Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Use Evaluation: Polypharmacy Associated with Sublingual Buprenorphine

Research Question 3:

1. Since removal of the prior authorization (PA) criteria for medication assisted treatment (MAT) of opioid use disorder (OUD), has there been a change in polypharmacy associated with buprenorphine and other controlled substances?

Conclusions:

- In patients prescribed sublingual buprenorphine, polypharmacy associated with controlled substance use decreased after removal of the PA criteria for MAT (from 51.4% to 42.5%).
- Few patients had claims for 3 or more controlled substances which overlapped with buprenorphine therapy during the study period (n=10; 7.8%).
- The most commonly prescribed concomitant sedating drugs with an overlap of at least 3 days included antiepileptic drugs (such as gabapentin; 20%), first-generation antihistamines (such as hydroxyzine; 15%), muscle relaxants (11%), and second-generation antipsychotics (10%).

Recommendations:

- No policy changes recommended.

Background

Based on accumulating evidence describing overdose risks associated with opioid use, there has been an increased number of notifications from regulatory agencies regarding safe opioid prescribing. Since 2014, the U.S. Food and Drug Administration (FDA) has recommended increased safety labeling changes for all opioids. While buprenorphine acts as a partial opioid agonist, it is associated with many of the same effects and risk factors as a full opioid agonist. Like other opioids, buprenorphine can be associated with respiratory depression, particularly when it is used in conjunction with other respiratory depressants. Buprenorphine is also associated with potential for addiction, abuse and misuse, and is currently classified as a Drug Enforcement Agency (DEA) schedule 3 controlled substance. In 2018, the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act required state Medicaid programs to enact policies to monitor prescribing of opioids and concurrent benzodiazepines or antipsychotics. While this requirement did not specifically apply to MAT for OUD, there is no high-quality evidence which demonstrates a lower risk of overdose or respiratory depression with buprenorphine compared to other opioids.[1] At least one small, short-term trial has described a plateau effect for respiratory depression with use of intravenous (IV) buprenorphine in a controlled clinical setting,[2] and much of the data documenting overdose risk is based on full opioid agonists rather than partial agonists.[3,4] However, data from well-designed clinical trials or large observational studies is lacking, and it is unclear if there is any difference in overdose risk when comparing buprenorphine to a full opioid agonist especially if combined with other central nervous system (CNS) depressants.[1]

In 2017, a safety communication from the FDA addressed use of MAT in combination with CNS depressants.[5] The FDA noted that MAT should not be withheld from patients taking other CNS depressants as the risks of untreated OUD likely outweigh potential harms associated with concurrent CNS depressant in most

patients.[5] However, they did note that concomitant use can be associated with increased risk of serious adverse effects and careful medication management may be warranted. Management strategies may include patient education regarding risks of concomitant use, management or monitoring of illicit drug use, tapering or discontinuation of the CNS depressant if possible, consideration of other treatment options for comorbid conditions, and coordination of care with other prescribers.[5]

In the Fee-for-Service (FFS) Oregon Health Plan, evaluation of concomitant prescribing of opioids and sedatives is currently performed via prospective drug utilization review (DUR) edits that notify the dispensing pharmacy of any overlapping therapy. The pharmacist can review these edits and choose to dispense the opioid or sedative if clinically appropriate. An override by the dispensing pharmacist is not currently required. Because use of polypharmacy with multiple controlled substances or sedating prescriptions may increase risk of overdose or be an early sign of potential buprenorphine misuse, the goal of this policy evaluation is to evaluate changes in polypharmacy associated with sublingual buprenorphine use since removal of the PA criteria for MAT in 2020.

Methods:

Patients were identified for inclusion in the study based on paid FFS claims for sublingual buprenorphine or buprenorphine-naloxone (identified using First Databank HICL sequence numbers [HSNs] 001762 or 024846; route: sublingual). The evaluation window for buprenorphine claims was from 10/1/2019 to 10/31/2019 for the control group and from 10/1/2020 to 10/31/2020 for the intervention group. Cohorts were assigned to the control or intervention groups based on the first paid FFS claim (the index event [IE]).

For each patient, the baseline and follow-up periods were based on the IE.

- The baseline period was defined as the 35 days prior to the IE (exclusive of the IE).
- The follow up period was defined as the 35 days following the IE (inclusive of the IE).

