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RetroDUR Proposal: Concurrent Use of Opioids and CNS depressants

Research Questions:

1. What is the evidence regarding safety issues associated with concurrent utilization of CNS depressants (i.e., benzodiazepines, muscle relaxants, sleep agents, antipsychotics) and opioid medications?
2. How frequently are CNS depressants prescribed in combination with chronic opioid therapy in the Medicaid Fee-For-Service (FFS) population? How frequently are CNS depressants prescribed in combination with chronic opioid therapy in the Medicaid Coordinated Care Organization (CCO) population?
3. What is the average duration of opioid therapy in these patients?
4. Which prescriber types and specialties are associated with concomitant prescribing of antipsychotics and opioids?
5. Are there any patient populations or subgroups who appear to be at higher risk of sedative overdose?

Conclusions:

1. Based on the trends of increased concomitant use of opioid analgesics and benzodiazepines as well as increased harms associated with concomitant use described in several studies, the Food and Drug Administration (FDA) required a new boxed warning about the serious risks of concomitant therapy to be added to the labeling of opioid analgesics, opioid cough medications and benzodiazepines in 2016.[1] One study analyzed the involvement of other CNS depressants (including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants) and found that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.[2] Based on this evidence, the FDA recommended the boxed warning for opioid analgesics and opioid cough medications also highlight the risk of concomitant use with other CNS depressants.[1]
2. Prescribing frequency of combination therapy with a CNS depressant and opioid
    a. Over the course of a year, over 48,000 patients were prescribed an opioid and another sedating medication with less than 4 months between prescriptions. Only a small proportion of patients (approximately 12%) had claims for overlapping opioid and sedative therapy for more than 6 weeks.
    b. The majority of patients (n=44,467) were enrolled in a CCO at the time they received their opioid prescription. However, because mental health medications like antipsychotics and benzodiazepines are carved-out and paid for by FFS, a significant number of patients enrolled in a CCO have claims for sedative therapy paid for by FFS. Twenty-five percent of CCO patients had a paid FFS claim for sedative therapy in the 30 days before the opioid and 25% had a subsequent FFS sedative claim in the 30 days after the member was prescribed an opioid.
3. Average duration of opioid therapy
    a. The majority of patients (61-65%) prescribed opioid therapy had a proportion of days covered (PDC) of less than 16% (less than about 30 days) in the 6 months after the opioid index event. About 16% of patients with claims for sedating medication had a PDC for opioids of more than 67% (or approximately 120 days).
4. Prescriber types for concomitant opioid and sedative therapy

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a. General practitioners (including physicians, advanced practice nurses, and physician assistants) account for the majority of prescribing in patients with combination therapy with an opioid and another sedating medication. In many cases multiple prescribers are involved in prescribing opioids and sedating medications. Only 43% of patients prescribed overlapping treatment for 6-12 weeks and 35% of patients prescribed combination treatment for more than 12 weeks received both the opioid and sedative from a single provider.

5. Patient populations or subgroups at higher risk of sedative overdose
    a. The overall incidence of hospitalization or emergency department visits due to sedative poisoning or sedative adverse events was small and occurred in only 0.6% of all patients prescribed opioids and sedatives.
    b. Patients prescribed sedatives and opioids from 3 or more prescribers and patients with a prior history of sedative overdose had a slightly higher incidence compared to the total population (2.5% and 5.5%, respectively).

Recommendations:

- Send an educational prescriber letter (**Appendix 1**) notifying them of combination opioid and sedative therapy in the following circumstances (see **Appendix 2** for specific inclusion criteria):
    - Patients with 3 or more unique prescribers of opioid and sedative therapy
    - Patients with a prior history of sedative poisoning

Background:

The Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act was signed into law on October 24, 2018 by President Trump.[3] This law requires state Medicaid programs to have drug utilization review safety edits for opioid refills and an automated claims review process to identify refills in excess of state defined limits, monitor concurrent prescribing of opioids and benzodiazepines or antipsychotics, and require managed care plans to have these processes in place by October 1, 2019.[3] The FDA issued an alert regarding safety issues associated with concomitant use of opioids with drugs that depress the central nervous system (CNS) in 2016.[1] An FDA review found combined use of opioid medicines with benzodiazepines or other CNS depressants has resulted in serious side effects, including slowed or difficult breathing and deaths.[1] The FDA recommended health care professionals should limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate.[1] If these medicines are prescribed together, the dosages and duration of each drug should be limited to the minimum possible while achieving the desired clinical effect.[1] The specific CNS depressants identified by the FDA are listed in **Appendix 3, Table A5.**

Concomitant Use of Opioids and Benzodiazepines

Two studies were identified that showed an increased trend in concomitant dispensing of opioid analgesics and benzodiazepines, and an increased frequency of combined benzodiazepine and prescription opioid misuse, abuse, and overdose, as measured by national emergency department (ED) visit and overdose death rates (from prescribed or greater than prescribed doses).[4] The first publication, a time series study, examined concomitant use patterns of opioid analgesics and benzodiazepines in United States (U.S.) outpatient retail settings.[4] Between 2002 and 2014, the annual number of patients dispensed an opioid analgesic increased 8 percent, from 75 million to 81 million, and the annual number of patients dispensed a benzodiazepine increased 31 percent, from 23 million to 30 million.[4] During this period, the proportion of opioid analgesic recipients receiving an overlapping benzodiazepine prescription increased by 41 percent, which translates to an increase of more than 2.5 million opioid analgesic users receiving concomitant benzodiazepines in 2014, compared to 2002.[4] Approximately half of these patients received both prescriptions from the same prescriber on the same day.[4] The patients with the highest probability of receiving concomitant prescriptions were women, patients older than 65, and chronic users of opioid analgesics (patients receiving opioids for 90 days or greater).[4] This study evaluated co-prescribing trends of opioids and benzodiazepines, but did not evaluate adverse event outcomes.

