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Policy Evaluation: Quantity Limits for Buprenorphine

Plain Language Summary

- Buprenorphine is a medicine that can help people who are dependent on opioids stop taking them. Buprenorphine may help people manage opioid withdrawal and helps people stay in treatment for their opioid dependence.
- The Food and Drug Administration has approved buprenorphine up to 24 mg daily for people who are dependent on opioids. Most people need at least 16 mg daily to stop taking heroin. But in Oregon, more and more people are using fentanyl instead of heroin. Fentanyl is a more potent opioid and may cause more severe withdrawal symptoms compared to heroin. There are no large studies that evaluate the most effective dose of buprenorphine for people who use fentanyl.
- Buprenorphine claims for people enrolled in the Oregon Health Plan fee-for-service program are currently limited to 24 mg daily. However, a review of claims data shows that some people may need higher doses to manage symptoms of opioid dependence. We recommend increasing the dose limit for buprenorphine to 32 mg daily.

Purpose:

The purpose of this policy evaluation is to quantify the daily doses of sublingual buprenorphine or buprenorphine/naloxone products prescribed to Oregon Health Plan (OHP) fee-for-service (FFS) members with opioid use disorder (OUD) and to evaluate the impact of the current FFS 24 mg daily dose limit.

Research Questions:

1. For people with paid claims for sublingual buprenorphine, what proportion of members have a daily dose greater than 24 mg or 32 mg?
2. For members with paid or denied FFS claims for sublingual buprenorphine, what diagnoses are present in medical claims that are potential indications for therapy?

Conclusions:

- Most guidelines recommend that the dose of sublingual buprenorphine be individualized and titrated to control symptoms and cravings associated with OUD. Available evidence shows that higher daily doses (≥16 mg) may increase treatment retention and decrease illicit opioid use, but the evidence was limited to people dependent on heroin and most studies have only evaluated buprenorphine up to 24 mg daily.
- The Food and Drug Administration (FDA) and Substance Abuse and Mental Health Service Administration (SAMHSA) recommend doses up to 24 mg daily.[1] The Veterans Association and Department of Defense (VA/DOD) recommend flexible dosing schedules up to 32 mg daily,[2] and the National Institute for Health and Care Excellence (NICE) does not make any specific recommendations for buprenorphine dose limits.[3]
- Although prevalence of illicit fentanyl continues to increase in Oregon, there is insufficient evidence to identify what dose of buprenorphine is needed to control symptoms in people dependent on fentanyl. Limited data from uncontrolled studies and patient surveys indicates that addition of buprenorphine in fentanyl dependence may be associated with increased rates of precipitated withdrawal and that doses higher than 24 mg daily may

be needed to control symptoms of OUD.[4-6] However, efficacy of specific doses in people who are dependent on fentanyl has yet to be confirmed in controlled trials.

- Despite the 24 mg daily dose limit in place by the FFS program, some FFS members are prescribed doses above this limit. Of members with paid claims for sublingual buprenorphine or buprenorphine/naloxone products from 10/1/21 to 9/30/22, about 13% (n=49) had an average daily dose between 24 and 32 mg in the 90 days following their first claim. About 2% had an average dose greater than 32 mg daily. Under the current policy members can get higher doses by being prescribed more than one formulation of buprenorphine or by consistently refilling prescriptions early. The current early refill threshold is set at 80%.
- Only 31 members had a denied FFS claim due to the 24 mg quantity limit and no paid claim on the same day from 10/1/21 to 9/30/22.
- The proportion of members with presence of an OUD diagnosis in medical claims was consistent across all buprenorphine doses (>87%). The proportion of members that had common comorbid pain diagnoses increased with larger daily doses of buprenorphine. Most members with denied claims had a diagnosis of OUD (76%).
- This evaluation is limited by the small number of members reviewed. However, a post-hoc analysis with less stringent inclusion and exclusion criteria demonstrated similar trends.

Recommendations:

1. Increase dose limit to 32 mg daily for sublingual buprenorphine formulations. Update current prior authorization (PA) criteria to permit use of higher doses for OUD with medical justification (**Appendix 2**).
2. Implement a days' supply limit for all sublingual buprenorphine formulations (in addition to the 32 mg daily quantity limit) to provide better enforcement of quantity limits.

