Title: *Changes in pharmacy are associated with gaps in medication possession in individuals treated with buprenorphine*

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Abstract

Aims: The objective of this study was to identify the prevalence of changes in pharmacy among incident buprenorphine users and to estimate the association between a change in pharmacy and a clinically significant gap in therapy of seven-days or longer.

Design: A retrospective, repeated measures, longitudinal cohort design was used.

Setting and Participants: Patients initiating treatment with a buprenorphine product indicated for opioid use disorder were identified from the 2016-2018 Texas Prescription Monitoring Program Prescription Dispensation Dataset. Patients were excluded if they filled fewer than three prescriptions or remained in therapy for less than seven-days.

Intervention and Measurement: The predictor of interest, a change in pharmacy, was defined by comparing the dispensary used between subsequent prescriptions. The outcome of interest was defined as a gap in medication possession of seven-days or longer based on the National Quality Forum's definition of continuity of pharmacotherapy for opioid use disorder. A random intercept, fixed slope mixed model with a logistic link was then used to measure the association between a change in pharmacy and a gap in therapy.

Findings: Of 13,375 eligible patients, 29.6% had at least one change in pharmacy and 51.6% of those did so more than once. The median time to initial change in pharmacy was 30 (IQR:13-66) days. Patients who changed pharmacies were significantly more likely to have a gap in therapy between 7 and 29 days (aOR:1.96, 95% CI=1.81-2.13).

Conclusion: Patients receiving buprenorphine based MOUD change pharmacies frequently and early in treatment which leads to clinically significant gaps in therapy. While qualitative explanatory work is needed to understand the reasons for such frequent changes in pharmacy, pharmacists and prescribers must ensure that patients have reliable access to a convenient and reliable source of buprenorphine to prevent changes in pharmacy.

Introduction

Safe and effective pharmacotherapy is foundational to the treatment of opioid use disorder (OUD). Of the available medications for OUD (MOUD), buprenorphine is unique in that it may be prescribed by a DATA-2000 waived prescriber and dispensed by retail pharmacies. This process of care allows OUD to be managed like other chronic conditions and eliminates the need for daily observed medication administration. Adding to these benefits, the risk of mortality in patients treated with buprenorphine is comparable to that in individuals treated with methadone and extended release naltrexone.(1) Treatment with buprenorphine also effectively reduces relapsed opioid use and healthcare utilization.(2) Reduced patient burden, comparable reductions in mortality, and lowered healthcare utilization make buprenorphine ideal for the treatment of OUD in the outpatient setting with one caveat: these benefits are all heavily predicated on treatment adherence and persistence.

Although there are many ways to measure medication adherence, proportion of days covered (PDC) provides a readily interpretable indicator that is easy to calculate and widely used in the adherence literature.(3) The PDC is calculated by counting the number of days an individual possessed medication and dividing this by an indicated duration of therapy. If therapy is indicated for 30-days and a patient only receives a single 15-day supply from the pharmacy, their proportion of days covered would be 50%. PDC is associated with improved outcomes in a variety of chronic disease states including chronic obstructive pulmonary disease(4), HIV(4), and diabetes.(4) In OUD, individuals with a PDC of 20% are more than twice as likely to experience relapsed opioid use and incur over \$11,000 more in healthcare expenditures over their first year of therapy compared to individuals with a PDC of 80%.(2)

PDC, however, is less than ideal in that by using a durational denominator, it cannot differentiate short gaps in therapy from poor adherence over the full period of measurement. A patient who takes their medication every other day reliably for a year would have the same PDC, 50%, as an individual who discontinues their medication outright after taking it every day for six-months. This makes PDC an inadequate adherence indicator in MOUD where patients are at twice the risk of mortality within the first fourteen days without medication possession.(5) Given the risks of short gaps in therapy, the National Quality Forum and Centers for Medicaid and Medicare Services suggest that successful continuity of pharmacotherapy for OUD be defined as 180-days of continuous MOUD with no more than a seven-day gap in therapy.(6) Identifying processes of care that promote adherence to this strict quality measure has the potential to significantly benefit morbidity and mortality among patients receiving MOUD.(7)