The second study used the Drug Abuse Warning Network (DAWN) to analyze ED visits due to nonmedical use of both prescription opioid analgesics and benzodiazepines, and the National Vital Statistics System Multiple Cause-of-Death file to analyze drug overdose deaths involving both prescription opioid analgesics and benzodiazepines.[5] Between 2004 and 2011, the rate of nonmedical use-related ED visits involving both opioid analgesics and benzodiazepines increased from 11 to 34.2 per 100,000 population (p-trend <0.0001).[5] During this same time period, drug overdose deaths, from taking prescribed or greater than prescribed doses and involving both opioid analgesics and benzodiazepines, increased from 0.6 to 1.7 per 100,000 (p-trend <0.0001).[5] The proportion of prescription opioid analgesic overdose deaths in which benzodiazepines were also implicated increased from 18 percent to 31 percent during this time period (p-trend <0.0001).[5]

Two additional studies provide additional evidence of increased risk of adverse events occurring in patients dispensed both opioid analgesics and benzodiazepines. A prospective observational cohort study conducted in North Carolina found the rates of overdose death among patients co-dispensed opioid analgesics and benzodiazepines were 10 times higher (7.0 per 10,000 person-years; 95% confidence interval [CI] 6.3-7.8) than among patients dispensed opioid analgesics alone (0.7 per 10,000 person-years; 95% CI 0.6-0.9).[6] A case-cohort study examined the Veterans Health Administration data from 2004-2009 and found the risk of death from drug overdose increased among those with concomitant opioid analgesic and benzodiazepine prescriptions.[7] Compared to patients taking opioid analgesics with no history of a benzodiazepine prescription, patients taking opioid analgesics with a history of a benzodiazepine prescription had an increased risk of fatal overdose (hazard ratio [HR]=2.33; 95% CI: 2.05-2.64), and those with a current benzodiazepine prescription had a similarly increased risk (HR=3.86; 95% CI: 3.49-4.26) for fatal overdose.[7] In addition, the risk of drug overdose death increased as the daily benzodiazepine dose increased.[7]

Based on the trends of increased concomitant use of opioid analgesics and benzodiazepines as well as increased harms associated with concomitant use described in these four studies, the FDA required a new boxed warning to be added to the labeling of opioid analgesics, opioid cough medications and benzodiazepines in 2016.[1]

Concomitant Use of Opioids and other CNS depressants

Recent studies show that concomitant use of opioid analgesics and CNS depressants other than benzodiazepines, including alcohol, is also associated with serious adverse events. One study analyzed the involvement of CNS depressants (including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants) and found that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.[2] Opioids were involved in the majority of deaths involving benzodiazepines (77.2%), antiepileptic and antiparkinsonism drugs (65.5%), antipsychotic and neuroleptic drugs (58.0%), antidepressants (57.6%), other analgesics, antipyretics, and antirheumatics (56.5%), and other psychotropic drugs (54.2%).[2] A second study analyzed 2010 DAWN data and found that alcohol was involved in 18.5 percent of opioid analgesic abuse-related ED visits and 22.1 percent of opioid analgesic-related deaths.[8] All of the studies were based on opioid analgesics; however, because of similar pharmacologic properties, the FDA noted it is reasonable to expect similar risks with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.[1] Based on these studies, the FDA recommended the boxed warning for opioid analgesics and opioid cough medications also highlight the risk of concomitant use with other CNS depressants.[1]

Concomitant use of Medication Assisted Treatment (MAT) and CNS depressants

An FDA drugs safety communication issued in 2017 cautioned about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants.[9] The FDA advises that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other CNS depressants.[9] The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks.[9] Careful medication management by health care professionals can reduce these risks.[9] The FDA required this

information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.[9]

Methods:

The patient population included current Medicaid patients (FFS and CCO) with an opioid index event from 4/1/2017 to 3/31/2018 and at least one claim for an additional sedating medication within the 4 months before or after then index event. Patients with Medicare or with only limited Medicaid drug coverage were excluded from the analysis (benefit plans: BMM, BMD, CWM, MED, MND, SMF, SMB). Patients with less than 75% Medicaid eligibility in the 6 months following the index event were excluded in order to ensure complete data was captured for included patients.

Definitions used for the analysis:

- The **index event** was defined as the first paid pharmacy claim for an opioid. Opioids from the following PDL classes were included in the analysis: Opioids, short-acting; Opioids, long-acting; and Cough and Cold (see **Appendix 3 Table A1**).
- **Concomitant sedative therapy** was assessed for the drugs listed in **Table A2**. They included pharmacy claims for benzodiazepines, sedative for insomnia, muscle relaxants, and antipsychotics. Concomitant sedating therapy was defined as at least 6 weeks of overlapping therapy with no more than a 7 day gap in coverage. Length of concomitant sedative therapy was defined as short-term (6-12 weeks) or long-term (>12 weeks). Type of concomitant sedative therapy was categorized by drug class and included both CCO and FFS claims. The total number of unique sedating drugs with overlapping therapy for these timeframes was also evaluated.
- **FFS and CCO utilization:** Patients were categorized according to the payer (FFS or CCO) of the opioid index event. In order to assess the number of patients with both FFS and CCO claims, patients were evaluated for sedative therapy in the 30 days before or after the index event. Patients were categorized according to the type of claim for the index event (FFS or CCO). All prior and subsequent claims for any sedative were evaluated in the 30 days before and after the index event. If patients were enrolled in both FFS and a CCO within this timeframe they may be counted more than once. Sedative therapy was categorized according to the claim type (FFS or CCO).
- **Duration of opioid or other sedative therapy** was assessed using proportion of days covered (PDC) in the 6 months following the index event. PDC was divided into 4 categories: a PDC of up to 16% (corresponding to approximately 1 month of treatment), PDC of 16-33% (1-2 months), PDC of 34-67% (2-4 months) and PDC greater than 67% (>4 months).
- **Prescriber type**: Prescribers of patients with combination opioid and sedative therapy were identified using the primary provider taxonomy associated with overlapping claims of concomitant opioids and sedatives. Patients were also categorized according to the number of unique providers involved in prescribing opioid and sedating medications in the 6 months following the index event and the number of unique providers who prescribe overlapping sedative and opioid therapy.
- **Hospitalizations, emergency department visits**, and patients with visits associated with a **sedative poisonings or adverse effects** were identified using codes shown in **Table A3** and diagnoses associated with sedative poisonings or adverse events listed in **Table A4**. Medical visits may be associated with more than one diagnosis and both primary and secondary diagnoses were included in the analysis. Two analyses were conducted.
    - The first analysis evaluates unique patients who had a hospital visit or ER visit in the 6 months following the index event. The number of patients is reported for the overall population (every patient with an IE) and for various patient groups in order to evaluate what patients may be at higher risk of sedative adverse events. Using this method avoids counting patients multiple times, but it may also potentially miss valuable information in patients with multiple medical visits.
    - A second analysis evaluated all hospitalizations or ER visits associated with a diagnosis of sedative poisoning or adverse events in the pre-specified population. Pharmacy claims paid for before the medical visit were evaluated to identify prescribing patterns which may be associated with more frequent visits. This analysis captures all ED visits or hospitalizations for sedative poisonings for patients during the study period, and

patients would be counted more than once if they had multiple medical visits. Subsequently, data for this analysis may be more heavily influenced by members with frequent ED visits or hospitalizations for sedative poisoning.

Results:

Demographics for patients prescribed opioid and sedative therapy is presented in **Table 1**. The majority of patients prescribed opioids and sedatives are white, female adults. Overall, 92% of patients were enrolled in a CCO at the time of the index event and only 4% of the population had a change in enrollment within 45 days of their opioid prescription. In total, over 48,000 patients were identified as filling prescriptions for an opioid and some type of sedative therapy within 4 months each other. For patients prescribed a subsequent sedative prescription, the average time between the opioid and sedative prescription was 29 days. In only 27% of patients prescribed both opioids and sedatives, sedative therapy was separated by more than 30 days from the time of the opioid prescription.

Table 1. Demographics for patients prescribed opioid and sedative therapy

	N=	48,186	%
Age			
Average (min - max)		41.9	(0-88)
<=18		1,317	2.7%
19-60		44,643	92.6%
>60		2,226	4.6%
Female		32,183	66.8%
Race			
White		26,051	54.1%
Hispanic		893	1.9%
African American		1,207	2.5%
Native American		2,517	5.2%
Enrollment at Index			
CCO		44,467	92.3%
FFS		3,719	7.7%
Change in enrollment within 45 days		2,066	4.3%
Average days to 1st subsequent sedative claim		29	(0-184)

Table 2 describes the frequency in which patients are prescribed opioids and sedative from both FFS and a CCO within one month before or after the opioid index event. In the majority of Medicaid members, both prescriptions were billed to the same entity (either FFS or a CCO). In FFS, 50-53% of patients received sedative therapy from FFS within 30 days before or after an opioid prescription. Only 9% had a subsequent sedative claim paid for by a CCO within 30 days. For members enrolled in a CCO, approximately 41% had a sedative claim paid by a CCO within the previous or subsequent 30 days. However, because mental health medications like antipsychotics and benzodiazepines are carved-out and paid for by FFS, a significant number of patients enrolled in a CCO have claims for

sedative therapy paid for by FFS. Of over 44,000 CCO patients with a paid opioid prescription, 25% had a paid FFS claim for sedative therapy in the 30 days before the opioid and 25% had a subsequent FFS sedative claim in the 30 days after the member was prescribed an opioid.

Table 2. Patients with at least one claim for sedative therapy in the 30 days before or after the index event. Patients were categorized according to the payer (FFS or CCO) for the index event. All prior and subsequent claims for a sedative were evaluated in the 30 days before and after the index event. Categories are not mutually exclusive. If patients were enrolled in both FFS and a CCO within this timeframe they may be counted more than once.