Background

Guidelines for the treatment of OUD recommend buprenorphine as one of the first-line treatment options for symptom management.[1,3,7] Both buprenorphine and methadone help maintain people in treatment and decrease use of illicit opioids.[7,8] Choice between these treatment options is typically dependent on individual patient characteristics and preferences. One primary difference in these treatment options is that buprenorphine can be administered in the clinic or dispensed by a pharmacy and self-administered by the patient at home, whereas methadone for OUD continues to remain available only to be administered in a clinic setting. Historically, use of buprenorphine for OUD has also been regulated under the federal Drug Addiction Treatment Act (DATA)-waiver program. However, recent changes to the program have removed this regulatory requirement.[9] Buprenorphine can be now prescribed by any provider with a Drug Enforcement Administration (DEA) number.

A 2014 Cochrane systematic review evaluated outcomes associated with different doses of buprenorphine.[8] The review included 31 RCTs (n=5430) and evaluated maintenance therapy with methadone or buprenorphine in people dependent on opioids.[8] Heroin was the most common type of opioid use reported. Trial durations ranged from 2 to 52 weeks.[8] Fifteen RCTs were conducted in the United States, 9 were conducted in Europe, 4 in the Middle East, 2 in Australia, and one in Asia. Most trials had small numbers of enrolled patients, but the largest trial enrolled 736 participants.[8] Flexible dosing to manage symptoms (rather than fixed dosing) was used in only 11 RCTs, which limits applicability to clinical practice. Buprenorphine was compared to methadone in 20 RCTs. Trials evaluating fixed doses of buprenorphine typically evaluated 16 mg daily or less.[8] Two RCTs with flexible dosing regimens reported doses up to 32 mg daily, but average dose for the enrolled participants in these trials was less than 24 mg.[8] Only one RCT reported and average dose over 24 mg daily.[8] The authors concluded that there was moderate quality evidence that buprenorphine doses of 16 mg daily or higher were better at suppressing illicit opioid use (by urinalysis) compared to lower doses (3 RCTs; n=729, standardized mean difference -1.17; 95% CI -1.85 to -0.49).[8]

Other systematic reviews have documented similar results with buprenorphine, noting increased treatment retention with daily doses above 16 mg daily compared to lower doses. [10,11] Importantly, they also note a lack of studies which evaluate doses higher than 24 mg daily. [10,11] A 2022 systematic review evaluated how buprenorphine impacts self-reported opioid cravings during maintenance therapy for OUD.[12] One included study documented that doses of 24 or 32 mg daily reduced opioid cravings compared to 8 mg daily after 3 months of treatment.[12] Doses of 8-16 mg daily also demonstrated decreased craving symptoms compared to 1 mg daily.[12]

One significant limitation of the current evidence is that most trials have included people who are dependent on heroin. However, the prevalence of synthetic opioids like fentanyl continues to increase. Fentanyl is an opioid that is over fifty times more potent than heroin and is often combined with other opioids or cocaine to increase its euphoric effects.[13] In Oregon, law enforcement seizures of counterfeit pills containing fentanyl has increased by almost 1200% since 2019 and by 85% since 2020.[14] Presence of fentanyl has also been driving an increase in overdose deaths. Provisional data indicate that overdose deaths of all types has increased by more than 76% from 2011 to 2021, with overdose deaths specifically related to fentanyl and other synthetic opioids increasing by 83% from 2020 to 2021.[15] Fentanyl or fentanyl analogues, including illicitly manufactured derivatives, were the most common type of opioid identified in 2021, present in 48% of all overdose deaths.[15]

There is currently a lack of published data to guide prescribing of buprenorphine dosing necessary to mitigate symptoms in some people dependent on fentanyl. A small case series (n=12) of people who were opioid-dependent and tested positive for fentanyl reported extended clearance of fentanyl and norfentanyl (average clearance of 7 and 13 days, respectively).[16] These longer durations of clearance may contribute to continued symptoms and increased rates of precipitated withdrawal. Small case series and patient surveys have documented increased incidence of precipitated withdrawal reported by patients when using buprenorphine in the presence of fentanyl.[4,5] Additionally, a recent observational study evaluated adherence to buprenorphine therapy based on data from a prescription drug monitoring program in Philadelphia, PA (n=10,669).[6] Study investigators noted that illicit fentanyl was prevalent in the drug supply, and estimated that about 30% of the study population was eligible for Medicaid. The study included members who initiated buprenorphine from January 1, 2017 to December 31, 2018. The primary outcome was adherence to therapy defined as at least 80% of days covered over 6 months.[6] Doses were categorized as low dose (<16 mg daily; n=2024), medium dose (16 to <24mg; n=7918) or high dose (≥24 mg; n=727). Most participants were prescribed medium doses (74%).[6] Overall, adherence at 6 months for the entire study population was 26.6%. [6] Compared to low dose prescriptions, members with medium and high dose prescriptions had increased odds of adherence at 6 months (medium: adjusted OR 1.76, 95% CI 1.55–2.00; high: adjusted OR 5.11, 95% CI 4.30–6.17).[6] Adherence also varied by age, sex, presence of claims for other opioids, zip code poverty level, and buprenorphine formulation (with improved adherence with the film compared to the tablet; OR 1.37 [95 % CI 1.25–1.50]).[6] While these results are consistent with previous randomized controlled trials demonstrating improved treatment retention with higher doses of buprenorphine, they should also be interpreted with caution as this observational study did not control for any potential confounding factors.

