code(s) in the range T40.0 to T40.4 and T40.6 (opioid poisoning).[21] Deaths that did not meet this definition were classified as "deaths from other causes" and categorized according to the National Center for Health Statistics list of 113 cause-of-death groups.[22]

Baseline Variables

Based on data availability and prior studies,[23,24] the following baseline variables were included in analyses: age group (18–24, 25–34, 35–44, 45–54, 55–64, 65+ years), sex (female, male), residency (rural, urban), and 3 indicators for dispensed controlled substance prescriptions in the 180 days before the initiation day (no, yes): (1) benzodiazepines, (2) nonopioid controlled substances other than benzodiazepines (eg, gabapentin, stimulants, muscle relaxants), and (3) opioid analgesics. Using the 2010 Rural-Urban Commuting Area (RUCA) codes,[25] we classified patients' residency as urban (RUCA 1–6) or rural (RUCA 7–10), based on resident ZIP codes. No racial and ethnic information is available in KASPER.

Statistical Analysis

Categorical baseline variables were summarized by frequencies and percentages. Time-to-event analyses were conducted, and opioid-involved overdose deaths and deaths from other causes were treated as competing risk events for each other. Patients who switched to LAI buprenorphine treatment during follow-up were censored on the day of switching, and patients who were alive at the end of the follow-up were censored at that time point. Cumulative incidence and corresponding curves were generated, stratified by TMbup dose. For all-cause deaths, cumulative incidences were compared using log-rank tests. For events with competing risks (opioid-involved overdose death; deaths from other causes), cumulative incidence functions (CIFs) were generated and were compared using Gray test.[26]

To evaluate the relative effect of TMbup dose on the cumulative incidence of each outcome, multivariable models were fitted, adjusting for baseline characteristics. We used a multivariable Cox proportional hazards model to estimate the association between the first 30-day TMbup dose and all-cause deaths. Accounting for the competing risks, we used multivariable Fine and Gray subdistribution hazard models to estimate the associations between the first 30-day TMbup dose and outcomes of interest (opioid-involved overdose deaths or deaths from other causes).[27] The results are reported as adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for Cox regression models and adjusted subdistribution hazard ratios (aSHRs) and 95% CIs for Fine and Gray models. To visualize the disparate cumulative incidences of opioid-involved overdose death across TMbup dose groups with different demographic characteristics, we generated predicted CIF plots of opioid-involved overdose deaths from the multivariable Fine and Gray model, using patient risk sets with different baseline variable combinations. Schoenfeld residuals were used to assess the proportional hazard assumption.[28] We excluded 107 patients with unknown sex from the multivariable models. In the sensitivity analysis, we included these patients as an "unknown sex" group to assess the potential impact on the results.

We conducted sensitivity analyses because of known clinical practice variations. In the initial days of buprenorphine treatment, the doses sometimes do not exceed 8 mg on the first day, depending on practice setting. To account for potential bias resulting from assigning dosing groups for patients who discontinued treatment early (lower doses are associated with dropout), we implemented a sensitivity analysis for the association between TMbup dose and opioid-involved overdose death. In this analysis, we restricted the cohort to patients who had ≥80% of days covered in treatment within the first 30-day period. Another sensitivity analysis focused on patients who had received opioid analgesics within the 180 days before buprenorphine initiation because they may be more readily initiated and retained on TMbup in the first 30 days if they are using primarily prescription opioids rather than illicitly obtained high-potency synthetic opioids such as fentanyl. There are reports of difficulties initiating and stabilizing patients using high-potency synthetic opioid on TMbup.[29] We also conducted sensitivity analyses, including dose category ">24 mg."

The widths of the CIs have not been adjusted for multiplicity, so intervals should not be used to infer definitive associations. A 2-sided P value <0.05 was considered statistically significant. Analyses were conducted with SAS Enterprise Guide v.8.3 (SAS Institute Inc, Cary, NC) and R (R Core Team 2022, Vienna, Austria) statistical software.

RESULTS

Descriptive Analysis

Among the 49,857 patients, the median age was 36 years, 53.6% were males, and 65.6% lived in urban areas (Table 1). In the 180-day period before treatment initiation, 2.2%, 14.6%, and 27.4% of the patients received at least 1 prescription for benzodiazepines, other nonopioid controlled substances, and opioid analgesics, respectively.