	FFS index event		CCO Index Event	
N=	**3,719**	**%**	**44,467**	**%**
Patients with a subsequent sedative claim	2,221	59.7%	26,141	58.8%
Subsequent sedative FFS claims	2,002	53.8%	11,000	24.7%
Subsequent sedative CCO claims	346	9.3%	18,309	41.2%
Patients with a prior history of sedative use	1,915	51.5%	26,171	58.9%
Prior sedative FFS claims	1,868	50.2%	11,291	25.4%
Prior sedative CCO claims	62	1.7%	18,040	40.6%

The majority of patients (61-65%) prescribed opioid therapy had a PDC of less than 16% (less than approximately 30 days) in the 6 months after the opioid index event (**Table 3**). About 16% of patients with claims for sedating medication had a PDC of more than 67% (or approximately 120 days). Almost 5,400 patients (~12% of patients prescribed opioid therapy) had overlapping claims for a sedative medication. Most patients with overlapping claims were prescribed long-term opioid and sedative therapy with a PDC of more than 67% for overlapping therapy in the 6 months following the index event. **Table 4** further describes patients who were prescribed continuous concomitant opioid and sedative therapy for more than 6 weeks. In most circumstances combination therapy included muscle relaxants and benzodiazepines. The majority of patients (80-94%) prescribed combination opioid-sedative therapy for more than 6 weeks were prescribed only one sedating medication in conjunction with an opioid.

Table 3. Proportion of covered days for patients prescribed opioid or other sedative therapy in the 6 months following the index event. For combination therapy the PDC describes the number of days covered by both an opioid and another sedative therapy.

	FFS IE		CCO IE	
	3,719	**%**	**44,467**	**%**
PDC of opioid therapy				
<=16%	2,275	61.2%	29,140	65.5%
17-33%	473	12.7%	4,452	10.0%
34-67%	389	10.5%	3,494	7.9%
>67%	582	15.6%	7,381	16.6%

PDC of any other sedative therapy (includes only patients prescribed subsequent sedative therapy)				
<=16%	1,244	33.4%	13,099	29.5%
17-33%	786	21.1%	7,990	18.0%
34-67%	541	14.5%	6,392	14.4%
>67%	679	18.3%	10,563	23.8%
PDC of opioid and another sedative therapy (includes only patients prescribed overlapping opioid and sedative prescriptions)				
<=16%	20	0.5%	209	0.5%
17-33%	118	3.2%	1,238	2.8%
34-67%	174	4.7%	1,804	4.1%
>67%	123	3.3%	2,141	4.8%

Table 4. Duration of concomitant opioid and sedative therapy. Type of combination sedative therapy was defined according to drug class.

	Short-term concomitant therapy (6-12 weeks)		**Long-term concomitant therapy (>12 weeks)**	
Total	**2,832**	**%**	**2,886**	
Sedative Class				
Antipsychotic	625	22.1%	608	21.1%
Barbiturate	9	0.3%	8	0.3%
Benzodiazepine	848	29.9%	1,026	35.6%
Muscle Relaxant	1,837	64.9%	1,579	54.7%
Sedative	324	11.4%	289	10.0%
Number of unique sedating drugs prescribed in combination with an opioid				
1	2,650	93.6%	2,302	79.8%
2	443	15.6%	499	17.3%
3	89	3.1%	82	2.8%
4	10	0.4%	16	0.6%
5	2	0.1%	2	0.1%

Prescribers involved in prescribing combination opioid and sedative medications for more than 6 weeks are listed in **Table 5**. Physicians account for over 75% of concomitant overlapping opioid and sedative claims. Advanced practice nurses, physician assistants, and mental health providers also account for a significant proportion of prescribed combination therapy. In many cases multiple prescribers are involved in prescribing opioids and sedating medications. Only 43% of patients prescribed overlapping treatment for 6-12 weeks and 35% of patients prescribed combination treatment for more than 12 weeks received both the opioid and sedative from a single provider. Less than 15% of patients had more than 3 providers prescribing combination sedating and opioid therapy.

Table 5. Prescriber characteristics Prescriber types stratified primary provider taxonomy which were associated with claims for overlapping combination treatment with opioids and sedatives.

		Short-term concomitant therapy (6-12 weeks)		Long-term concomitant therapy (>12 weeks)	
		2,832	**%**	**2,886**	
Patient counts for Top 10 prescriber types associated with claims for concomitant overlapping sedative therapy					
1	Physician	2,126	75.1%	2,296	79.6%
2	Advance Practice Nurse	1,025	36.2%	1,132	39.2%
3	Physician Assistants	728	25.7%	767	26.6%
4	MH Provider	307	10.8%	369	12.8%
5	Dentist	80	2.8%	74	2.6%
6	Adv Comp Health Care	72	2.5%	90	3.1%
7	Podiatrist	12	0.4%	12	0.4%
8	Nurse	9	0.3%	4	0.1%
9	Chiropractor	2	0.1%	1	0.0%
10	Pharmacist	1	0.0%	1	0.0%
Patient counts by number of prescribers associated with claims for overlapping sedative therapy					
1		1,215	42.9%	1,002	34.7%
2		976	34.5%	971	33.6%
3		398	14.1%	518	17.9%
4		136	4.8%	223	7.7%
5		64	2.3%	110	3.8%
6		27	1.0%	40	1.4%
7		8	0.3%	12	0.4%
8		4	0.1%	5	0.2%
9		3	0.1%	3	0.1%
≥10		1	0.0%	1	0.0%

The overall incidence of hospitalization or emergency department visits due to sedative poisoning or adverse events was small and occurred in only 0.6% of patients prescribed opioids and sedatives (**Table 6**). The duration of therapy did not demonstrate consistent trends for incidence of hospitalization, emergency department visits and sedative poisonings. However, patients prescribed sedatives and opioids from 3 or more prescribers and patients with a prior history of sedative overdose had a slightly higher incidence compared to the total population (2.5% and 5.5%, respectively). Similarly, all cause emergency department visits and hospitalizations occurred with higher frequency in patients with prescriptions from multiple providers and those with a prior history of sedative poisoning.