Specific organizations have made recommendations on appropriate buprenorphine dosing for OUD. The 2021 guideline from the VA/DOD recommends initial induction doses of 2-8 mg daily with titration by 2-4 mg daily until withdrawal symptoms and cravings are relieved.[2] Maintenance doses are targeted to control cravings and illicit opioid use at daily doses ranging from 12-16 mg (up to 32 mg/day).[2] Regimens should be individualized based on patient factors, including dose reduction for hepatic impairment or divided daily doses (two or three times daily) for patients with comorbid chronic pain.[2] The National Institute for Health and Care Excellence also updated their published guidance for buprenorphine and methadone for management of opioid dependence in 2016.[3] While the evidence evaluated for these recommendations was based primarily on buprenorphine doses of 16 mg or less, they support flexible dosing to manage symptoms of opioid dependence.[3] Specific recommendations for maximum daily dosing were not included.

According to FDA labeling for sublingual buprenorphine products, maintenance doses typically range from 4 to 24 mg per day depending on each individual patient and their clinical response.[17] Current labeling states daily doses greater than 24 mg have not demonstrated a clinical advantage.[17] Clinical information submitted by the manufacturer for approval of Suboxone® (buprenorphine/naloxone) tablets and Subutex® (buprenorphine) tablets included 98 publications. Information from these publications spanned over 15 years and included a variety of study designs for both controlled and uncontrolled trials.[18] The FDA designated 3 studies as pivotal trials evaluated for the efficacy in OUD. These trials for buprenorphine enrolled primarily heroin users and had a high proportion of patients with concomitant cocaine use.[18] The first compared buprenorphine/naloxone or buprenorphine monotherapy tablets 4 to 24 mg daily to placebo over 4 weeks (n=497). [18] Buprenorphine monotherapy and combination therapy demonstrated improvements in negative urine drug screens (17.8% for buprenorphine/naloxone; 20.7% for buprenorphine; and 5.8% for placebo) and opiate craving score.[18] The other pivotal studies compared buprenorphine solution at doses of 4 mg, 8 mg or 16 mg daily to buprenorphine 1 mg solution or methadone 20 and 60 mg daily over 16 weeks (n=1631 participants).[18] The proportion of patients with negative urine drug screens was higher for buprenorphine (34.5%) compared to methadone 20 mg (15.3%) and comparable to methadone 60 mg (27.4%).[18] A larger proportion of members had clean urine drug screens when 8 mg solution daily was compared to 1 mg daily (20.2% vs. 11.6%). There was no statistical difference in negative urine drug screens between 4 mg (20.2%), 8 mg (21.7%), or 16 mg (28.8%) groups.[18] Retention in treatment was also improved with buprenorphine solution 4 mg (52%), 8 mg (53%) or 16 mg (61%) daily compared to 1 mg (40%).[18]

Of note, buprenorphine solution, tablets, and sublingual film are not bioequivalent on a 1:1 mg basis. FDA reviewers noted that sublingual tablets have a relative bioequivalence of about 50-70% compared to sublingual solution in the 4-16 mg range.[18] These differences in absorption between the tablet and solution get larger at higher doses (e.g., 24 mg).[18] FDA reviewers noted similar concerns with bioequivalence between sublingual films and tablets with increased absorption with the films compared to the tablets.[19] When switching between Suboxone® films and tablets, current labeling recommends starting the same dosage of the previously administered product, monitoring for symptoms of over-dosing or under-dosing, and adjusting the dose as needed based on response.[17]