During the first 30 days of treatment, 10,496 patients (21.1%) received TMbup dose of 8 mg (Table 1), 24,533 (49.2%) received >8 to 16 mg, and 14,828 (29.7%) received >16 mg. The average prescription days' supply for these groups were 7.6, 7.7, and 8.4 days, and the average numbers of days covered in treatment for these groups were respectively 16.4, 23.4, and 25.9 days. About 13% of the patients had >16 mg TMBup dose on the first day; 19.1% had >16 mg during the first 7 days (Supplementary Table 2, http://links.lww.com/JAM/A500). Compared with other age groups, patients aged 18 to 24 years had the highest proportion (28.5%) of receiving doses of 8 mg. Compared with rural patients, a higher proportion of

TABLE 1. Baseline Characteristics Stratified by Average Daily Dose of Transmucosal Buprenorphine for Days Covered within the First 30 Days of Treatment n = 49,857)

	Average Daily Dose of TM Buprenorphine for Days Covered within the First 30 Days of Treatment			
	8 mg	>8 to 16 mg	>16 mg	Total
	n = 10,496	n = 24,533	n = 14,828	n = 49,857
	n (Row)	n (Row)	n (Row)	n (Column)
Age at initiation, y				
18–24	1015 (28.5%)	1643 (46.1%)	908 (25.5%)	3566 (7.2%)
25–34	4592 (24.1%)	9008 (47.3%)	5462 (28.7%)	19,062 (38.2%)
35–44	3153 (19.0%)	8222 (49.7%)	5180 (31.3%)	16,555 (33.2%)
45–54	1188 (16.2%)	3841 (52.5%)	2293 (31.3%)	7322 (14.7%)
55–64	476 (16.2%)	1576 (53.8%)	879 (30.0%)	2931 (5.9%)
≥65	72 (17.1%)	243 (57.7%)	106 (25.2%)	421 (0.8%)
Residency				
Urban	8493 (26.0%)	15,633 (47.8%)	8597 (26.3%)	32,723 (65.6%)
Rural	2003 (11.7%)	8900 (51.9%)	6231 (36.4%)	17,134 (34.4%)
Sex				
Unknown	9 (8.4%)	53 (49.5%)	45 (42.1%)	107 (0.2%)
Female	4988 (21.6%)	11,517 (50.0%)	6545 (28.4%)	23,050 (46.2%)
Male	5499 (20.6%)	12,963 (48.6%)	8238 (30.9%)	26,700 (53.6%)
Receipt of benzodiazepines in 180 d before treatment initiation				
No	10,317 (21.2%)	23,996 (49.2%)	14,461 (29.6%)	48,774 (97.8%)
Yes	179 (16.5%)	537 (49.6%)	367 (33.9%)	1083 (2.2%)
Receipt of nonopioid controlled substances other than benzodiazepines in 180 d before treatment initiation				
No	9189 (21.6%)	20,912 (49.1%)	12,475 (29.3%)	42,576 (85.4%)
Yes	1307 (18.0%)	3621 (49.7%)	2353 (32.3%)	7281 (14.6%)
Receipt of opioid analgesics in 180 d before treatment initiation				
No	7855 (21.7%)	17,976 (49.7%)	10,343 (28.6%)	36,174 (72.6%)
Yes	2641 (19.3%)	6557 (47.9%)	4485 (32.8%)	13,683 (27.4%)

urban patients (26.0% vs 11.7%) received average daily doses of 8 mg. Compared with patients with a history of dispensed controlled substances, a higher proportion of the patients with no history of dispensed controlled substances received doses of 8 mg.

During the 365-day follow-up period, 131 patients switched to LAI buprenorphine and 686 patients died. A total of 227 opioid-involved overdose deaths were recorded, constituting 33.1% of all deaths. Among these opioid-involved overdose deaths, 97, 89, and 41 deaths were from patients who received TMbup doses of 8 mg, >8 to 16 mg, and >16 mg, respectively. There were 459 deaths (66.9%) from other causes, and the most frequent other causes were nonopioid overdose deaths (n = 38; 17 involved stimulants or benzodiazepines, 21 death certificates did not list any specific drugs), motor vehicle accidents (n = 31), chronic lower respiratory diseases (n = 27), and septicemia (n = 14).