The process of buprenorphine pharmacotherapy is designed similarly to that of other chronic conditions; however, patients must overcome multiple barriers to access prior to initiating care. First, because buprenorphine cannot be prescribed by all providers, patients are routinely required to travel long distances, a median distance of 49 miles in one Pennsylvania cohort, to access care.(8) Furthermore, not all pharmacies stock buprenorphine. In a survey of West Virginia pharmacists, only 74.8% of respondents said they routinely stocked buprenorphine(9) and in Texas, only 49% of pharmacies dispensed buprenorphine in 2018.(10) Because buprenorphine is not routinely available, patients may fill their initial prescriptions at a pharmacy familiar to their physician but unfamiliar or less than convenient to themselves. Attempts to identify a more convenient pharmacy may be challenged by the fact that pharmacists are often reluctant to accept new buprenorphine patients due to misplaced concerns of Drug Enforcement Administration oversight.(11) Additional literature demonstrating a primary lack of trust and poor communication between DATA waived physicians and community pharmacists points to salient barriers that stand in the way of a patient's ability to establish themselves at new, more convenient community pharmacies.(12) Changes in pharmacy are associated with non-adherence in prevalent chronic disease states where medication is widely available.(13) Stigma toward patients with opioid use disorder, the unwillingness of pharmacies to accept new patients, and tenuous relationships between buprenorphine prescribers and pharmacists all threaten the initiation and continuation of pharmacist patient relationships and may increase the likelihood of frequent and challenging changes in pharmacy in this population. The consequences of changes in pharmacy in OUD are unknown but may be significant given the scarcity of buprenorphine in the community setting and the risk of mortality associated with even short disruptions of fourteen days or less in MOUD.(5) The objective of this study was to identify the prevalence of changes in pharmacy among incident buprenorphine users and to estimate the association between a change in pharmacy and a clinically significant gap in therapy of seven-days or longer.(5, 6)

Methods

Data Source

All analyses were performed in a cohort of incident buprenorphine users identified from the Appriss Health® 2016-2018 Texas Prescription Monitoring Program prescription fill database. This is a record of all controlled substance prescriptions dispensed in Texas pharmacies regardless of payer type and has been used extensively in longitudinal studies of controlled substances utilization in Texas.(14, 15) Each observation in the dataset represents a single prescription dispensation and includes linkable patient, prescriber, and pharmacy identifiers, prescription parameters (i.e., day's supply, quantity, national drug code [NDC], quantity, refill status, drug dose, date written, date filled), and limited patient demographic information including patient age, payment type, and five-digit zip code. While the data do not include diagnostic information, its completeness and inclusion of cash-paying patients makes it a valuable tool to understand controlled substance utilization.

Study Design and Sample

We used a retrospective repeated measures design to measure the association between a change in pharmacy and clinically significant gaps in therapy. The entire study duration was January 1, 2016-December 31, 2018. Index use of buprenorphine was defined by the initial prescription of a buprenorphine product indicated for opioid use disorder(14, 16, 17) during the identification period between June 30, 2016 and July 1, 2018. To ensure that only incident buprenorphine patients were included, we excluded individuals who used any buprenorphine product between January 1 and July 1, 2018. We also excluded individuals prescribed any opioid, including buprenorphine products, indicated for pain, after their index buprenorphine for OUD prescription. In the absence of diagnostic information, this approach was chosen to avoid including individuals using buprenorphine for the management of a painful condition. Patients who changed residential ZIP code at any point in treatment were also excluded.

Prescriptions for eligible individuals filled within 180-days of the index date(6) or until a gap in therapy of 30-days or longer were included in the repeated measures analysis. To allow for accurate specification of the exposure of interest, change in pharmacy, we required that all individuals in the cohort receive at least three prescriptions. Measurement began, however, with the first dispensation.

Exposure and Outcome

The exposure of interest, a change in pharmacy, was defined as filling two-subsequent prescriptions at two different pharmacies. This was performed by lagging the pharmacy identifier from the previous fill to the next, if the two pharmacy identifiers were different, the binary change in pharmacy variable was coded as one and as zero if they were the same. As individuals could change pharmacies multiple times over the course of therapy, this was repeated for each prescription the individual filled. The outcome variable, a gap in therapy of seven-days or longer, was chosen based on the National Quality Forum's definition of continuity of pharmacotherapy for opioid use disorder.(6) This was defined by lagging the sum of the day's supply and duration of therapy from the previous prescription to the next. If the date the next prescription was filled exceeded this date by seven or more days, it was classified as a gap in therapy. Using a last carried forward approach allowed us to capture periods with a concomitant change of pharmacy and gap in therapy. Other variables included the age of the patient, rurality defined by Rural Urban Commuting Area code, benzodiazepine use in the baseline period, and initial dose of buprenorphine dichotomized at greater or equal to 12 mg daily or less than 12 mg daily.(18) Prior prescription opioid use was defined as either acute or chronic. Acute opioid users were those that filled at least one opioid prescription in the baseline period and chronic prescription opioid use was defined as possession of prescription opioids on 90 out of 120 days prior to initiating buprenorphine therapy. Patient payment type was dichotomized into cash and insurance. The insurance category included individuals who used either public, private, or workers compensation to pay for their prescriptions. Except for a change in pharmacy, which was measured between each prescription, all other covariates were measured at the index date and held fixed throughout the observation period.