None of the controlled studies used to assess efficacy of sublingual buprenorphine for FDA approval evaluated doses higher than 24 mg daily. However, doses up to 32 mg daily of the buprenorphine solution or 24 mg daily of buprenorphine/naloxone (Suboxone®) tablets were included in open-label safety studies.[18,19] The FDA estimated that at the time of FDA approval, 84 patients (9% of members in pooled studies of buprenorphine solution) received 32 mg daily (7578 person-days, with an average duration of therapy of 90 days per person).[18] Safety concerns observed in clinical trials included risk for abuse and misuse, risk for respiratory depression (especially in conjunction with benzodiazepines), and hepatic adverse events. FDA reviewers also noted concern for diversion of the Suboxone® film. During clinical trials conducted at 3 different study sites, about 12,900 buprenorphine films were provided in excess of the amount that patients were instructed to use. Of these doses, 46% (5,918 films) were missing and not returned.[19] Prescription of higher strength films or tablets may mitigate some of this diversion risk. The maximum dose of buprenorphine/naloxone currently supplied on the market is 12 mg films making it necessary to dispense at least 2 films to achieve a dose of 24 mg daily. With higher quantities, it makes it easier for patients to manage their symptoms of opioid use with a lower dose and still share or sell tablets with others. Because of these concerns, SAMHSA recommends maintenance doses up to 24 mg daily.[1] Because higher doses may unintentionally increase risk of diversion, SAMHSA includes recommendations to document clinical justification for higher doses and have a diversion control plan in place.[1] They also recommend that patients who do not respond 24 mg daily of buprenorphine be considered for methadone treatment.[1]

Beginning 1/1/2020, Oregon legislation was enacted which prohibited use of PA during the first 30 days of medication-assisted treatment for both opioid- and alcohol-related substance use disorders. In accordance, the Pharmacy and Therapeutics Committee updated their policy to remove PA for all products to treat OUD. Because higher doses of sublingual buprenorphine can be used off-label for pain, quantity limits of 24 mg daily were maintained for buprenorphine. The goal of this policy evaluation is to evaluate the ongoing utility and impact of the 24 mg quantity limit, in light of increased illicit fentanyl availability.

Methods:

Members were identified for inclusion in the study based on FFS claims for sublingual buprenorphine (First Databank HICL sequence numbers [HSNs] 001762 or 024846; route: sublingual). Members with paid claims and members with denied claims were reported in separate populations. The evaluation window for buprenorphine claims was from 10/1/2021 to 9/30/2022, and the index event (IE) was defined as the first claim in the evaluation window. For each patient, the baseline and follow-up periods were based on the IE.

- The baseline period was defined as the 6 months prior to the IE (exclusive of the IE).
- The follow up period was defined as the 90 days following the IE (inclusive of the IE)

Population 1: Members with Paid Claims for Sublingual Buprenorphine

Inclusion Criteria:

1. Medicaid members with a paid FFS claim sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window

Exclusion criteria:

1. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow-up period
2. Non-continuous Medicaid eligibility during the baseline period
3. Non-continuous FFS eligibility during the follow-up period
4. Members with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these members may be incomplete. Members 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

Groups were assigned based on the average dose for buprenorphine claims in the 90 days following the IE. The average daily dose was calculated by summing the total dose dispensed with each prescription (quantity dispensed*drug strength*days' supply) divided by the total days covered by buprenorphine (from the first to the last claim in the follow-up period). The days covered by buprenorphine was based on the first date of service and the last date of service plus the days' supply on the last claim and eliminating any days for which there was a gap in care.

Outcomes evaluated in this analysis included:

1. Proportion of members with a diagnosis of OUD in the baseline period (ICD-10 F11x);
2. Proportion of members with a max daily dose of buprenorphine of 24 to 32 mg daily or >32mg daily for the last 7 days covered by buprenorphine during the follow-up period; and
3. Proportion of members who were also included in population #2 (members with denied claims)

Population 2: Members with Denied Claims

Inclusion Criteria:

1. Medicaid members with a denied FFS claim for sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window. Denied claims were included based on error codes for the 24 mg daily quantity limit (error#: 4167) and excluded denials with error codes related to billing (see **Appendix 1**). The first claim in the evaluation window was defined as the IE.

Exclusion criteria

1. Paid claim for sublingual buprenorphine on the same date of service as the denied IE
2. Non-continuous Medicaid eligibility during the baseline period
3. Primary insurance coverage (i.e., TPL) at any time during the baseline period
4. Members with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline period. Claims data for these members may be incomplete. Members 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

Groups were assigned based on the daily dose for the IE. Buprenorphine doses were categorized into 24-32mg and >32mg daily.