Crude Cumulative Incidence

The 365-day cumulative incidence of opioid-involved overdose death among patients who received doses of 8 mg was 0.9% (95% CI, 0.8%–1.1%), more than 2 times higher than the cumulative incidence of 0.4% (95% CI, 0.3%–0.5%), and 0.3% (95% CI, 0.2%–0.4%) for patients in the >8 to 16 mg, and >16 mg dose groups, respectively (data not shown). The 365-day cumulative incidence of death from other causes was 1.1% (95% CI, 0.9%–1.3%), 1.0% (95% CI, 0.8%–1.1%), and 0.8% (95% CI, 0.6%–0.9%) for patients who received doses of 8 mg, >8 to 16 mg, and >16 mg, respectively. The 365-day cumulative incidence of all-cause death was 2.0% (CI, 1.7%–2.3%), 1.3% (CI, 1.2%–1.5%), and 1.0% (CI, 0.8%–1.2%) for patients who received first 30-day TMbup doses of 8 mg, >8 to 16 mg, and >16 mg, respectively. Cumulative incidence curves are shown in Figure 2. Results from log-rank or Gray tests indicated differences in cumulative incidence of each outcome among the three TMbup dose groups ($P < 0.05$).

Multivariable Models

After adjustment for baseline variables (Table 2), higher first 30-day TMbup doses were associated with lower incidence of opioid-involved overdose death, death from other causes, and all-cause death. In the multivariable Fine and Gray model, compared with the 8 mg group, the aSHR of opioid-involved overdose death decreased as the dose increased (aSHR, 0.45; 95% CI, 0.34–0.60, for patients with TMbup doses of >8 to 16 mg; aSHR, 0.36; 95% CI, 0.25–0.52, for doses >16 mg). Findings for death from other causes were similar: aSHRs were 0.78 (95% CI, 0.62–0.98) for doses of >8 to 16 mg group and 0.62 (95% CI, 0.47–0.80) for doses >16 mg, compared with the 8 mg group (Table 2). In the multivariable Cox regression model, compared with the 8 mg group, we found reductions in the incidence of all-cause deaths in patients with TMbup dose >8 to 16 mg (aHR, 0.63; 95% CI, 0.53–0.75) and >16 mg (aHR, 0.50; 95% CI, 0.40–0.61). The complete results of the multivariable models can be found in the supplementary materials (Supplementary Table 3, http://links.lww.com/JAM/A500). In sensitivity analyses that included the patients with unknown sex, the direction of the results remained unchanged.

Figure 3 illustrates predicted CIFs of opioid-involved overdose death for some patient risk sets. The 2 age groups were selected as they accounted for 71.4% of all patients. Urban male

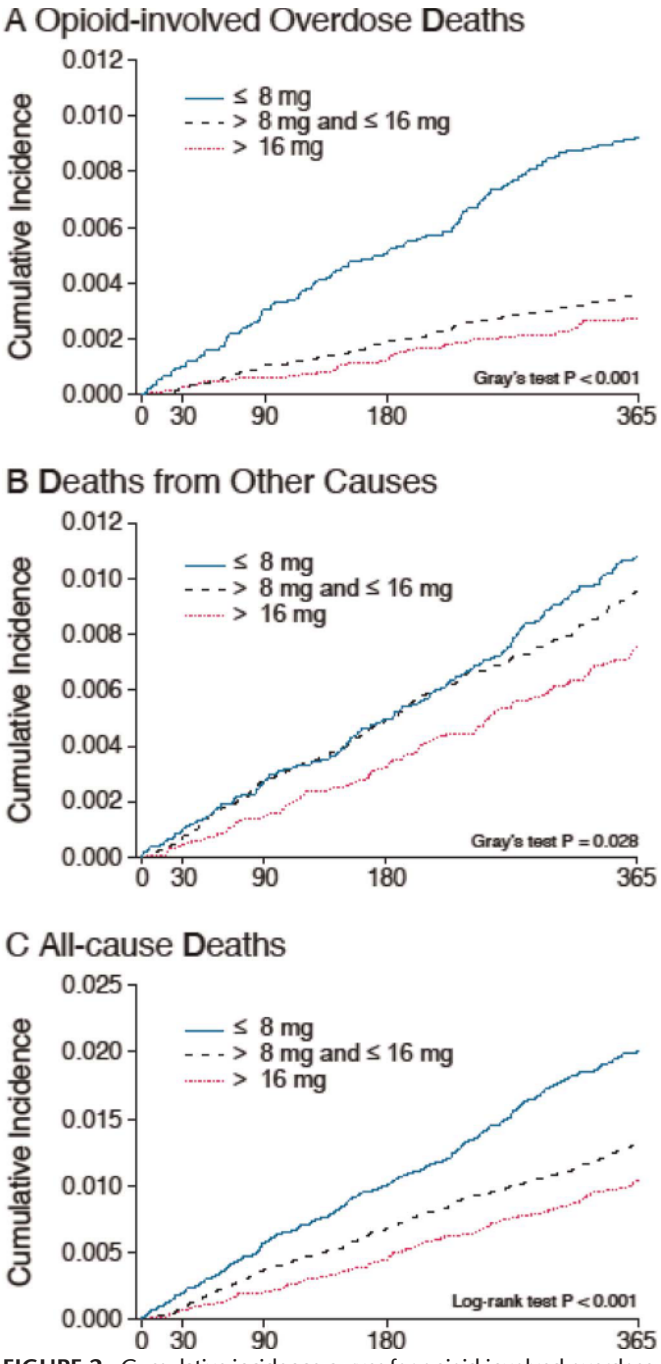

FIGURE 2. Cumulative incidence curves for opioid-involved overdose death, death from other cause, and all-cause death. Note: The equivalence of the cumulative incidence among dose groups at all time points was compared using Gray's test for opioid-involved death and death from other causes and log-rank test for all-cause death.

patients aged 35 to 44 years, without history of dispensed controlled substances (Fig. 3B), had higher CIFs than those aged 25 to 34 years (Fig. 3A), holding other variables constant. Similarly, female urban patients, aged 25 to 34 years (Fig. 3C), had lower CIFs compared with male patients (Fig. 3A). Lower CIFs were also found for rural male patients aged 25 to 34 years (Fig. 3D) compared with their urban counterparts (Fig. 3A).

In sensitivity analyses, we restricted the cohort to patients with at least 80% of days covered within the first 30 days of treatment. The sample size was reduced by 63%, 33.5%, and 18.0% for the patients in dose groups 8 mg, >8 to 16 mg, and >16 mg, respectively, resulting in lower statistical power. The direction of the subdistribution hazard ratios for opioid-involved overdose mortality remained consistent with the primary analysis, but the effect size decreased (Supplementary Table 4, http://links.lww.com/JAM/A500). For example, the aSHR for opioid-involved overdose death was 0.61 (95% CI, 0.36–1.02) for patients with TMbup doses of >8 to 16 mg versus 8 mg (compared with aSHR, 0.45; 95% CI, 0.34–0.60, for the same dose groups in the primary analysis). In another sensitivity analysis, we restricted the cohort to patients with recent history of dispensed opioid prescriptions. The results were consistent with the findings from the primary analysis (Supplementary Table 4, http://links.lww.com/JAM/A500). In the last sensitivity analysis, the aSHR of opioid-involved overdose death for patients in the group >24 mg (n = 930; 1.9%) was 0.36 (95% CI, 0.11–1.13) compared with the 8 mg group (Supplementary Table 5, http://links.lww.com/JAM/A500).

DISCUSSION

To our knowledge, this is the first study to examine the association between the first 30-day average daily TMbup dose and the incidence of deaths in the following 365 days. We found that higher prescribed doses during the first 30 days were associated with lower subsequent mortality risk.

Higher TMbup doses have been associated with improved treatment retention and decreased relapse risk in some observational studies.[11,15] In addition to these reported associations, our findings suggest an association between higher first 30-day TMbup doses and decreased subsequent mortality. The association might be related to improved treatment retention and needs further investigation. In our study, deaths from other causes were approximately twice as many as deaths from opioid-involved overdoses. Patients with OUD demonstrate many comorbidities (eg, mental health, infectious diseases associated with injection drug use, and chronic pain) and are at increased risk for death from causes other than opioid-involved overdose.[30] A prior study reported that high (≥16 mg) and perceived adequate TMbup doses were associated with reduced acquisition of hepatitis C virus in patients with OUD.[31] The association we found between higher TMbup doses and decreased death from other causes might result from decreased drug injection behavior that reduced injection-related illness. Alternatively, higher TMbup doses may increase treatment retention, providing an opportunity to treat comorbid conditions. Thus, on the policy level, state laws/regulations that limit TMbup doses (eg, Kentucky[32,33]) may hamper benefits that could be achieved to prevent deaths.