Statistical Analysis

Frequencies and proportions were used to summarize categorical covariates and the mean and standard deviation of the time to initial change in pharmacy was also described. Random intercept repeated measures logistic regression (Proc GLIMMIX, SAS/STAT Version 9.4, SAS Institute Inc., Cary, NC, USA) was used to estimate the association between a change in pharmacy as a time-dependent covariate and a seven-day gap in therapy. In this approach, a regression line is fit for each patient with a slightly different intercept reflecting the patient's baseline propensity to have a gap in therapy. This allows for control of correlation between observations, prescription fills in this case, within participants.(19, 20) The association between each covariate and the outcome, the slope of this line, is then held fixed between participants.(20) Given that days' supply and gaps between

prescriptions varied within patients, we estimated the model under unstructured covariance assumptions.(19) The covariates described above, patient age, payment type, rurality, benzodiazepine use, buprenorphine dose, and baseline opioid use, were measured at baseline and included in the model as patient-level covariates.

Results

A total of 13,375 incident buprenorphine users met all criteria for inclusion (**Figure 1**). Most patients (70.4%) were insured, 32.3% were between the ages of 35 and 44, 84.1% resided in an urban area, and 72.0% had no record of prior prescription opioid use (**Table 1**). In this cohort, 3,953 (29.6%) changed pharmacies at least one time over the course of therapy. Among those who changed pharmacies, 51.5% had more than one change in pharmacy over the course of therapy. The median time to initial change in pharmacy was 30 days (IQR: 13-66 days). Insured individuals, older individuals, patients with no prior prescription opioid use or chronic prescription opioid use, older patients, insured patients, and those who lived in rural areas were all significantly less likely to change pharmacies over the course of therapy (**Table 2**).

In this cohort, 5,925 (44.3%) completed a full 180-day course of therapy. In those who did not complete 180-days of buprenorphine pharmacotherapy, the median duration of treatment was 50 days (IQR=28-92). In total, 5,395 (40.3%) of patients had at least one gap in therapy between seven and twenty-nine days in length. Half (49.8%) of those who changed pharmacies had a gap in therapy compared to 36.4% of those who did not change. A total of 9,493 gaps in therapy were observed between the 99,623 prescriptions included in the final cohort. Changes in pharmacy were associated with a significant increase in the odds of a gap in therapy of seven days or longer 1.96 (95% CI: 1.81-2.13) after adjustment for payment type, patient age, rurality, initial dose of buprenorphine, prior prescription opioid use, and prior benzodiazepine use (**Table 3**). Discriminant capability of the model was demonstrated by an area under the receiver operator curve (C statistic) of 0.89.

Discussion

Changes in pharmacy are associated with the incidence of seven-day gaps in therapy in patients prescribed buprenorphine for the treatment of opioid use disorder. A gap of seven-days or longer places patients at risk of mortality and opioid related harm.(5, 6) Identifying processes of care that promote continuity of pharmacotherapy is therefore critical to improving the clinical outcomes of individuals undergoing treatment for opioid use disorder. Ensuring that patients can remain at one pharmacy and have a reliable source of buprenorphine is one such process.