Outcomes evaluated in this analysis included:

1. Proportion of members with a diagnosis of OUD in the baseline period (ICD-10 F11x)
2. Proportion of members with common chronic pain diagnoses in the baseline period (see list of ICD codes)

Results:

<u>Evaluation of Paid Claims for Sublingual Buprenorphine Formulations</u>

Of members with paid FFS claims for sublingual buprenorphine or buprenorphine/naloxone for the 1-year period from 10/1/21 to 9/30/22, about 22% (n=371) were included in this analysis. Most FFS members are automatically enrolled in coordinated care organizations (CCOs) and many were excluded because they were not enrolled in FFS for 90 days following the first claim for buprenorphine (**Table 1**). Baseline demographics for members in the analysis are listed in **Table 2**. The average age of included members was 38 years for members prescribed less than 32 mg daily and 35 for members prescribed over 32 mg daily. All included members were adults. Most members were female and identified as Native American or Alaskan Native. About half of included members had no recent paid claims for sublingual buprenorphine formulations in the 90 days before their first claim in the reporting period. Average Elixhauser Score was slightly higher

in members with higher doses potentially indicating increased comorbidities for this group. The Elixhauser 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.[20] 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 be used to predict risk of in-hospital mortality (the "M" index) and risk for 30-day readmission (the "R" index).[20]

The current 24 mg quantity limit is enforced per prescription, and members can attain a higher dose if they have multiple concurrent prescriptions for buprenorphine or refill a single prescription early. The average daily dose in the 90 days following the first claim was less than or equal to 24 mg daily for 85% of members. Thirteen percent of members (n=49) had an average daily dose from 24 to 32 mg daily and 2% of members (n=8) had a dose above 32 mg daily.

Presence of OUD diagnosis in the 6 months before the IE was high for all groups (**Table 3**). About 87% of members had a diagnosis of OUD in their medical claims. This analysis also evaluated for presence or absence of common chronic pain conditions. While the list of these conditions in not all inclusive, comorbid OUD and pain conditions were identified for 20% of members with doses of less than or equal to 24 mg daily, 35% of members with 24-32mg daily, and 62% for members with greater than 32 mg daily.

The buprenorphine dose is typically titrated to control symptoms of OUD. To evaluate doses over time, **Table 4** compares average dose over covered days in the entire 90-day follow-up period compared to average dose in the last 7 days covered by buprenorphine. Many members (85%) who had an average dose of 21-32 mg daily over the 90-day period were prescribed 24 mg or less in the last 7 days covered by buprenorphine. This pattern could be a result of:

1) Members with early refills for prescriptions of less than 24 mg daily
2) Dose de-escalation after members are stabilized on buprenorphine
3) Failure to fill a second prescription for members prescribed 2 doses or formulations

Only a small percentage of members with paid claims for buprenorphine also had denied claims for the 24 mg quantity limit (2.5%; n=8).

Table 1. Included population of members with paid claims.

	Total	
Number of included members	#	%
Paid FFS claim for sublingual buprenorphine from 10/1/2021 to 9/30/2022	**1,668**	
After exclusion of Medicare, TPL, and limited drug eligibility groups	1,376	82.5%
After exclusion of non-continuous FFS enrollment in the 90-day follow-up period	449	26.9%
After exclusion of non-continuous Medicaid enrollment in 6-month baseline period	**371**	22.2%

Table 2. Demographics for members with paid claims.

Average Daily Dose	**≤ 24mg daily**		**24.1-32 mg daily**		**>32 mg daily**	
	314	**84.6%**	**49**	**13.2%**	**8**	**2.2%**

Female	168	53.5%	34	69.4%	2	25.0%
Age – mean (range)	38	(18-64)	38	(18-62)	35	(27-41)
<18	0	0.0%	0	0.0%	0	0.0%
18-35	156	49.7%	23	46.9%	4	50.0%
36-64	158	50.3%	26	53.1%	4	50.0%
>=65	0	0.0%	0	0.0%	0	0.0%
Race						
White	28	8.9%	7	14.3%		0.0%
American Indian/Alaskan Native (HNA)	274	87.3%	38	77.6%	8	100.0%
Other	3	1.0%	1	2.0%		0.0%
Unknown	9	2.9%	3	6.1%		0.0%
*Average Elixhauser Score "M"	6		11		-	
*Average Elixhauser Score "R"	20		23		24	
New Start (no paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	163	51.9%	23	46.9%	5	62.5%
Continuation (paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	151	48.1%	26	53.1%	3	37.5%

*Amongst members who had a score

Table 3. Indications for members with paid buprenorphine claims.