Guidelines and FDA-approved labeling indicate that most patients with OUD will stabilize on 4 to 24 mg daily.[12,13,17] Maintenance doses should suppress opioid withdrawal, reduce opioid craving, weaken euphoric effects, minimize side effects, and reduce illicit opioid use.[13] Labeling recommends a target maintenance dose of 16 mg,[20] and providers dosing outside of

TABLE 2. Associations Between Average Daily Dose of Transmucosal Buprenorphine for Days Covered Within the First 30 Days and the Incidence of Death

Average Daily Dose of Days Covered Within the Initial 30-d Treatment Window	Opioid-Involved Overdose Death	Death From Other Causes	All-Cause Death
	aSHR (95 CI)*	aSHR (95 CI)*	aHR (95 CI)
8 mg	Reference	Reference	Reference
>8 to 16 mg	0.45 (0.34–0.60)‡	0.78 (0.62–0.98)‡	0.63 (0.53–0.75)‡
>16 mg	0.36 (0.25–0.52)‡	0.62 (0.47–0.80)‡	0.50 (0.40–0.61)‡

*aSHR is subdistribution hazard ratio adjusted for age, sex, rural/urban residency, receipt of benzodiazepines, receipt of nonopioid controlled substances other than benzodiazepines, and receipt of opioid analgesics in 180 days before initiation.

†aHR is hazard ratio adjusted for age, sex, rural/urban residency, receipt of benzodiazepines, receipt of nonopioid controlled substances other than benzodiazepines, and receipt of opioid analgesics in 180 days before initiation.

‡*P* value of <0.001.

FDA recommendations are encouraged to document their clinical rationale with risks and benefits.[13] It is noteworthy that some clinicians prescribe higher dosing than the FDA recommends for maintenance,[34] and our study confirms this; approximately 30% of patients received >16 mg daily within the first 30 days of treatment. In this study, the estimated CIF and aSHR for opioid-involved overdose deaths were lower in patients who received first 30-day TMbup dose >16 mg compared with those receiving 8 mg, suggesting a potential protective effect of higher first 30-day TMbup doses. Although FDA-approved labeling states that clinical advantage of doses above 24 mg have not been demonstrated, some studies suggest that daily doses of TMbup up to 32 mg are safe and that higher doses predict better retention.[10,35,36] A recently published review concluded that updating the label to recommend dosing up to 32 mg/d and eliminating the 16 mg/d target dose would enhance treatment effectiveness and save lives.[36] Notably, newer LAI buprenorphine formulations often provide buprenorphine exposures higher than the equivalent of 24 mg TMbup daily.[37] However, there are practical barriers to dosing above 16 or 24 mg daily because of regulations in some states.[33,38] One factor preventing the recommendation of higher TMbup doses is the concern of diversion. Conceptually, higher doses require more units dispensed, which could have ramifications for diversion; however, higher doses may also reduce extralegal behavior, and observational studies on this topic are inconsistent.[39] Thus, future studies investigating optimal buprenorphine doses that balance improved survival with diversion risk while ensuring broad treatment access are of great importance.

Our study is subject to limitations. Our results are from a single state with specific policies on buprenorphine MOUD prescribing and coprescribing of controlled substances,[32,33] which may not be representative of other states or other countries. Patients who initiated TMbup in nonoutpatient settings