Still, changes in pharmacy are quite common and often happen early in treatment. In this cohort, 25% and 50% of individuals who changed pharmacies did so within thirteen and thirty days of treatment initiation, respectively. Patients are most vulnerable to discontinuation within the first thirty days of treatment.(21) Anywhere between 27%(21) and 48%(14) of individuals treated with buprenorphine will discontinue therapy prior to completing 180-days of treatment. The incidence of changes in pharmacy early in treatment and the robust association between changes in pharmacy and treatment discontinuation identified in this study are concerning when considered together. In the first thirty-days of treatment, prescribers and patients must work closely together to identify a buprenorphine dose that effectively minimizes opioid cravings and withdrawal symptoms.(22, 23) As doses are adjusted, patients are required to make frequent visits to both their provider and pharmacy until an effective dose is identified for that patient. While providers may be familiar with this patient-centered process, pharmacists may not be as aware of the level of support that new buprenorphine patients require.(24) Pharmacists stigma toward persons with opioid use disorder is well documented in both the naloxone(25, 26) and syringe exchange(27, 28) literature, yet little work has been done to adequately describe the relationship between pharmacists and individuals prescribed buprenorphine. Previous work, however, has demonstrated that as many as one-third of pharmacists are unwilling to even stock buprenorphine(9, 29) and that much of this unwillingness may stem from a lack of knowledge of OUD treatment and a fundamental distrust of buprenorphine patients and prescribers.(11)

In a recent qualitative study of pharmacists in Kentucky, twelve of fifteen pharmacists admitted that they refused to fill prescriptions for new buprenorphine patients due to concerns that filling too many buprenorphine prescriptions would raise regulatory concerns from the DEA.(11) This point calls attention to a key limitation of this study and serves as a clear call for additional research to understand the complex interplay between buprenorphine patients, prescribers, and pharmacists. Our results show that many patients change pharmacies over the course of treatment and that when they change pharmacies, they are likely to experience a clinically meaningful gap in therapy. We cannot explain why this happens or identify potential solutions without qualitative

explanatory research that leads to the design and implementation of evidence-based interventions. There is a growing body of evidence suggesting that the low availability of buprenorphine in community pharmacies creates a pseudo-pharmacy desert for patients with opioid use disorder. In one recent telephone survey of Texas pharmacies, only 34.1% had sufficient buprenorphine in stock to dispense a one-week supply.(30) Geospatial access to pharmacy resources is a critical predictor of medication adherence(31), if buprenorphine were widely stocked and pharmacists were more willing to accept new buprenorphine patients then changes in pharmacy should not be nearly as disruptive as our findings suggest. Qualitative findings describing strained relationships between buprenorphine patients and the findings presented above suggest that community-based interventions aimed at improving buprenorphine availability and patient, pharmacist, physician relationships are urgently needed.

This study does have some limitations. As mentioned earlier, the explanatory utility of this work is limited without future qualitative work. Furthermore, the chosen data, while complete, does not contain detailed socioeconomic or demographic information which raises the potential for uncontrolled confounding. The E-value test demonstrates that an unobserved confounder would require an estimated odds ratio of 3.9 (95% CI: 3.02-3.68) to nullify the observed effect of a change in pharmacy.(32) Because we did not have diagnostic information, it is possible that some individuals were receiving buprenorphine for the treatment of painful conditions. Our chosen medication use criteria were intended to limit this by only including individuals receiving a buprenorphine product indicated for OUD.(14, 16, 17) Although we excluded individuals changed residential ZIP code at any point while receiving buprenorphine, some individuals may have moved into the state in the six-months prior to initiating treatment leading to misclassification as incident users. Leaving the state would not be expected to impact exposure or outcome measurement as gaps and changes in pharmacy were recorded in the record after they had occurred. Leaving the state may, however, have affected the duration of follow-up for each patient. To mitigate this potential, we only included patients who filled three or more buprenorphine prescriptions and adjusted statistically for duration of treatment.

Conclusions

Patients receiving buprenorphine for the treatment of OUD change pharmacies early and often over the course of a 180-day recommended episode of care. Changes in pharmacy are associated with a clinically meaningful seven-day gap in care and may put patients at risk of opioid related harm. To support continuity of pharmacotherapy for opioid use disorder, providers should work with patients to help them identify a convenient pharmacy at the time of treatment initiation and pharmacies should ensure that they maintain a reliable supply of buprenorphine products to meet the needs of patients with opioid use disorder. Future qualitative work is needed to identify determinants of willingness to stock buprenorphine in community pharmacies and patient level barriers to pharmacy access.

Figure 1: Participant flow demonstrating application of inclusion criteria to identify the final cohort.

Table 1: Characteristics of a cohort of patients who filled an initial buprenorphine prescription between June 30, 2016 and July 1, 2018 identified from the Texas Prescription Monitoring Program.