Table 6. Patient groups associated with hospitalization, emergency department visit, or visits with a diagnosis of sedative overdose or adverse effects in the 6 months following the index event. Percentages are calculated as a proportion of each group.

As Percent of Group	Total Patients in Each Category	Patients with Hospitalization		Patients with ED Visit		Patients with Hospitalization or ED Visit due to sedative poisoning or adverse effects	
All patients with IE	48,186	4,713	9.8%	22,907	47.5%	312	0.6%
Patients with no concomitant sedative therapy (< 6 weeks)	42,468	4,115	9.7%	20,794	49.0%	272	0.6%
Patients with short-term (6-12 weeks) concomitant sedative therapy	2,832	382	13.5%	1,231	43.5%	23	0.8%
Patients with long-term (>12 weeks) concomitant sedative therapy	2,886	256	8.9%	1,053	36.5%	18	0.6%
Number of prescribers of sedative therapy in the 6 months after the IE							
1	26,450	1,993	7.5%	11,434	43.2%	95	0.4%
2	9,969	1,191	11.9%	5,395	54.1%	69	0.7%
>=3	4,874	1,117	22.9%	3,285	67.4%	**123**	**2.5%**
Patients with a history of prior sedative poisoning or adverse event in the 1 year before the IE	889	192	21.6%	590	66.4%	**49**	**5.5%**

Prescribing patterns for patients with a hospitalization or emergency department visit for sedative poisoning or sedative adverse events were also evaluated prior to each event on a visit by visit basis. **Table 7** shows prescribing patterns in the 120 days prior to each visit. Only 13-16% of visits for sedative poisoning occurred when patients received prescriptions written from a single provider in the 120 days before the event. For approximately 27% of visits, patients had prescriptions from 2 providers, and over 50% of visits occurred when patients filled prescriptions from 3 or more providers in the prior 120 days. There was no apparent pattern based on the type or number of prescribed agents.

Table 7. ED or hospital visits associated with a diagnosis of sedative poisoning or adverse events. Claims for opioids and sedatives were assessed 120 days before each visit.

	Hospital Visit		ED Visit	
N = number of visits =	**141**	**%**	**334**	**%**
Paid prescriptions prior to the visit				
Naloxone	5	3.5%	5	1.5%
Benzodiazepine	70	49.6%	166	49.7%
Antipsychotic	67	47.5%	143	42.8%
Opioid	122	86.5%	296	88.6%
Sedative, muscle relaxant, or barbiturate	87	61.7%	184	55.1%
Opioid and benzodiazepine	66	46.8%	153	45.8%
Opioid and antipsychotic	59	41.8%	130	38.9%
Opioid and either sedative, muscle relaxant, or barbiturate	76	53.9%	166	49.7%
Number of prescribers of opioid and sedative therapy				
1	19	13.5%	54	16.2%
2	39	27.7%	90	26.9%
>=3	81	57.4%	179	53.6%
Number of unique sedating agents (based on HSN)				
1	48	34.0%	119	35.6%
2	39	27.7%	92	27.5%
>=3	45	31.9%	88	26.3%

Limitations:

Data presented in this report are based on Medicaid claims history which have several inherent limitations. For example, information on provider type may be inaccurate, out-of-date, or incomplete for some providers, and prescribers with multiple specialties or designations may not be identified. In addition, use of PDC attempts to estimate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, and patients may not always be categorized appropriately. Similarly, information based on diagnosis of sedative poisoning or overdose may be delayed, incomplete, or inaccurate. This data only captures patients who have a hospital encounter (either a hospital admission or emergency department visit) as a result of sedative poisoning. It is likely that a significant proportion of patients who do not receive hospital services for sedative overdose are not captured with these data. Similarly, while data indicate patients prescribed opioids and sedatives from multiple prescribers may have a higher risk of sedative overdose, the data is observational and based on a small proportion of patients. There may be multiple confounding factors which contribute to higher risk of overdose in these populations and cause and effect relationships or statistical significance between populations cannot be determined.

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Appendix 1: Provider Educational Letter

HEALTH SYSTEMS DIVISION
Provider Services
500 Summer St NE
Salem, OR 97301

Date issued: <July 1, 2019>

Voice: 800-336-6016
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<PROVIDER First Name><Last Name>
<1234 MAIN STREET>
<SUITE 100>
<PORTLAND, OR 97227>

For billing ID: «Billing_Provider_Medicaid_ID»

Subject: Concurrent Prescribing of Opioids and CNS Depressants
for <Patient Name>
ID: XXXXXXX DOB: <MM/DD/YYYY>

Dear Prescriber:

The Oregon Health Plan Fee-for-Service (OHP-FFS) pharmacy program reviews the dispensing of outpatient prescription medications to ensure medically appropriate and safe use.

What is the concern?

OHP-FFS pharmacy paid claims data indicate that your patient recently filled a prescription for **<Drug A>** in combination with another sedating agent from a different prescriber which is still active on the patient's profile.

Concomitant use of opioids with other CNS depressants (benzodiazepines, gabapentinoids, antipsychotics, etc) greatly increases patient risk of hypotension, profound sedation, coma, or fatal respiratory depression.[1]

What should you do?