Inclusion Criteria:

1. At least one FFS paid claim for sublingual buprenorphine during the evaluation window for buprenorphine claims

Exclusion Criteria:

1. Patients not assigned to either the control or intervention groups
2. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow up periods
3. Patients with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods as data for these patients may be incomplete. Patients were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug
	BMD	Oregon Health Plan with Limited Drug
	MED	Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND	Transplant package
	CWM	Citizenship Waived Emergency Medical
	SMF	Special Low-Income Medicare Beneficiary Only
	SMB	Special Low-Income Medicare Beneficiary Only

4. Non-continuous Medicaid eligibility during the baseline period
5. Non-continuous FFS eligibility during the follow-up period
6. Patients included in both the control or intervention groups

Outcomes evaluated in this analysis included the proportion of patients with polypharmacy associated with controlled substance use and types of therapy concomitantly prescribed.

- Claims for concomitant drug therapy were evaluated during the baseline and follow-up periods and included both FFS and coordinated care organization (CCO) claims. Patients were categorized as having concomitant drug therapy if the medication overlapped with buprenorphine treatment by at least 3 consecutive days. Days covered by a claim were calculated by adding the days' supply submitted on the claim to the date of service.

Results:

Demographics of patients with paid claims for sublingual buprenorphine are shown in **Table 1.** About 50% of patients were female and 60% were young adults (≤35 years of age). The largest racial groups identified in the study were patients identifying as American Indian/Alaskan Native (47-64%) and White (13-21%). There were a larger proportion of American Indian/Alaskan Native patients in 2020 (after PA removal) compared to 2019 (before removal of the PA).

The Elixhauser Comorbidity Index, used to estimate disease burden in the population, was comparable in both the before and after groups indicating similar disease burden in the population over time. The index is a weighted measure based on relevant diagnoses submitted on medical claims during the baseline period. The presence or absence of diagnoses are identified in medical claims and categorized into 29 comorbidity variables. Each category is assigned a weighted score from -7 to +12. Lower scores indicate lower disease burden whereas higher scores are indicative of higher disease burden. The index is reported as 2 separate measures which can predict risk of in-hospital mortality (the "M" index) and risk for 30-day readmission (the "R" index).[6]

Table 2 describes patients with paid claims for buprenorphine and overlapping therapy. In patients prescribed sublingual buprenorphine, polypharmacy associated with controlled substance use decreased after removal of the PA criteria for MAT (from 51.4% to 42.5%). The most common overlapping therapy included antiepileptic drugs (such as gabapentin or pregabalin; 20%), first-generation antihistamines (such as hydroxyzine; 15%), muscle relaxants (11%), and second-generation antipsychotics (10%). After removal of the PA, fewer patients had overlapping sedating drugs and buprenorphine compared to the control period. Similarly, the number of patients with overlapping use of controlled substances decreased from the before period to the after period. Forty-eight percent of patients in the before period had claims for only buprenorphine compared to 57% in the period after removal of the PA for buprenorphine. Very few patients prescribed buprenorphine had claims for 3 or more additional controlled substances (n=10; 7.9%).

Table 1. Demographics for paid FFS pharmacy claims

	Before		**After**	
	105	%	127	%
Female	52	49.5%	67	52.8%
Age – mean (range)	35	(20-63)	36	(19-63)
<18	0	0.0%	0	0.0%
18-35	68	64.8%	72	56.7%
36-64	37	35.2%	55	43.3%
>=65	0	0.0%	0	0.0%
Race				

White	22	21.0%	16	12.6%
Unknown	29	27.6%	29	22.8%
American Indian/Alaskan Native (HNA)	50	47.6%	82	64.6%
Other	4	3.8%	0	0.0%
Average Elixhauser Score "M"	-6.61		-7.82	
Average Elixhauser Score "R"	17.65		17.74	

*Weighted index based on diagnoses on medical claims in the baseline period.

Table 2. Patients with concomitant claims with at least 3 days overlap with sublingual buprenorphine

	Before		**After**	
Drug claims (by PDL class)	**Patient Count**		**Patient Count**	
SL Buprenorphine (denominator)	105	%	127	%
Benzodiazepines	3	2.9%	4	3.1%
Opioid (long-acting or short-acting)	2	1.9%	2	1.6%
Sedatives	1	1.0%	1	0.8%
Muscle relaxant, oral	8	7.6%	14	11.0%
Antihistamine, first generation	16	15.2%	19	15.0%
ADHD drugs (DEA schedule 2 only)	3	2.9%	10	7.9%
Other stimulants	0	0%	0	0%
Cough and cold	0	0%	2	1.6%
Antiepileptics (non-injectable)	27	25.7%	25	19.7%
Antipsychotics, 2nd-generation	17	16.2%	13	10.2%
Number of controlled substances (by HSN)				
0	51	48.6%	73	57.5%
1	34	32.4%	24	18.9%
2	15	14.3%	20	15.7%
3	4	3.8%	6	4.7%
4	1	1.0%	1	0.8%
5	0	0%	2	1.6%
6	0	0%	0	0%
7	0	0%	1	0.8%

Limitations:

- This study evaluates a short “snapshot” in time for patients with prescriptions for buprenorphine and data were based on claims history which may not accurately reflect true medication use. Ongoing therapy or polypharmacy for long periods was not assessed. Polypharmacy was defined as at least a 3

day overlap with buprenorphine for sedating or controlled substance drugs. However, a short overlap of 3 days could be explained by switches in therapy rather than ongoing concomitant treatment. In patients with multiple prescriptions for controlled substances, therapy could represent subsequent prescriptions for different medications rather than overlapping treatment for all drugs at the same time.

- Many controlled substances or sedating medications have their own utilization controls. For example, use of benzodiazepines or sedatives for longer than 30 days and use of opioids for longer than 7 days requires a PA. However, in circumstances where Medicaid has utilization controls, patients may elect to pay cash rather than navigate the PA process. This evaluation only included claims paid by Medicaid, and any potential cash claims would not be included.
- A significant proportion of patients were excluded because they had potentially incomplete claims data due to other primary insurance or were not eligible for Medicaid for the required 35-day baseline or follow-up periods. **Table 3** describes how individual exclusion criteria influenced the number of patients eligible for inclusion in the study. After all exclusion criteria, approximately 30% of all patients with claims for sublingual buprenorphine were included in the study. This study assumes that included patients would still be representative of most patients prescribed MAT in Medicaid.

Table 3. Population of Included Patients

	Before		After	
Number of included patients	#	%	#	%
With paid buprenorphine claim from 10/1/2019-10/31/2019 (pre) or from 10/1/2020-10/31/2020 (post)	**349**		**378**	
And after exclusion of limited benefit packages, Medicare, TPL in baseline period	292	83.7%	291	77.0%
And after continuous Medicaid enrollment requirement in the 35 days before the IE	276	79.1%	277	73.3%
And after continuous Medicaid enrollment requirement in the 35 days after the IE	186	53.3%	208	55.0%
And after removal of duplicate patients in control/experimental periods	105	30.1%	127	33.6%

References:

1. Canadian Agency for Drugs and Technologies in Health. Buprenorphine for Chronic Pain: A Review of the Clinical Effectiveness: rapid response report. 2017. Available from https://www.cadth.ca/buprenorphine-chronic-pain-review-clinical-effectiveness. Accessed March 21, 2022.
2. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth.* 2006;96(5):627-632.
3. Wightman RS, Perrone J, Scagos R, Krieger M, Nelson LS, Marshall BDL. Opioid Overdose Deaths with Buprenorphine Detected in Postmortem Toxicology: a Retrospective Analysis. *J Med Toxicol.* 2021;17(1):10-15.
4. Centers for Disease Control and Prevention. Proposed 2022 CDC Clinical Practice Guideline for Prescribing Opioids (DRAFT). 2022. Available from https://www.regulations.gov/document/CDC-2022-0024-0002. Accessed March 21, 2022.
5. US Food and Drug Administration. 2017. FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications. Accessed March 21, 2022.
6. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying Increased Risk of Readmission and In-hospital Mortality Using Hospital Administrative Data: The AHRQ Elixhauser Comorbidity Index. *Medical care.* 2017;55(7).

Appendix 1: Key Inclusion Criteria

	Key question #3: Polypharmacy
Population	patients with continuous Medicaid eligibility of at least 35 days prior to the index event (IE) and fee-for-service (FFS) eligibility in the 35 days after the IE
Intervention	Initiation of sublingual buprenorphine (index event)
Comparator	Patients initiating buprenorphine sublingual (SL) from 10/1/2019-10/31/2019 vs Patients initiating buprenorphine SL from 10/1/2020-10/31/2020 (before vs. after removal of prior authorization [PA] criteria)
Outcomes	Polypharmacy associated with concurrent controlled substances
Setting	FFS