Average Daily Dose	**≤24mg daily**		**24.1-32 mg daily**		**>32 mg daily**	
	314	**%**	**49**	**%**	**8**	**%**
OUD Diagnosis in the baseline period						
Present	274	87.3%	43	87.8%	8	100.0%
Absent	40	12.7%	6	12.2%	0	0.0%
Common chronic pain diagnosis in the baseline period	80	25.5%	18	36.7%	5	62.5%
Chronic pain G892x, G894	36	11.5%	9	18.4%	3	37.5%
Dorsalgia M54x	41	13.1%	9	18.4%	3	37.5%
Fibromyalgia M797	7	2.2%	1	2.0%	0	0.0%
Myalgia M791x	10	3.2%	4	8.2%	1	12.5%
Joint Pain M255x	37	11.8%	7	14.3%	1	12.5%

Members in both groups (with pain and OUD)	65	20.7%	17	34.7%	5	62.5%
Members in neither group (no common pain or OUD diagnosis)	25	8.0%	5	10.2%	0	0.0%

Table 4. Doses for members with paid buprenorphine claims.

Average Daily Dose	<= 24mg daily		24.1-32 mg daily		>32 mg daily	
	314	%	49	%	8	%
Average daily dose over the last 7 days covered by buprenorphine						
≤ 24 mg daily	312	99.4%	42	85.7%	4	50.0%
24.1-32 mg daily	0	0.0%	7	14.3%	1	12.5%
> 32 mg daily	2	0.6%	0	0.0%	3	37.5%
Members who were included in population #2 (with denied claims for higher dose)	3	1.0%	2	4.1%	3	37.5%

Evaluation Denied Claims for Sublingual Buprenorphine Formulations

A second analysis evaluated diagnoses in members with denied claims for sublingual buprenorphine or buprenorphine/naloxone combinations. Over the course of a 1-year period from 10/1/21 to 9/30/22, 64 FFS members had denied claims for greater than 24 mg daily of buprenorphine or buprenorphine naloxone. About one-third of these members (n=21) had complete claims data and were included in this analysis (**Table 5**). The small number of members included in this analysis makes any conclusions from this analysis highly uncertain, and inclusion of a larger group of members may change these results.

Members included in this analysis were adults with an average age of about 35 years. Most identified as white or Native American/Alaskan Native (**Table 6**). Overall, diagnoses present in medical claims were similar to members who had paid claims for sublingual buprenorphine. About 76% of members (n=17) with a denied claim for 24-32 mg daily had a diagnosis of OUD present in their medical claims 6 months before the IE (**Table 7**). Of the 4 members with claims more than 32 mg daily, all had a diagnosis of OUD. Common comorbid pain diagnoses were present for almost half of members who had a denied buprenorphine claim with a dose greater than 24 mg daily.

Table 5. Included population with denied claims for sublingual buprenorphine.

Number of included members	Total	
	#	%
Denied FFS claim for sublingual buprenorphine from 10/1/2021 to 9/30/2022	**64**	
After exclusion of members with paid claim for sublingual buprenorphine on the same day	31	48.4%

After exclusion of Medicare, TPL, and limited drug eligibility groups	27	42.2%
After exclusion of non-continuous Medicaid enrollment in 6-month baseline period	**21**	32.8%

Table 6. Demographics for members with denied claims.

Average Daily Dose	24-32 mg		>32 mg	
	17	**%**	**4**	**%**
Female	8	47.1%	1	25.0%
Age – mean (range)	35	(26-45)	36	(28-45)
<18	0	0.0%	0	0.0%
18-35	10	58.8%	2	50.0%
36-64	7	41.2%	2	50.0%
>=65	0	0.0%	0	0.0%
Race				
White	5	29.4%	1	25.0%
American Indian/Alaskan Native (HNA)	9	52.9%	3	75.0%
Other	0	0.0%	0	0.0%
Unknown	3	17.6%	0	0.0%
*Average Elixhauser Score "M"	12		-	
*Average Elixhauser Score "R"	24		17	
New Start (no paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	9	52.9%	1	25.0%
Continuation (paid claims [FFS or CCO] for SL buprenorphine in the 90 days before the IE)	8	47.1%	3	75.0%

*Amongst members who had a score

Table 7. OUD diagnoses in the baseline period for members with denied claims.

Average Daily Dose	24-32 mg		>32 mg	
	17	**%**	**4**	**%**
OUD Diagnosis in the baseline period				
Present	13	76.5%	4	100.0%

Absent	4	23.5%	0	0.0%
Common chronic pain diagnosis in the baseline period	8	47.1%	1	25.0%
Chronic pain G892x, G894	2	11.8%	0	0.0%
Dorsalgia M54x	4	23.5%	1	25.0%
Fibromyalgia M797	0	0.0%	0	0.0%
Myalgia M791x	2	11.8%	0	0.0%
Joint Pain M255x	5	29.4%	0	0.0%
Members in both groups (with pain and OUD)	8	47.1%	1	25.0%
Members in neither group (no common pain or OUD diagnosis)	4	23.5%	0	0.0%

Limitations:

As a claims-based analysis, this study has several important limitations:

- Diagnostic data is based on claims history which may be incomplete or not accurately reflect true patient diagnoses. Social stigma associated with OUD diagnoses (from patients or providers) may result in incomplete or missing diagnoses billed on medical claims. Diagnostic data was evaluated only over a 6-month period, and diagnoses for patients on stable maintenance therapy may be missed if they had infrequent provider visits. Pain diagnoses identified in medical claims only included common diagnoses and do not represent a comprehensive list of pain conditions.
- This analysis does not evaluate use of buprenorphine when administered in a clinical setting. Buprenorphine may be billed using a variety of mechanisms (both pharmacy and medical), but only pharmacy claims were included in this analysis.
- A significant proportion of members identified with paid FFS claims for sublingual buprenorphine were ineligible for inclusion in the study due to the inclusion and exclusion criteria (78%). Most members identified with a sublingual buprenorphine claim were ineligible because they did not remain in FFS for the 90 days following their first prescription for buprenorphine (many members transition into a CCO). This study assumes that included members are still representative of the entire Medicaid population. A post-hoc analysis was conducted which eliminated the 90-day follow-up requirement. Dose for members following their first claim for buprenorphine was calculated based on the average daily dose until CCO enrollment, lost eligibility, or 90 days, whichever was less. This resulted in inclusion of a larger number of members in this study, but shorter follow-up period for many of them. This post-hoc analysis demonstrated similar trends in doses prescribed for included members.
- Because doses for buprenorphine can be titrated based on symptoms and because members can get multiple prescriptions for the similar medications, this analysis used the average daily dose over a 90-day period as a method to determine total daily dose for included members. However, for members whose dose changes over time, this may not be an accurate marker of how many members would be impacted by the 24 mg daily quantity limit.
- Additionally, this analysis relies on claims paid by Medicaid to evaluate doses which may not be an accurate indicator of what dose the member actually takes. This analysis does not include claims for which the member paid cash, and we are unable to quantify actual adherence or any potential diversion.
- Public health data indicates that prevalence of fentanyl use is increasing in Oregon. Fentanyl is a more potent opioid heroin and may lead to more severe withdrawal symptoms upon discontinuation. Some providers may prescribe higher doses of buprenorphine to manage cravings in opioid use disorder for members who are dependent on fentanyl and when symptoms are inadequately controlled with lower doses. For members included in this analysis, we are unable to quantify the type of opioid dependence or the proportion of Medicaid members who are dependent on fentanyl. If illicit fentanyl continues to become more prevalent, then Medicaid members may need higher doses of buprenorphine to adequately manage symptoms of OUD.

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Appendix 1: Drug Coding

Table A1. Error codes for denied claims

Error Status Code	Error Status Description	Inclusion or exclusion in analysis
4167	DRUG QUANTITY PER DAY LIMIT EXCEEDED	**Include**
2017	RECIPIENT SERVICES COVERED BY HMO PLAN	Exclude
4999	THIS DRUG IS COVERED BY MEDICARE PART D	Exclude
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE	Exclude
4002	Non-Covered Drug	Exclude
513	RECIPIENT NAME AND NUMBER DISAGREE	Exclude
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)	Exclude
238	RECIPIENT NAME IS MISSING	Exclude
2809	DOB IS INVALID	Exclude
628	Other Coverage Reject Code Required for OCC 3	Exclude
643	INVALID OTHER COVERAGE CODE	Exclude
503	DATE DISPENSED AFTER BILLING DATE	Exclude
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER	Exclude
221	DAYS SUPPLY MISSING	Exclude
576	CLAIM HAS THIRD-PARTY PAYMENT	Exclude
205	PRESCRIBING PROVIDER ID MISSING	Exclude
268	BILLED AMOUNT MISSING	Exclude
270	HEADER TOTAL BILLED AMOUNT INVALID	Exclude

Table A2. Buprenorphine doses

Generic Name	GSN	Form	Dose	Buprenorphine Strength
buprenorphine HCl	029312	TAB SUBL	2 mg	2
buprenorphine HCl	029313	TAB SUBL	8 mg	8
buprenorphine HCl/naloxone HCl	051640	TAB SUBL	2 mg-0.5 mg	2
buprenorphine HCl/naloxone HCl	051641	TAB SUBL	8 mg-2 mg	8
buprenorphine HCl/naloxone HCl	066635	FILM	2 mg-0.5 mg	2
buprenorphine HCl/naloxone HCl	066636	FILM	8 mg-2 mg	8
buprenorphine HCl/naloxone HCl	070259	FILM	4 mg-1 mg	4
buprenorphine HCl/naloxone HCl	070262	FILM	12 mg-3 mg	12
buprenorphine HCl/naloxone HCl	071189	TAB SUBL	1.4 mg-0.36 mg	1.4
buprenorphine HCl/naloxone HCl	071190	TAB SUBL	5.7 mg-1.4 mg	5.7
buprenorphine HCl/naloxone HCl	073424	TAB SUBL	8.6 mg-2.1 mg	8.6
buprenorphine HCl/naloxone HCl	073425	TAB SUBL	11.4 mg-2.9 mg	11.4
buprenorphine HCl/naloxone HCl	074685	TAB SUBL	2.9 mg-0.71 mg	2.9

buprenorphine HCl/naloxone HCl	076981	TAB SUBL	0.7 mg-0.18 mg	0.7

Table A3. PICOS for analysis of Paid claims

Population	Medicaid members with a paid FFS claim sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window. AND continuous FFS eligibility in the follow-up period AND continuous Medicaid enrollment in the baseline period
Intervention	Group 1: Members with an average daily dose =<24mg for the days covered by their prescription in the follow-up period
Comparators	Group 2: Members with an average daily dose of 25-32 mg for the days covered by their prescriptions in the follow-up period Group 3: Members with an average daily dose >32mg daily for the days covered by their prescriptions in the follow-up period
Outcomes	1. Proportion of Members with a diagnosis of OUD in the baseline period (ICD-10 F11x) 2. Proportion of Members with a max daily dose of buprenorphine >=24 mg for the last 7 days covered by buprenorphine 3. Proportion of Members who were also included in population #2 (Members with denied claims)
Timing	Evaluation window for sublingual buprenorphine claims: 10/1/21 to 09/30/22. The first claim in the evaluation window is the index event (IE). Baseline period: 6 months before the IE Follow-up period: 90 days after the IE

Table A4. PICOS for analysis of Denied claims

Population 2	Medicaid members with a denied FFS claim for sublingual buprenorphine or buprenorphine/naloxone (HSNs 024846 and 001762, route: SL) in the evaluation window. Denied claims were included based on error codes for the 24 mg QL (error#: 4167) and excluded claims with error codes related to billing errors (see **Appendix 1; Table A1**). The first claim in the evaluation window is the index event (IE). AND continuous Medicaid enrollment in the baseline period AND no paid claim for sublingual buprenorphine on the same date of service
Intervention	Group 1: Daily dose 24-32 mg for the IE
Comparators	Group 2: Daily dose >32mg for the IE
Outcomes	OUD diagnosis in the baseline period (ICD-10 F11x) Common chronic pain diagnoses in the baseline period (see list of ICD codes)
Timing	Evaluation window for sublingual buprenorphine claims: 10/1/21 to 09/30/22 Baseline period: 6 months before the IE

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose transmucosal buprenorphine products for off-label indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Transmucosal buprenorphine products that exceed an average daily dose of 32 mg per day

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is the diagnosis funded by the OHP?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 32 mg (e.g., >32 mg/day or >64 mg every other day)?	**Yes:** Go to #4	**No:** Go to #8
4. Is there documentation of inadequate symptom improvement with 32 mg daily?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there recent documentation (within past month) from a urine drug screen indicating that buprenorphine is being taken?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Has the prescriber evaluated the PDMP in the past 3 months?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Does the member have access to naloxone?	**Yes:** Approve for 30 days. Subsequent requests for continuation of therapy will require documentation of objective clinical benefit with higher doses (e.g. improved management of OUD), documentation of a comprehensive treatment plan for OUD, and ongoing monitoring plan for safety risks.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested medication a preferred agent?	**Yes:** Approve for 6 months. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #9
9. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for 6 months. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *8/23 (SS); 2/23 (DM); 12/22; 12/20;11/19; 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *TBD; 1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*