- Consider prescribing naloxone in patients with high risk for overdose
- Check the Oregon PDMP to evaluate co-prescribing of opioids with other sedatives
- Consider tapering or discontinuing your patient's chronic opioid and/or CNS depressant therapy whenever risks (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability) outweigh benefits. An opioid taper guide may be found here: https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf.[2]

For more information, feel free to check the box below:

☐ **Please send me a copy of my patient's recent pharmacy claims history → FAX to (503) 945-xxxx)**

Questions?

For pharmacy point of sale questions, you may call the Oregon Pharmacy Call Center at 888-202-2126.

References:

1. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed March 20, 2019.
2. Centers for Disease Control and Prevention (U.S.) Pocket Guide: Tapering Opioids for Chronic Pain. https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf. Accessed March 20, 2019.

Appendix 2: Retrospective DUR Inclusion/Exclusion Criteria and Reporting Parameters

Inclusion criteria:

- Patients currently enrolled in Medicaid (either fee-for-service [FFS] or a coordinated care organization [CCO]) AND
- Patients prescribed both an opioid and another sedating medication (as defined above) within the past 120 days AND
- At least one of the following characteristics:
    - Patients with prescriptions for opioids and sedatives which overlap by at least 7 days written by more than one provider OR
    - Patients with prescriptions for opioids and sedatives from 3 or more unique providers in the past 120 days OR
    - Members with a history of sedative poisoning or adverse events within the past 2 years

Exclusion criteria:

Exclude patients meeting any of the following criteria:

- Patients not currently enrolled in Medicaid
- Patients who have been had a letter sent within the past 3 months
- Providers who have been messaged for the same patient within the past 12 months

The prescriber of the most recent sedative or opioid prescription will receive the provider letter.

Reporting Parameters

The program will be added to the quarterly retrospective DUR reports with the following reporting parameters:

- Patients identified
- Prescribers identified
- Prescribers successfully notified
- Patients with discontinuation of therapy within the next 90 days (discontinuation defined as no new prescriptions filled for the drug class)
    - Opioid
    - Benzodiazepine
    - Antipsychotic
- Patients with a new prescription for naloxone within the next 90 days
- Average number of sedative drugs dispensed within the next 90 days
- Average number of sedative prescribers writing prescriptions in the next 90 days

Appendix 3

Table A1. Codes for Opioid Analgesics

Class	HSN	Generic
Cough and Cold	035501	bromphenira/pseudoephed/codein
Cough and Cold	035361	brompheniramine/p-eph/codeine
Cough and Cold	036713	chlorphen/pseudoephed/codeine
Cough and Cold	000347	chlorpheniramine/codeine phos
Cough and Cold	037229	chlorpheniramine/PE/codeine

Cough and Cold	000206	codeine phosphate/guaifenesin
Cough and Cold	009011	codeine phosphate/pyrilamine
Cough and Cold	000348	codeine poli/chlorphenir polis
Cough and Cold	035645	dexchlorphen/phenyleph/codeine
Cough and Cold	000209	guaifenesin/hydrocodone
Cough and Cold	039314	hydrocodone bit/homatrop me-br
Cough and Cold	000352	hydrocodone/chlorphen p-stirex
Cough and Cold	000487	hydrocodone/cpm/pseudoephed
Cough and Cold	000265	hydrocodone/pseudoephed/guaif
Cough and Cold	000419	PE/codeine/acetaminophen/cpm
Cough and Cold	000424	phenyleph/hydrocodon/pyrilamin
Cough and Cold	000421	phenylephrine HCl/cod/pyril
Cough and Cold	000334	phenylephrine/cod/cpm/pot iod
Cough and Cold	035441	phenylephrine/codeine/guaifen
Cough and Cold	000425	phenylephrine/hydrocodone/cpm
Cough and Cold	000277	pot guaiaco/hydrocodone
Cough and Cold	000345	promethazine HCl/codeine
Cough and Cold	000420	promethazine/phenyleph/codeine
Cough and Cold	000484	pseudoephed/cod/chlorphenir
Cough and Cold	035174	pseudoephed/codeine/guaifen
Cough and Cold	005359	pseudoephed/codeine/triprolidn
Cough and Cold	000488	pseudoephed/hydrocodone
Cough and Cold	042426	triprolidine/phenyleph/codeine
Opioids, Long-Acting	001731	hydrocodone bitartrate
Opioids, Long-Acting	001695	hydromorphone HCl
Opioids, Long-Acting	001743	levorphanol tartrate
Opioids, Long-Acting	001745	methadone HCl
Opioids, Long-Acting	001694	morphine sulfate
Opioids, Long-Acting	036577	morphine sulfate/naltrexone
Opioids, Long-Acting	001742	oxycodone HCl
Opioids, Long-Acting	043376	oxycodone myristate
Opioids, Long-Acting	001696	oxymorphone HCl
Opioids, Long-Acting	036411	tapentadol HCl
Opioids, Long-Acting	008317	tramadol HCl
Opioids, Short-Acting	001717	acetaminophen with codeine