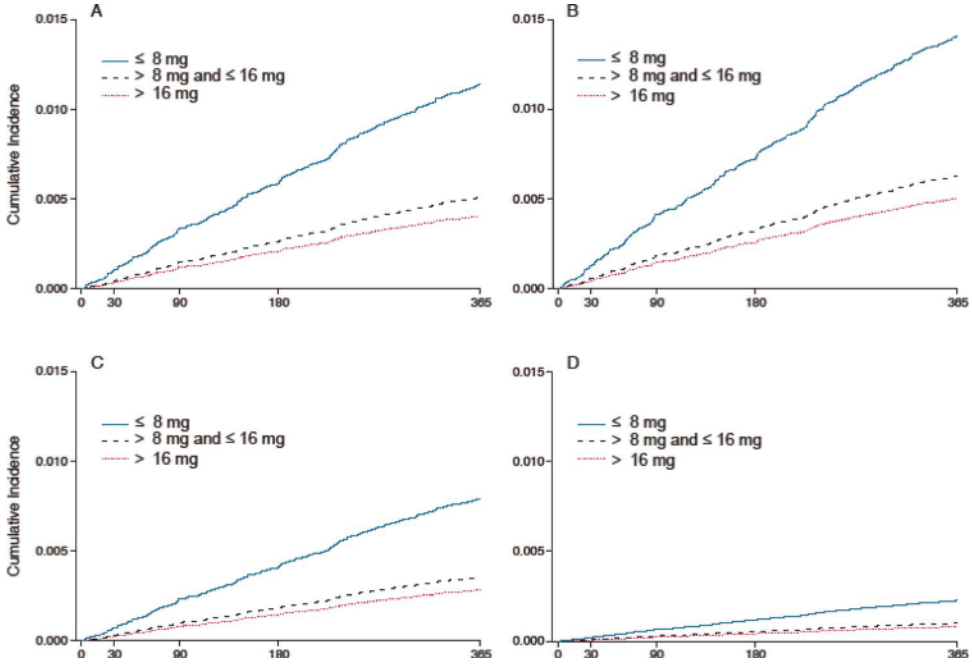

FIGURE 3. Predicted CIF of opioid-involved overdose death from the subdistribution hazard model, by given patient risk sets. A, Twenty-five to 34 years old at initiation, male, and urban residency. B, Thirty-five to 44 years old at initiation, male, and urban residency. C, Twenty-five to 34 years old at initiation, female, and urban residency. D, Twenty-five to 34 years old at initiation, male, and rural residency. A, B, C, and D: No controlled substance dispensing during the 180 days before transmucosal buprenorphine treatment initiation for opioid use disorder.

or other states could have been misclassified as new TMbup initiates. Prescriptions for Kentucky residents dispensed in other states are not reported to the KASPER system. KASPER has limited demographic and clinical information; we could not include confounders such as baseline comorbidities, socioeconomic status, and information on counseling/behavioral therapies accompanying buprenorphine prescribing. There could be confounding by indication and unbalanced risk among the TMbup dose groups, even after confounding adjustment. Racial disparities in opioid-related overdose deaths have been well documented, with minority populations often experiencing higher mortality.[40] Thus, the absence of race and ethnicity information is also a limitation. Records for in-office LAI buprenorphine treatment are not captured in KASPER. We calculated TMbup doses from prescription information, but we could not confirm whether patients took the medication as prescribed. The study is observational and not intended to draw causal inferences from reported associations. Thus, presented *P* values should be considered as exploratory hypothesis generating and informing of future studies.

Our study provides new information on critical research questions that cannot be easily addressed in randomized clinical trials because of issues of rare/low frequency events and ethical considerations. The use of real-world data from clinical and administrative records is a timely and cost-efficient way to examine patient-generated evidence from noninterventional studies on the potential benefits or risks of treatments beyond those captured in standard clinical trials. Our study used statewide prescription monitoring data, allowing identification of patients initiating TMbup treatment, without restrictions based on insurance status, continuity of coverage, age, or changes in treatment providers. The linkage with statewide death certificate data allowed a sufficient follow-up to capture mortality outcomes reliably, which is often not possible with studies limited to administrative claims or electronic health records.

CONCLUSIONS

Our findings suggested potential benefits of a higher first 30-day TMbup dose in reducing mortality using real-world data, aiming to stimulate further research and facilitate the design of future studies to estimate causal treatment effects. Future research is needed to investigate the buprenorphine dose as a time-varying exposure, the relation between dose and retention in treatment, and the causal relationships between dosage and patient mortality, enriching our understanding of buprenorphine treatment for OUD. We hope that results from the current and future studies will inform clinical guidelines and policies to optimize OUD treatment and improve patients' survival and quality of life.

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