(N=13,375)	Freq	%
Change in Pharmacy		
No change in pharmacy	9,422	70.4%
At least one change in pharmacy	3,953	29.6%
Gap in Therapy		
No gap in therapy	7,980	59.7%
At least one gap in therapy, 7 days or longer	5,395	40.3%
Payment Type		
Cash	2,829	21.2%
Insurance	10,546	78.8%
Patient Age		
15-24	357	2.7%
25-34	3,704	27.7%
35-44	4,316	32.3%
45-54	2,322	17.4%
55-64	1,890	14.1%
65 years or older	786	5.9%
Rural Urban Commuting Area		
Rural	2,125	15.9%
Urban	11,250	84.1%
Initial Daily Dose of Buprenorphine		
Less than 12 mg	6,212	46.4%
12 mg or more	7,163	53.6%
Prior prescription opioid use		
No Prior Prescription Opioid Use	9,624	72.0%
Acute opioid use	2,245	16.8%
Chronic opioid use	1,506	11.3%
Prior benzodiazepine use		
No prior benzodiazepine use	11,423	85.4%
Benzodiazepine use at baseline	1,952	14.6%

Table 2: Characteristics of a cohort of patients who filled an initial buprenorphine prescription between June 30, 2016 and July 1, 2018 identified from the Texas Prescription Monitoring Program stratified by change in pharmacy.

No Change in Pharmacy	Changed Pharmacy
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	Freq	%	Freq	%	Sig.
(N=13,375)	n=9,422		n=3,953		
Gap in therapy greater than seven days					
No gap in therapy	5,996	63.6%	1,984	50.2%	<0.001
Gap in therapy	3,426	36.4%	1,969	49.8%	
Payment Type					
Cash	1,890	20.1%	939	23.8%	<0.001
Insurance	7,532	79.9%	3,014	76.3%	
Patient Age					
15-24	233	2.5%	124	3.1%	<0.001
25-34	2,504	26.6%	1,200	30.4%	
35-44	2,983	31.7%	1,333	33.7%	
45-54	1,658	17.6%	664	16.8%	
55-64	1,432	15.2%	458	11.6%	
65 years or older	612	6.5%	174	4.4%	
Rural Urban Commuting Area					
Rural	1,448	15.4%	677	17.1%	0.012
Urban	7,974	84.6%	3,276	82.9%	
Initial Daily Dose of Buprenorphne					
Less than 12 mg	4,411	46.8%	1,801	45.6%	0.184
12 mg or more	5,011	53.2%	2,152	54.4%	
Prior prescription opioid use					
No Prior Prescription Opioid Use	6,930	73.6%	2,694	68.2%	<0.001
Acute opioid use	1,486	15.8%	759	19.2%	
Chronic opioid use	1,006	10.7%	500	12.7%	
Prior benzodiazepine use					
No prior benzodiazepine use	8,079	85.8%	3,344	84.6%	0.085
Benzodiazepine use at baseline	1,343	14.3%	609	15.4%	

Table 3: Results of a random intercept, repeated measures logistic regression demonstrating the adjusted association between a change in pharmacy and a seven-day gap in therapy over 180-days in a cohort of incident buprenorphine users from the Texas Prescription Monitoring Program.

	Freq	%
Change in Pharmacy		
No change in pharmacy	1.00	Ref.
Change in pharmacy	1.96	1.81-2.13
Payment Type		
Cash	1.00	Ref.
Insurance	1.04	0.96-1.12
Patient Age		
15-24	1.00	Ref.
25-34	1.21	0.95-1.54
35-44	0.89	0.81-0.98
45-54	1.00	0.89-1.12
55-64	1.00	0.88-1.13
65 years or older	0.90	0.75-1.08
Rural Urban Commuting Area		
Rural	1.00	Ref.
Urban	1.19	1.07-1.32
Initial Daily Dose of Buprenorphine		
Less than 12 mg	1.00	Ref.
12 mg or more	1.02	0.94-1.10
Prior prescription opioid use		
No Prior Prescription Opioid Use	1.00	Ref.
Acute opioid use	0.87	0.79-0.97
Chronic opioid use	0.62	0.54-0.71
Prior benzodiazepine use		
No prior benzodiazepine use	1.00	Ref.
Benzodiazepine use at baseline	1.13	1.01-1.26
Current Duration of Treatment		
Weeks from induction	1.12	1.11-1.13

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