Opioids, Short-Acting	001739	acetaminophen/caff/dihydrocod
Opioids, Short-Acting	034574	aspirin/caffein/dihydrocodeine
Opioids, Short-Acting	001734	aspirin/caffeine/dihydrocodein
Opioids, Short-Acting	001711	aspirin/codeine phosphate
Opioids, Short-Acting	044795	benzhydrocodone/acetaminophen
Opioids, Short-Acting	001713	butalbit/acetamin/caff/codeine
Opioids, Short-Acting	001702	cod/ASA/salicylmd/acetamin/caf
Opioids, Short-Acting	001722	codeine sulfate
Opioids, Short-Acting	001699	codeine/butalbital/ASA/caffein
Opioids, Short-Acting	001727	hydrocodone bitartrate/aspirin
Opioids, Short-Acting	001730	hydrocodone/acetaminophen
Opioids, Short-Acting	014296	hydrocodone/ibuprofen
Opioids, Short-Acting	001695	hydromorphone HCl
Opioids, Short-Acting	026757	ibuprofen/oxycodone HCl
Opioids, Short-Acting	001687	meperidine HCl
Opioids, Short-Acting	001694	morphine sulfate
Opioids, Short-Acting	001742	oxycodone HCl
Opioids, Short-Acting	001741	oxycodone HCl/acetaminophen
Opioids, Short-Acting	004576	oxycodone HCl/aspirin
Opioids, Short-Acting	001696	oxymorphone HCl
Opioids, Short-Acting	001781	pentazocine HCl/naloxone HCl
Opioids, Short-Acting	001769	propoxyphene HCl
Opioids, Short-Acting	001767	propoxyphene HCl/acetaminophen
Opioids, Short-Acting	001768	propoxyphene nap/acetaminophen
Opioids, Short-Acting	001763	propoxyphene/aspirin/caffeine
Opioids, Short-Acting	036411	tapentadol HCl
Opioids, Short-Acting	008317	tramadol HCl
Opioids, Short-Acting	022880	tramadol HCl/acetaminophen

Table A2. Codes for Concomitant Sedating Medications

Class	HSN	Generic
Antipsychotics, 1st Gen	001621	chlorpromazine HCl
Antipsychotics, 1st Gen	001626	fluphenazine HCl
Antipsychotics, 1st Gen	001662	haloperidol
Antipsychotics, 1st Gen	001661	haloperidol lactate

Antipsychotics, 1st Gen	039886	loxapine
Antipsychotics, 1st Gen	001664	loxapine succinate
Antipsychotics, 1st Gen	001627	perphenazine
Antipsychotics, 1st Gen	001637	pimozide
Antipsychotics, 1st Gen	001631	thioridazine HCl
Antipsychotics, 1st Gen	001668	thiothixene
Antipsychotics, 1st Gen	001667	thiothixene HCl
Antipsychotics, 1st Gen	001630	trifluoperazine HCl
Antipsychotics, 2nd Gen	024551	aripiprazole
Antipsychotics, 2nd Gen	036576	asenapine maleate
Antipsychotics, 2nd Gen	042283	brexpiprazole
Antipsychotics, 2nd Gen	042552	cariprazine HCl
Antipsychotics, 2nd Gen	004834	clozapine
Antipsychotics, 2nd Gen	037321	lurasidone HCl
Antipsychotics, 2nd Gen	011814	olanzapine
Antipsychotics, 2nd Gen	034343	paliperidone
Antipsychotics, 2nd Gen	043373	pimavanserin tartrate
Antipsychotics, 2nd Gen	014015	quetiapine fumarate
Antipsychotics, 2nd Gen	008721	risperidone
Antipsychotics, 2nd Gen	021974	ziprasidone HCl
Benzodiazepines	001617	alprazolam
Benzodiazepines	001656	amitriptyline/chlordiazepoxide
Benzodiazepines	001611	chlordiazepoxide
Benzodiazepines	001610	chlordiazepoxide HCl
Benzodiazepines	002037	chlordiazepoxide/clidinium Br
Benzodiazepines	001894	clonazepam
Benzodiazepines	001612	clorazepate dipotassium
Benzodiazepines	001615	diazepam
Benzodiazepines	004846	lorazepam
Benzodiazepines	001616	oxazepam
Muscle Relaxants, Oral	001949	baclofen
Muscle Relaxants, Oral	001944	carisoprodol
Muscle Relaxants, Oral	001942	carisoprodol/aspirin
Muscle Relaxants, Oral	001720	carisoprodol/aspirin/codeine
Muscle Relaxants, Oral	001941	chlorzoxazone

Muscle Relaxants, Oral	001950	cyclobenzaprine HCl
Muscle Relaxants, Oral	001947	dantrolene sodium
Muscle Relaxants, Oral	001945	metaxalone
Muscle Relaxants, Oral	001938	methocarbamol
Muscle Relaxants, Oral	001936	methocarbamol/aspirin
Muscle Relaxants, Oral	001906	orphenadrine citrate
Muscle Relaxants, Oral	001791	orphenadrine/aspirin/caffeine
Muscle Relaxants, Oral	011582	tizanidine HCl
Sedatives	004480	diphenhydramine HCl
Sedatives	001650	doxepin HCl
Sedatives	004482	doxylamine succinate
Sedatives	006036	estazolam
Sedatives	026791	eszopiclone
Sedatives	001593	flurazepam HCl
Sedatives	001619	midazolam HCl
Sedatives	045030	midazolam/ketamine/ondansetron
Sedatives	001595	quazepam
Sedatives	033126	ramelteon
Sedatives	041333	suvorexant
Sedatives	040927	tasimelteon
Sedatives	001592	temazepam
Sedatives	001594	triazolam
Sedatives	020347	zaleplon
Sedatives	007842	zolpidem tartrate
Barbiturate	001566	butabarbital sodium
Barbiturate	001570	secobarbital sodium
Barbiturate	001561	phenobarbital

Table A3. Health Outcome Codes

ED Visits	Procedure Codes OR Revenue Center Codes	99281-99285, 99288 0450-0459 or 0981
Hospitalizations	Claim Type = I	Claim Type = I

Table A4. Diagnosis codes associated with sedative poisoning or adverse effects

ICD-10 code	Description
T42.3X1xx-T42.3X5xx	Poisoning by, adverse effect of barbiturates
T42.4X1xx-T42.4X5xx	Poisoning by, adverse effect of benzodiazepines
T42.6X1xx-T42.6X5xx	Poisoning by, adverse effect of other antiepileptic and sedative-hypnotic drugs
T42.7X1xx-T42.7X5xx	Poisoning by, adverse effect of unspecified antiepileptic and sedative-hypnotic drugs
T42.8X1xx-T42.8X5xx	Poisoning by, adverse effect of antiparkinsonism drugs and other central muscle-tone depressants
T40.0X1xx-T40.0X5xx	Poisoning by, adverse effect of opium
T40.1X1xx-T40.1X5xx	Poisoning by, adverse effect of heroin
T40.2X1xx-T40.2X5xx	Poisoning by, adverse effect of other opioids
T40.3X1xx-T40.3X5xx	Poisoning by, adverse effect of methadone
T40.4X1xx-T40.4X5xx	Poisoning by, adverse effect of synthetic narcotics
T40.601xx-T40.605xx	Poisoning by, adverse effect of other and unspecified narcotics
T40.691xx-T40.695xx	Poisoning by, adverse effect of other narcotics
T48.1X1xx-T48.1X5xx	Poisoning by, adverse effect of skeletal muscle relaxants [neuromuscular blocking agents]
T48.3X1xx-T48.3X5xx	Poisoning by, adverse effect of antitussives
T48.5X1xx-T48.5X5xx	Poisoning by, adverse effect of other anti-common-cold drugs
T48.901xx-T48.905xx	Poisoning by, adverse effect of unspecified agents primarily acting on the respiratory system
T48.991xx-T48.995xx	Poisoning by, adverse effect of other agents primarily acting on the respiratory system
T43.3X1xx-T43.3X5xx	Poisoning by, adverse effect of phenothiazine antipsychotics and neuroleptics
T43.4X1xx-T43.4X5xx	Poisoning by, adverse effect of butyrophenone and thiothixene neuroleptics
T43.501xx-T43.505xx	Poisoning by, adverse effect of unspecified antipsychotics and neuroleptics
T43.591xx-T43.595xx	Poisoning by, adverse effect of other antipsychotics and neuroleptics
T43.8X1xx-T43.8X5xx	Poisoning by, adverse effect of other psychotropic drugs
T43.9X1xx-T43.9X5xx	Poisoning by, adverse effect of unspecified psychotropic drug

Table A5. List of Benzodiazepines and Other CNS depressants identified by the FDA*[1]

Generic Name	Brand Name(s)
Benzodiazepines	
alprazolam	Xanax, Xanax XR
chlordiazepoxide	Librium, Librax
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed

lorazepam	Ativan
oxazepam	No brand name currently marketed
quazepam	Doral
temazepam	Restoril
triazolam	Halcion
Other Sleep Drugs and Tranquilizers	
butabarbital sodium	Butisol
eszopiclone	Lunesta
pentobarbital	Nembutal
ramelteon	Rozerem
secobarbital sodium	Seconal sodium
suvorexant	Belsomra
zaleplon	Sonata
zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist
Muscle Relaxants	
baclofen	Gablofen, Lioresal
carisoprodol	Soma, Soma Compound, Soma Compound w/ codeine
chlorzoxazone	No brand name currently marketed
cyclobenzaprine	Amrix
dantrolene	Dantrium, Revonto, Ryanodex
metaxalone	Skelaxin
methocarbamol	Robaxin, Robaxin-750
orphenadrine	No brand name currently marketed
tizanidine	Zanaflex
Antipsychotics	
aripiprazole	Abilify, Abilify Maintena, Aristada
asenapine	Saphris
cariprazine	Vraylar
chlorpromazine	No brand name currently marketed
clozapine	Clozaril, Fazaclo ODT, Versacloz
fluphenazine	No brand name currently marketed
haloperidol	Haldol
iloperidone	Fanapt
loxapine	Adasuve
lurasidone	Latuda
molindone	No brand name currently marketed
olanzapine	Symbyax, Zyprexa, Zyprexa Relprevv, Zyprexa Zydis

paliperidone	Invega, Invega Sustenna, Invega Trinza
perphenazine	No brand name currently marketed
pimavanserin	Nuplazid
quetiapine	Seroquel, Seroquel XR
risperidone	Risperdal, Risperdal Consta
thioridazine	No brand name currently marketed
thiothixene	Navane
trifluoperazine	No brand name currently marketed
ziprasidone	Geodon

*****This is not a comprehensive list.

Table A6. List of Prescription Opioids and Cough Medicines identified by the FDA

Generic Name	**Found in Brand Name(s)**
alfentanil	Alfenta
buprenorphine	Belbuca, Buprenex, Butrans
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Soma Compound w/ codeine, Tylenol w/ codeine, Prometh VC w/ codeine (cough), Triacin-C (cough), Tuzistra-XR (cough)
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER, Flowtuss (cough), Hycofenix (cough), Obredon (cough), Rezira (cough), Tussicaps (cough), Tussigon (cough), Tussionex Pennkinetic (cough), Vituz (cough), Zutripro (cough)
hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER