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Drug Use Evaluation: Gabapentin Use in the FFS Population

Research Questions:

- How have gabapentin prescription claims and dosing patterns changed in relation to opioid claims following the release of the Center for Disease Control (CDC) 2016 guideline for chronic opioid use?
- Has there been an increase in emergency department visits, hospitalizations, or overdoses associated with gabapentin prescription claims since the release of the CDC guidelines?
- Is gabapentin being prescribed appropriately for FDA-approved indications (i.e. postherpetic neuropathy) in the Oregon Health Plan (OHP) fee-for-service (FFS) patient population?

Conclusions:

- Gabapentin utilization in the OHP FFS population has modestly increased by an average of 2 prescriptions per 1000 enrolled members per month over the past three years, which coincides with the publication of the CDC's 2016 Guidelines for chronic opioid use. Increased utilization is due to a 51% increase in new prescriptions, of which less than 15% exceed 90 days. Seventy-five percent of gabapentin claims are prescribed for an average daily dose of less than 1,800 mg/day, which is similar for claims before and after the publication of the CDC recommendations. Daily doses do not appear to be higher in patients with concurrent opioid use.
- There has been no increase in hospitalizations or emergency department (ED) visits associated with a gabapentin prescriptions, based on assessment of claims data. There were 8.9% and 35.6%, respectively, in the pre-cohort and 8.2% and 31.4%, respectively in the post cohort.
- Chronic musculoskeletal pain accounted for 50% of new gabapentin starts despite a lack of evidence for efficacy in this population. Some of this utilization may be related to overall decreases in opioid utilization in the OHP FFS population (32.5% decrease).

Recommendations:

- As there are no clear safety issues identified with this evaluation, no changes are recommended at this time.

Background:

Gabapentin currently has no restrictions or prior authorization (PA) criteria for use by OHP patients. The FDA-approved indications for gabapentin include treatment of partial onset seizures and postherpetic neuralgia. However, it is commonly prescribed for a number of off-label indications. According to a recent report, the volume of gabapentin prescriptions has increased from 2012 to 2016 in the United States (U.S.).[1] In 2016, gabapentin was the tenth most commonly prescribed medication in the U.S. with 64 million prescriptions (compared to 39 million in 2012).[1] This is concerning given increasing off-label use with poor quality evidence to support efficacy in pain management. A 2017 Cochrane meta-analysis examined 37 placebo-controlled trials of gabapentin in a variety of neuropathies (primarily postherpetic and diabetic neuropathy but also including spinal cord injury, phantom limb pain, complex regional pain syndrome, HIV-

associated neuropathy, and radicular leg pain).[2] Evidence was rated as moderate for use in diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) but very low in other neuropathic conditions due to limited data.[2] Small population size, short duration, and inconsistent outcome reporting limited the quality of these studies.[2] The authors concluded gabapentin was likely to provide pain relief at doses of 1,800-3,600 mg/day for postherpetic and diabetic neuropathies (number needed to treat [NNT] 6.9; 95% confidence interval [CI] 5.5 to 9.4 and NNT 6.9; 95% CI 4.6 to 8.3, respectively for 50% or greater reduction in pain relative to placebo).[2] This was limited by a higher rate of adverse events relative to placebo leading to withdrawal of therapy (11 vs. 8.2%, number needed to harm [NNH] 30; 95% CI 20 to 66).[2]

In addition to various off-label uses, increasing gabapentin utilization may be influenced in part by new PA restrictions implemented for opioids following the March 2016 publication of the Centers for Disease Control and Prevention (CDC) Opioid Use in Chronic Pain Guidelines.[3] These guidelines discuss the general lack of evidence for efficacy with chronic opioid use in conjunction with the clear risk of harm associated with higher morphine equivalent doses (MED).[3] As such, caution is recommended with MED greater than or equal to 50 mg/day while MED greater than or equal to 90 mg/day is not recommended.[3] Opioid and gabapentinoid use may be closely connected.[4] An analysis of PA restrictions on pregabalin use in Medicaid patients in two undisclosed states found decreasing pregabalin use associated with a subsequent increase in opioid utilization.[4]

An increase in gabapentin utilization is also concerning given case reports of gabapentin misuse – including but not limited to use of another person's medication, use by non-recommended route of administration, or use of a higher dose than prescribed – which may be increasing concurrently.[5,6] In one study, the estimated prevalence of gabapentin misuse was 1% among the general population and 15% to 22% in patients with a history of opioid abuse.[5] A national sample of law-enforcement and regulatory agencies also reported 407 drug diversion cases with increasing rates over time (from zero cases per 100,000 population in 2002 to 0.027 cases per 100,000 population in 2015).[6] Surveys of law enforcement personnel suggest gabapentin abuse is associated with prescription opioids and heroin abuse.[6] A systematic review published in 2016 gathered 11 epidemiologic studies and 23 case studies describing gabapentin misuse.[5] Over half of these studies identified current substance abuse or history of substance abuse in those misusing gabapentin.[5] In another study, gabapentin misuse was evident in 22% of patients presenting for inpatient opioid detoxification.[7]

Increasing utilization of gabapentin and pregabalin has prompted the publication of an advisory the National Health Service in the United Kingdom on the potential for misuse and abuse with these medications.[8] Concerns for misuse and lack of clinical studies demonstrating efficacy for low back pain of these agents led to a 2017 meta-analysis of gabapentinoid use in chronic back pain.[9] Three randomized controlled trials with an overall low evidence rating due to small sample sizes and a high risk of selection bias were reviewed.[9] Gabapentin was not found to differ from placebo in pain relief as measured by change in 1-10 numerical rating scale (very low level confidence in effect estimate).[9] Over 6 to 12 weeks of treatment, gabapentin was associated with increases in dizziness (NNH 7; 95% CI 4 to 30) and fatigue (NNH 8; 95% CI 4 to 44) when compared to placebo (very low level of confidence in effect estimate).[9] Gabapentin was also associated with a higher incidence of visual disturbance (NNH 6; 95% CI 4 to 13, moderate level of confidence in effect estimate) and difficulties with mentation (NNH 6; 95% CI 4 to 15, low level of confidence in effect estimate).[9]

Gabapentin has also been used off-label for management of postoperative pain.[10] The American Pain Society recommends gabapentin or pregabalin as part of a multimodal pain management strategy in patients undergoing surgery.[10] The evidence for the recommendation was rated as moderate quality based on decreased postoperative pain scores and opioid requirements.[10] Another recent randomized, controlled trial compared gabapentin to placebo and did not find

significant differences in time to pain cessation between the two groups but did see quicker cessation of opioid therapy in the gabapentin group (median 25 days [interquartile range (IQR) 8-53 days] vs. median 32 days [IQR 9-55 days]).[11] Treatment was started preoperatively and continued for 72 hours following surgery.[11]

An analysis completed in a commercial insurance population assessed the use of gabapentin alongside other drugs of abuse using a Lorenz curve from 2013 to 2015.[12] Lorenz curves stratify an amount of medication used or dispensed as a function of time or days covered and are a useful tool for identifying medications that are prone to overuse by a small proportion of the population.[13-16] In the gabapentin analysis, the top 1% of gabapentin utilizers accounted for 19% of use with a mean of 11,274 mg/day and median use of 9,534 mg/day.[12] When simultaneous gabapentin and opioid use was examined, abuse potential (defined as patients with three or more claims exceeding the dose threshold of either 50 MED/day or gabapentin 3,600 mg/day within the past 12 months) occurred in 24% of patients.[12] These findings are particularly concerning given the observations recently published in a case-control study of 1,256 patients with fatal opioid overdose.[17] When comparing these patients to 4,169 controls matched for age, duration on opioids, and disease risk index, gabapentin exposure was associated with an increased risk of death (odds ratio [OR] 1.49; 95% CI: 1.18-1.88) after adjusting for potential confounders.[17] Odds of death increased with doses ≥1,800 mg/day (OR 1.58; 95% CI: 1.09-2.27).[17]

This report aims to gather information on current patterns of gabapentin use in the OHP FFS population including indication, dose, duration of therapy, and risks for gabapentin overdose.

Methods:

To assess utilization and dosing trends, a cross-sectional design was developed to characterize chronic gabapentin use in OHP FFS members. In order to identify average use over a period of time following the publication of the CDC opioid guidelines (Post-CDC Cohort), members were chosen for inclusion on the basis of a paid FFS paid pharmacy claim for gabapentin from 7/1/2016 to 6/30/2017 to allow for a four month period of time for the CDC prescribing recommendations to impact prescribing practices. A historical control group from 2/1/15 to 1/31/16 was chosen prior to publication of the CDC guidelines (Pre-CDC Cohort), to establish trends in utilization and provide a basis for analysis in changes over time. In order to examine chronic gabapentin use, patients were included if they had at least 90 days of continuous gabapentin use during the cohort span (with no more than 14 days gap between the end of one claim and the start of the next claim). To ensure completeness of data, patients had to have at least 75% days of OHP eligibility from the month of their first claim to one month after the end of their last claim during the study period. Patients were excluded if they had any of the following benefit packages which indicate Medicare Part D coverage: benefit packages BMM, BMD, MND, CWM, SMF, SNB, or MED. Patients were also excluded if they had a seizure disorder diagnosis (**Appendices 1 and 2**) from one year prior to the cohort span or any time during the cohort span.

Baseline characteristics, including age, gender, and ethnicity, are presented in **Table 1**. Average daily dose (ADD) of gabapentin for each patient was calculated as (strength * quantity dispensed / day supply) for each claim, and averaged for each patient. Concurrent opioid use was determined on the basis of a paid FFS pharmacy claim for any prescription opioid listed in **Appendix 3** for at least 90 days concurrently with gabapentin claims. Average and median daily gabapentin dose was calculated for the patients in both cohorts which was further analyzed based on concomitant opioid use (presented in **Table 2**).

All-cause hospitalizations and ED visits within 30 days of a paid gabapentin claim were also recorded for these patients based on billing codes (**Appendix 4**). Comparisons were made between the two cohorts and included breakdowns based on daily gabapentin dose (greater than 1,800 mg to 2,400 mg, greater than 2,400 mg to 3,600 mg, and greater than 3,600 mg).

In order to assess changes in utilization over time, overall FFS gabapentin and opioid pharmacy utilization trends are shown in **Figure 1** from 2015 to the present, reported as unique utilizing members per enrolled member per month (PMPM).

To assess prescribing trends, patients starting gabapentin (new starts) were also compared during the same pre- and post-CDC guideline time periods described above. A new start is defined as a patient with a gabapentin claim and no other gabapentin claims in the previous 6 months. The first claim is called the index event. In order to be included for this analysis, patients had to have 75% OHP eligibility in the 6 months prior to the index date. As described previously, patients were excluded for having a seizure diagnosis or Medicare Part D coverage. Patients were also excluded if the gabapentin claim was for 15 days or less as these would likely be peri-procedural. Indications were identified within the six months prior to the index date. These were categorized as FDA approved, non-FDA approved but with evidence for use, non-FDA approved without evidence for use, and no indication found (**Table 3**). If an FDA-approved indication is identified, no further search for off-label indications were performed. Similarly, indications with evidence for use were chosen regardless of whether the patient had other indications that the gabapentin could have been prescribed for. A list of all ICD codes and characterizations appears in **Appendices 1 and 2**.

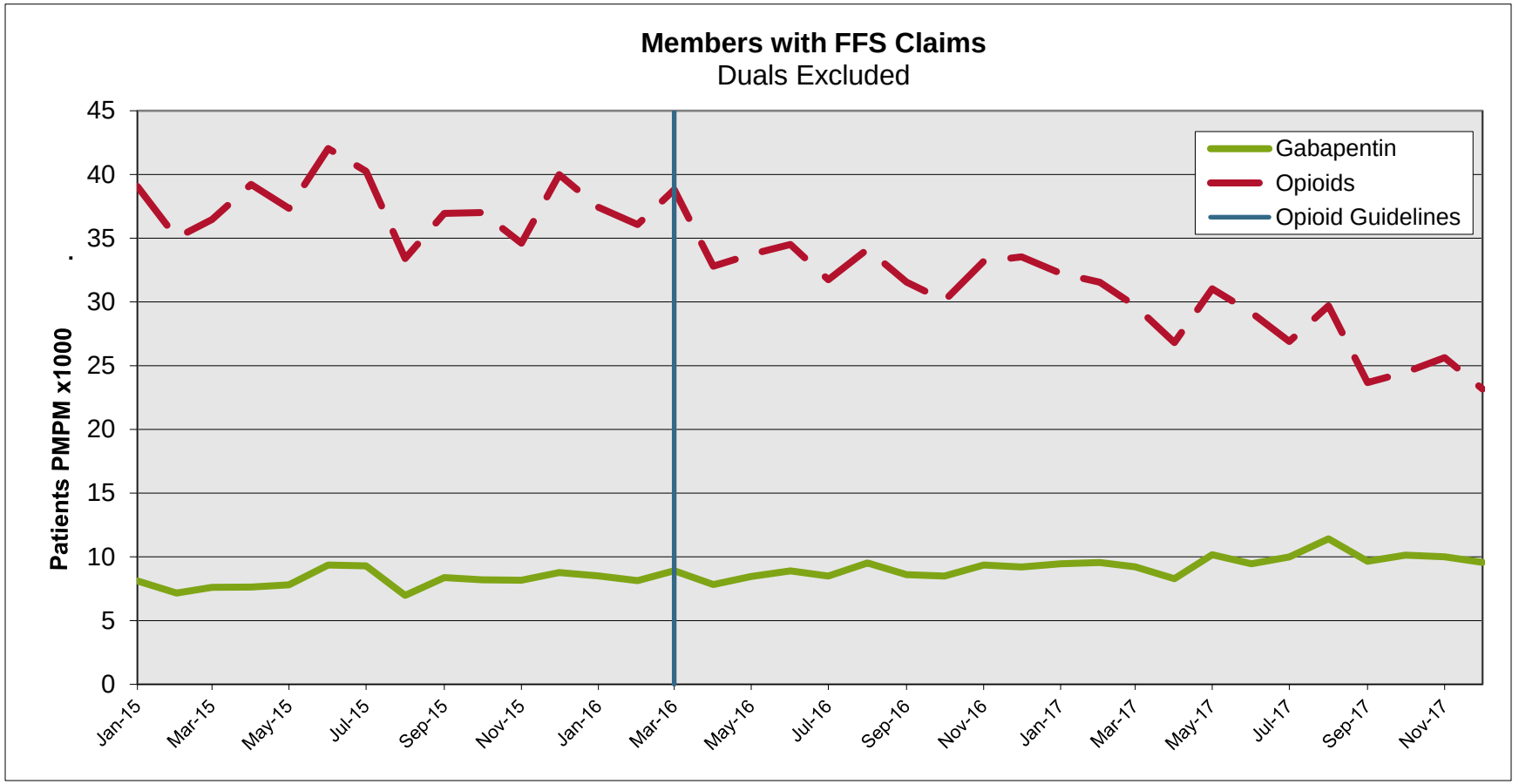
Results:

Table 1. Demographics of Chronic Gabapentin Users

	Pre Cohort		Post Cohort	
N=	828		894	
Average Age (min/max)	46	(6-75)	45	(8-75)
<19	15	1.8%	15	1.7%
19-64	808	97.6%	869	97.2%
>64	5	0.6%	10	1.1%
Female	567	68.5%	606	67.8%
White	457	55.2%	429	48.0%

Demographics of chronic gabapentin users in the OHP FFS population are presented in **Table 1**. Around two-thirds of the study population are female with 51.5% of them being Caucasian with an average age of 45-46 years.

Figure 1. Total Monthly Prescriptions for Gabapentin and Opioids from 1/1/15 to 8/30/17



Overall, gabapentin utilization in the FFS population increased an average of 2 claims x 1000 PMPM from January 2015 to December 2017. (**Figure 1**). During this same time period, opioid utilization decreased an average of 14 claims x 1000 PMPM.

Table 2. Chronic Gabapentin Dosing Pre- and Post-CDC Guideline Publication

	Pre Cohort						Post Cohort					
	Overall		With Opioid		Without Opioid		Overall		With Opioid		Without Opioid	
N=	828		203	24.5%	625	75.5%	894		174	19.5%	720	80.5%
Average Daily Dose	1,334		1,532		1,270		1,329		1,611		1,261	
Median Daily Dose	1,138		1,200		900		1,018		1,572		900	
By Max Dose												
>3600 mg/day	10	1.2%	4	2.0%	6	1.0%	7	0.8%	1	0.6%	6	0.8%
>2700 mg/day	58	7.0%	18	8.9%	40	6.4%	69	7.7%	19	10.9%	50	6.9%
>1800 mg/day	140	16.9%	42	20.7%	98	15.7%	143	16.0%	39	22.4%	104	14.4%
>900 mg/day	259	31.3%	69	34.0%	190	30.4%	277	31.0%	58	33.3%	219	30.4%
<=900 mg/day	361	43.6%	70	34.5%	291	46.6%	398	44.5%	57	32.8%	341	47.4%

There was more chronic gabapentin use in the post CDC-guideline cohort compared to the pre-CDC guideline cohort (894 vs. 828, respectively) (**Table 2**). The number of chronic gabapentin users co-prescribed an opioid decreased by 5% (from 24.5% to 19.5%); these patients received on average 300-400 mg higher daily doses of gabapentin than those without a concurrent opioid. Approximately 75% of patients received daily gabapentin doses of 1,800 mg or less with about 45% of patients receiving daily doses less than 900 mg. The gabapentin average daily dose between the two cohorts is largely unchanged.

Despite the increased utilization, gabapentin use associated with a hospitalization or ED visit was largely unchanged in chronic users. Percentage of chronic gabapentin users with a hospitalization or ED visit within 30 days following a paid gabapentin claim were 8.9% and 35.6%, respectively, in the pre-cohort and 8.2% and 31.4%, respectively, in the post-cohort. Hospitalization or ED visits occurred in 94 (out of 208) patients in the pre-cohort and 100 (out of 219) patients in the post-cohort with an average daily dose greater than 1,800 mg. Relative percentage of patients with a hospitalization or ED visit in the two cohorts was similar across different dosing thresholds.

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Table 3. Gabapentin Users by Indication in 6 Months Prior to New Start

	Pre Cohort		Post Cohort	
N=	2,105		3,189	
FDA Approved	**32**	**1.5%**	**37**	**1.2%**
Postherpetic neuropathy	32	1.5%	37	1.2%
With diabetes	4	0.2%	4	0.1%
Non-FDA approved with evidence for use	**88**	**4.2%**	**7**	**0.2%**
Diabetic neuropathy	76	3.6%		0.0%
Neuropathy (painful polyneuropathy, phantom limb pain, chemotherapy-induced neuropathy, spinal cord injury pain)	12	0.6%	7	0.2%
With diabetes	78	3.7%	0	0.0%
Non-FDA approved without evidence for use	**1,167**	**55.4%**	**1,895**	**59.4%**
Neuropathy (HIV neuropathy, central post-stroke pain, trigeminal neuralgia)	722	34.3%	612	19.2%
Migraine headache prophylaxis	169	8.0%	255	8.0%
Chronic musculoskeletal pain	523	24.8%	1,416	44.4%
By Total Days Supply				
<= 30	343	65.6%	1,021	72.1%
>30 and <=90	115	22.0%	251	17.7%
>90	65	12.4%	144	10.2%
Fibromyalgia	247	11.7%	243	7.6%
With diabetes	187	8.9%	384	12.0%
Any of the Above	**1,287**	**61.1%**	**1,939**	**60.8%**
With diabetes	269	12.8%	388	12.2%
None of the Above	**818**	**38.9%**	**1,250**	**39.2%**
With diabetes	157	7.5%	281	8.8%

Table 4. Gabapentin New Starts by Total Day Supply in Cohort Span
Note: Patients with 15 days' supply or less were excluded

	Patient Count			
	Pre Cohort		Post Cohort	
N=	2,105		3,189	
Total days' supply				
<= 30	1,352	64.2%	2,234	70.1%
>30 and <=90	439	20.9%	596	18.7%
>90	314	14.9%	359	11.3%

The number of new patients starting on gabapentin between the two cohorts increased by 51% between 2/1/15-1/31/16 and 7/1/2016-6/30/2017 (**Table 3).** Fewer patients were identified in the post-cohort as having diabetic neuropathy compared to the pre-cohort. Conversely, more patients were identified as having some form of chronic musculoskeletal pain in the post-cohort (44.4%) compared to the pre-cohort (24.8%). However, the percentage of patients with a diagnosis of diabetes was largely unchanged between the two time periods (20.2% and 20.9% for the pre- and post-cohorts, respectively). Compelling indications for use were not readily apparent in a majority of patients in either the pre- or post-cohorts. Patients in the post-cohort, identified as having chronic musculoskeletal pain, used gabapentin for a shorter period of time compared to the pre-cohort, a trend that was observed in overall utilization by patients in the post-cohort (**Table 4**).

Discussion:

Overall, increased gabapentin utilization in the OHP FFS population following the publication of the 2016 CDC opioid guidelines has been modest. Based on FFS claims data more patients were initiated on gabapentin, but most patients only received a short-term supply of gabapentin, with few repeated claims indicating possible chronic use. However, much of this use seems to be for indications without compelling evidence for use, as a large percentage of patients appeared to receive gabapentin for chronic musculoskeletal pain (44%). Off-label use may be related in part to Guideline Note 60 on the OHP Prioritized List which restricts approval of opioid claims for back and spine conditions to acute use only. In addition, recent changes to the FFS opioid PA criteria that aims to decrease long-term use and restrict daily doses to 90 mg morphine equivalents/day or less may be encouraging providers to prescribe alternative medications for pain management.

Of note, many of the patients on chronic gabapentin do not seem to be receiving evidence-based doses (1,800 mg/day or higher). However, this is difficult to accurately assess as gabapentin requires renal dose adjustments and analysis of renal function cannot be calculated based on claims data. Based on the average age of the patients who received gabapentin (19-64), this is unlikely a factor. It is unclear from these data if short term utilization (less than 15% of prescriptions

were over 90 days in length) is related to discontinuation due to side effects of gabapentin versus a trial of use stopped prior to reaching a therapeutic dose. The lower doses observed in claims data may also reflect patients in the midst of titrating upwards on gabapentin therapy.

Between the pre- and post-cohorts, there was a decrease in the number of patients co-prescribed gabapentin and opioids (203 vs. 174 [24.5% vs. 19.5%], respectively) with an increase in the number of patients co-prescribed opioids (625 compared to 720 [75.5% vs. 80.5%], respectively). Much of this may be related to the changes in opioid management policies for OHP FFS patients that have placed larger restrictions on opioid prescribing. A difference in the relative number of patients reaching doses 1,800 mg/day or greater is not apparent between the pre- and post-cohorts. Patients with a concurrent opioid prescription claims were more likely to have higher gabapentin doses compared with patients not taking opioids, 21% compared to 15% for daily doses of 1,800 mg to less than 2,700 mg/day and 10% compared to 7% for daily doses 2,700 mg to less than 3,600 mg/day.

In summary, gabapentin use seems to be modestly increasing as opioid use decreases without an apparent increase in utilization of emergency services or hospitalization. In the FFS population, a large majority of utilization is for short durations of therapy and is prescribed for patients with diagnoses of musculoskeletal pain. There is insufficient evidence to support the use of gabapentin in musculoskeletal pain. Additionally, doses seen in Oregon Medicaid patients who use gabapentin chronically are lower than the therapeutic doses found to have efficacy in randomized, clinical trials (≥1800 mg/day). Given that more than two-thirds of OHP patients have received gabapentin for 30 days or less, it is possible that ineffectiveness or adverse effects were a factor that impacted duration of therapy. Currently there are no PA criteria for gabapentin and although use has increased, much of this seems to be as an alternative to opioid therapy. Creating a barrier to this use may drive prescribing back to opioids which have clear risks of harm, something that is not immediately apparent in these data with gabapentin. Future research exploring use in the Medicaid population managed by the Coordinated Care Organizations may reveal differences from this analysis as these insurers are more likely to retain patients longer than FFS.

Limitations:

These data are not without their limitations since examination of claims data is accompanied with a large number of assumptions. For one, just because a patient picked up a prescription for gabapentin does not mean they adhered to prescribing recommendations. Conversely, just because there is not a claim does not mean a patient did not pay cash or obtain gabapentin through some other means. There are also limitations evident in the stratification of gabapentin usage by disease state. Per data analysis of specific ICD9/10 codes for diabetic neuropathy, it appears gabapentin use has decreased, but when general ICD9/10 codes for diabetes as a whole were analyzed, both the pre- and post- cohort had a similar percentage of patients with a diagnosis of diabetes. This may be due to the differences in the complexity of the two coding systems and the wide array of available diagnoses that ICD10 offers. Similarly, an examination of hospitalization and ED visits can only be done through the correlation of claims data, making it difficult to conclude that gabapentin use is necessarily what drove the patient to seek that care.

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Appendix 1: ICD9 codes

Seizures
345 Epilepsy and recurrent seizures
Postherpetic neuropathy
053 Herpes zoster
Diabetic neuropathy
357.2 Polyneuropathy in diabetes
249.6 Secondary diabetes mellitus with neurological manifestations
250.6 Diabetes with neurological manifestations
Neuropathy with evidence for use (phantom limb pain, chemotherapy-induced neuropathy, spinal cord injury pain)
353.6 Phantom limb (syndrome)
357.3 Polyneuropathy in malignant disease
952 Spinal cord injury without evidence of spinal bone injury
Non-evidenced neuropathy (HIV neuropathy, central post-stroke pain, trigeminal neuralgia, other neuropathy)
350 Trigeminal nerve disorders
042 Human immunodeficiency virus [HIV] disease
430 Subarachnoid hemorrhage
431 Intracerebral hemorrhage
432 Other and unspecified intracranial hemorrhage
433 Occlusion and stenosis of precerebral arteries
434 Occlusion of cerebral arteries
435 Transient cerebral ischemia
436 Acute, but ill-defined, cerebrovascular disease
437 Other and ill-defined cerebrovascular disease
438 Late effects of cerebrovascular disease
953 Injury to nerve roots and spinal plexus
954 Injury to other nerve(s) of trunk excluding shoulder and pelvic girdles
955 Injury to peripheral nerve(s) of shoulder girdle and upper limb
956 Injury to peripheral nerve(s) of pelvic girdle and lower limb
957 Injury to other and unspecified nerves
729.2 Neuralgia, neuritis, and radiculitis, unspecified
338 Pain, not elsewhere classified
355 Mononeuritis of lower limb and unspecified site
356 Hereditary and idiopathic peripheral neuropathy
357.0 Acute infective polyneuritis
357.1 Polyneuropathy in collagen vascular disease
357.4 Polyneuropathy in other diseases classified elsewhere
357.5 Alcoholic polyneuropathy
357.6 Polyneuropathy due to drugs
357.7 Polyneuropathy due to other toxic agents
357.8 Other inflammatory and toxic neuropathy
357.81 Chronic inflammatory demyelinating polyneuritis
357.82 Critical illness polyneuropathy
357.89 Other inflammatory and toxic neuropathy
357.9 Unspecified inflammatory and toxic neuropathy
Migraine headache prophylaxis
346 Migraine
Chronic musculoskeletal pain
720 Ankylosing spondylitis and other inflammatory spondylopathies
721 Spondylosis and allied disorders
722 Intervertebral disc disorders
Fibromyalgia
729.1 Fibromyalgia
Diabetes
249.XXX-250.XXX

Appendix 2: ICD10 Codes

Seizures
G40 Epilepsy and recurrent seizures
Postherpetic neuropathy
B02 Zoster [herpes zoster]
Diabetic neuropathy
E08.40 Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified
E08.41 Diabetes mellitus due to underlying condition with diabetic mononeuropathy
E08.42 Diabetes mellitus due to underlying condition with diabetic polyneuropathy
E08.43 Diabetes mellitus due to underlying condition with diabetic autonomic (poly)neuropathy
E08.44 Diabetes mellitus due to underlying condition with diabetic amyotrophy
E08.49 Diabetes mellitus due to underlying condition with other diabetic neurological complication
E08.610 Diabetes mellitus due to underlying condition with diabetic neuropathic arthropathy
E09.40 Drug or chemical induced diabetes mellitus with neurological complications with diabetic neuropathy, unspecified
E09.41 Drug or chemical induced diabetes mellitus with neurological complications with diabetic mononeuropathy
E09.42 Drug or chemical induced diabetes mellitus with neurological complications with diabetic polyneuropathy
E09.43 Drug or chemical induced diabetes mellitus with neurological complications with diabetic autonomic (poly)neuropathy
E09.44 Drug or chemical induced diabetes mellitus with neurological complications with diabetic amyotrophy
E09.49 Drug or chemical induced diabetes mellitus with neurological complications with other diabetic neurological complication
E09.610 Drug or chemical induced diabetes mellitus with diabetic neuropathic arthropathy
E10.40 Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41 Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42 Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43 Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44 Type 1 diabetes mellitus with diabetic amyotrophy
E10.49 Type 1 diabetes mellitus with other diabetic neurological complication
E10.610 Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E11.40 Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41 Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42 Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43 Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44 Type 2 diabetes mellitus with diabetic amyotrophy
E11.49 Type 2 diabetes mellitus with other diabetic neurological complication
E11.610 Type 2 diabetes mellitus with diabetic neuropathic arthropathy
E13.40 Other specified diabetes mellitus with diabetic neuropathy, unspecified
E13.41 Other specified diabetes mellitus with diabetic mononeuropathy
E13.42 Other specified diabetes mellitus with diabetic polyneuropathy
E13.43 Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy
E13.44 Other specified diabetes mellitus with diabetic amyotrophy
E13.49 Other specified diabetes mellitus with other diabetic neurological complication
E13.610 Other specified diabetes mellitus with diabetic neuropathic arthropathy
Neuropathy with evidence for use (phantom limb pain, chemotherapy-induced neuropathy, spinal cord injury pain)
G54.6 Phantom limb syndrome with pain
G13.0 Paraneoplastic neuromyopathy and neuropathy
S34 Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level
Non-evidenced neuropathy (HIV neuropathy, central post-stroke pain, trigeminal neuralgia, other neuropathy)
G50 Disorders of trigeminal nerve
B20 Human immunodeficiency virus [HIV] disease
I60 Nontraumatic subarachnoid hemorrhage
I61 Nontraumatic intracerebral hemorrhage
I62 Other and unspecified nontraumatic intracranial hemorrhage
I63 Cerebral Infarction
I67 Other cerebrovascular diseases
I69 Sequelae of cerebrovascular disease
B26.84 Mumps polyneuropathy
G13.1 Other systemic atrophy primarily affecting central nervous system in neoplastic disease
G50.1 Atypical facial pain
G51.0 Bell's palsy
G51.1 Geniculate ganglionitis
G51.2 Melkersson's syndrome
G51.3 Clonic hemifacial spasm
G51.4 Facial myokymia
G51.8 Other disorders of facial nerve
G51.9 Disorder of facial nerve, unspecified
G52.0 Disorders of olfactory nerve
G52.1 Disorders of glossopharyngeal nerve
G52.2 Disorders of vagus nerve
G52.3 Disorders of hypoglossal nerve
G52.7 Disorders of multiple cranial nerves
G52.8 Disorders of other specified cranial nerves
G52.9 Cranial nerve disorder, unspecified
G53 Cranial nerve disorders in diseases classified elsewhere
G54.0 Brachial plexus disorders
G54.1 Lumbosacral plexus disorders
G54.2 Cervical root disorders, not elsewhere classified
G54.3 Thoracic root disorders, not elsewhere classified
G54.4 Lumbosacral root disorders, not elsewhere classified
G54.5 Neuralgic amyotrophy
G54.8 Other nerve root and plexus disorders
G54.9 Nerve root and plexus disorder, unspecified
G55 Nerve root and plexus compressions in diseases classified elsewhere

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G56.00 Carpal tunnel syndrome, unspecified upper limb
G56.01 Carpal tunnel syndrome, right upper limb
G56.02 Carpal tunnel syndrome, left upper limb
G56.03 Carpal tunnel syndrome, bilateral upper limbs
G56.10 Other lesions of median nerve, unspecified upper limb
G56.11 Other lesions of median nerve, right upper limb
G56.12 Other lesions of median nerve, left upper limb
G56.13 Other lesions of median nerve, bilateral upper limbs
G56.20 Lesion of ulnar nerve, unspecified upper limb
G56.21 Lesion of ulnar nerve, right upper limb
G56.22 Lesion of ulnar nerve, left upper limb
G56.23 Lesion of ulnar nerve, bilateral upper limbs
G56.30 Lesion of radial nerve, unspecified upper limb
G56.31 Lesion of radial nerve, right upper limb
G56.32 Lesion of radial nerve, left upper limb
G56.33 Lesion of radial nerve, bilateral upper limbs
G56.40 Causalgia of unspecified upper limb
G56.41 Causalgia of right upper limb
G56.42 Causalgia of left upper limb
G56.43 Causalgia of bilateral upper limbs
G56.80 Other specified mononeuropathies of unspecified upper limb
G56.81 Other specified mononeuropathies of right upper limb
G56.82 Other specified mononeuropathies of left upper limb
G56.83 Other specified mononeuropathies of bilateral upper limbs
G56.90 Unspecified mononeuropathy of unspecified upper limb
G56.91 Unspecified mononeuropathy of right upper limb
G56.92 Unspecified mononeuropathy of left upper limb
G56.93 Unspecified mononeuropathy of bilateral upper limbs
G57.00 Lesion of sciatic nerve, unspecified lower limb
G57.01 Lesion of sciatic nerve, right lower limb
G57.02 Lesion of sciatic nerve, left lower limb
G57.03 Lesion of sciatic nerve, bilateral lower limbs
G57.10 Meralgia paresthetica, unspecified lower limb
G57.11 Meralgia paresthetica, right lower limb
G57.12 Meralgia paresthetica, left lower limb
G57.13 Meralgia paresthetica, bilateral lower limbs
G57.20 Lesion of femoral nerve, unspecified lower limb
G57.21 Lesion of femoral nerve, right lower limb
G57.22 Lesion of femoral nerve, left lower limb
G57.23 Lesion of femoral nerve, bilateral lower limbs
G57.30 Lesion of lateral popliteal nerve, unspecified lower limb
G57.31 Lesion of lateral popliteal nerve, right lower limb
G57.32 Lesion of lateral popliteal nerve, left lower limb
G57.33 Lesion of lateral popliteal nerve, bilateral lower limbs
G57.40 Lesion of medial popliteal nerve, unspecified lower limb
G57.41 Lesion of medial popliteal nerve, right lower limb
G57.42 Lesion of medial popliteal nerve, left lower limb
G57.43 Lesion of medial popliteal nerve, bilateral lower limbs
G57.50 Tarsal tunnel syndrome, unspecified lower limb
G57.51 Tarsal tunnel syndrome, right lower limb
G57.52 Tarsal tunnel syndrome, left lower limb
G57.53 Tarsal tunnel syndrome, bilateral lower limbs
G57.60 Lesion of plantar nerve, unspecified lower limb
G57.61 Lesion of plantar nerve, right lower limb
G57.62 Lesion of plantar nerve, left lower limb
G57.63 Lesion of plantar nerve, bilateral lower limbs
G57.70 Causalgia of unspecified lower limb
G57.71 Causalgia of right lower limb
G57.72 Causalgia of left lower limb
G57.73 Causalgia of bilateral lower limbs
G57.80 Other specified mononeuropathies of unspecified lower limb
G57.81 Other specified mononeuropathies of right lower limb
G57.82 Other specified mononeuropathies of left lower limb
G57.83 Other specified mononeuropathies of bilateral lower limbs
G57.90 Unspecified mononeuropathy of unspecified lower limb
G57.91 Unspecified mononeuropathy of right lower limb
G57.92 Unspecified mononeuropathy of left lower limb
G57.93 Unspecified mononeuropathy of bilateral lower limbs
G58.0 Intercostal neuropathy
G58.7 Mononeuritis multiplex
G58.8 Other specified mononeuropathies
G58.9 Mononeuropathy, unspecified
G59 Mononeuropathy in diseases classified elsewhere
G60.0 Hereditary motor and sensory neuropathy
G60.2 Neuropathy in association with hereditary ataxia
G60.3 Idiopathic progressive neuropathy
G60.8 Other hereditary and idiopathic neuropathies
G60.9 Hereditary and idiopathic neuropathy, unspecified
G61.1 Serum neuropathy
G61.81 Chronic inflammatory demyelinating polyneuritis
G61.82 Multifocal motor neuropathy
G61.89 Other inflammatory polyneuropathies
G61.9 Inflammatory polyneuropathy, unspecified
G62.0 Drug-induced polyneuropathy
G62.1 Alcoholic polyneuropathy
G62.2 Polyneuropathy due to other toxic agents
G62.81 Critical illness polyneuropathy
G62.82 Radiation-induced polyneuropathy
G62.89 Other specified polyneuropathies
G62.9 Polyneuropathy, unspecified
G63 Polyneuropathy in diseases classified elsewhere
G64 Other disorders of peripheral nervous system
G65.0 Sequelae of Guillain-Barré syndrome
G65.1 Sequelae of other inflammatory polyneuropathy
G65.2 Sequelae of toxic polyneuropathy
G70.1 Toxic myoneural disorders
G70.2 Congenital and developmental myasthenia
G70.89 Other specified myoneural disorders
G70.9 Myoneural disorder, unspecified
G83.4 Cauda equina syndrome
G90.01 Carotid sinus syncope

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G90.09 Other idiopathic peripheral autonomic neuropathy
G90.2 Horner's syndrome
G90.4 Autonomic dysreflexia
G90.50 Complex regional pain syndrome I, unspecified
G90.511 Complex regional pain syndrome I of right upper limb
G90.512 Complex regional pain syndrome I of left upper limb
G90.513 Complex regional pain syndrome I of upper limb, bilateral
G90.519 Complex regional pain syndrome I of unspecified upper limb
G90.521 Complex regional pain syndrome I of right lower limb
G90.522 Complex regional pain syndrome I of left lower limb
G90.523 Complex regional pain syndrome I of lower limb, bilateral
G90.529 Complex regional pain syndrome I of unspecified lower limb
G90.59 Complex regional pain syndrome I of other specified site
G90.8 Other disorders of autonomic nervous system
G90.9 Disorder of the autonomic nervous system, unspecified
G99.0 Autonomic neuropathy in diseases classified elsewhere

M21.331 Wrist drop, right wrist
M21.332 Wrist drop, left wrist
M21.339 Wrist drop, unspecified wrist
M21.511 Acquired clawhand, right hand
M21.512 Acquired clawhand, left hand
M21.519 Acquired clawhand, unspecified hand
M21.521 Acquired clubhand, right hand
M21.522 Acquired clubhand, left hand
M21.529 Acquired clubhand, unspecified hand
M21.531 Acquired clawfoot, right foot
M21.532 Acquired clawfoot, left foot
M21.539 Acquired clawfoot, unspecified foot
M34.83 Systemic sclerosis with polyneuropathy
M79.2 Neuralgia and neuritis, unspecified
S04 Injury of cranial nerve
S14 Injury of nerves and spinal cord at neck level
S24 Injury of nerves and spinal cord at thorax level
S34 Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level

S44 Injury of nerves at shoulder and upper arm level
S54 Injury of nerves at forearm level
S64 Injury of nerves at wrist and hand level
S74 Injury of nerves at hip and thigh level
S84 Injury of nerves at lower leg level
S94 Injury of nerves at ankle and foot level
Migraine headache prophylaxis
G43 Migraine
Chronic musculoskeletal pain
M50 Cervical disc disorders
M51 Thoracic, thoracolumbar, and lumbosacral...
M53 Other and unspecified dorsopathies, not ...
M54 Dorsalgia
Fibromyalgia
M79.7 Fibromyalgia
Diabetes
E08XXX-E13.XXX

Appendix 3: List of Opioids

GENERIC NAME	BRAND NAME	FORM
ACETAMINOPHEN WITH CODEINE	ACETAMINOPHEN W/CODEINE	ELIXIR
ACETAMINOPHEN WITH CODEINE	ACETAMINOPHEN-CODEINE	SOLUTION
ACETAMINOPHEN WITH CODEINE	ACETAMINOPHEN-CODEINE	TABLET
ACETAMINOPHEN WITH CODEINE	CAPITAL W-CODEINE	ORAL SUSP
ACETAMINOPHEN WITH CODEINE	TYLENOL-CODEINE NO.3	TABLET
ACETAMINOPHEN WITH CODEINE	TYLENOL-CODEINE NO.4	TABLET
BUPRENORPHINE	BUPRENORPHINE	PATCH TDWK
BUPRENORPHINE	BUTRANS	PATCH TDWK
BUPRENORPHINE HCL	BELBUCA	FILM
BUTALBIT/ACETAMIN/CAFF/CODEINE	BUTALB-ACETAMINOPH-CAFF-CODEIN	CAPSULE
BUTALBIT/ACETAMIN/CAFF/CODEINE	FIORICET WITH CODEINE	CAPSULE
BUTORPHANOL TARTRATE	BUTORPHANOL TARTRATE	SPRAY
CODEINE SULFATE	CODEINE SULFATE	TABLET
CODEINE/BUTALBITAL/ASA/CAFFEIN	ASA-BUTALB-CAFFEINE-CODEINE	CAPSULE
CODEINE/BUTALBITAL/ASA/CAFFEIN	ASCOMP WITH CODEINE	CAPSULE
CODEINE/BUTALBITAL/ASA/CAFFEIN	BUTALBITAL COMPOUND-CODEINE	CAPSULE
CODEINE/BUTALBITAL/ASA/CAFFEIN	FIORINAL WITH CODEINE #3	CAPSULE
FENTANYL	DURAGESIC	PATCH TD72
FENTANYL	FENTANYL	PATCH TD72
FENTANYL	SUBSYS	SPRAY
FENTANYL CITRATE	ABSTRAL	TAB SUBL
FENTANYL CITRATE	ACTIQ	LOZENGE HD
FENTANYL CITRATE	FENTANYL CITRATE	LOZENGE HD
FENTANYL CITRATE	FENTORA	TABLET EFF

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FENTANYL CITRATE	LAZANDA	SPRAY/PUMP
HYDROCODONE BITARTRATE	HYSINGLA ER	TAB ER 24H
HYDROCODONE BITARTRATE	ZOHYDRO ER	CAP ER 12H
HYDROCODONE/ACETAMINOPHEN	CO-GESIC	TABLET
HYDROCODONE/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	SOLUTION
HYDROCODONE/ACETAMINOPHEN	HYDROCODONE-ACETAMINOPHEN	TABLET
HYDROCODONE/ACETAMINOPHEN	LORCET	TABLET
HYDROCODONE/ACETAMINOPHEN	LORCET HD	TABLET
HYDROCODONE/ACETAMINOPHEN	LORCET PLUS	TABLET
HYDROCODONE/ACETAMINOPHEN	LORTAB	SOLUTION
HYDROCODONE/ACETAMINOPHEN	LORTAB	TABLET
HYDROCODONE/ACETAMINOPHEN	NORCO	TABLET
HYDROCODONE/ACETAMINOPHEN	VICODIN	TABLET
HYDROCODONE/ACETAMINOPHEN	VICODIN ES	TABLET
HYDROCODONE/ACETAMINOPHEN	VICODIN HP	TABLET
HYDROCODONE/ACETAMINOPHEN	ZAMICET	SOLUTION
HYDROCODONE/IBUPROFEN	HYDROCODONE-IBUPROFEN	TABLET
HYDROCODONE/IBUPROFEN	IBUDONE	TABLET
HYDROCODONE/IBUPROFEN	REPREXAIN	TABLET
HYDROCODONE/IBUPROFEN	XYLON 10	TABLET
HYDROMORPHONE HCL	DILAUDID	LIQUID
HYDROMORPHONE HCL	DILAUDID	TABLET
HYDROMORPHONE HCL	EXALGO	TAB ER 24H
HYDROMORPHONE HCL	HYDROMORPHONE ER	TAB ER 24H
HYDROMORPHONE HCL	HYDROMORPHONE HCL	LIQUID
HYDROMORPHONE HCL	HYDROMORPHONE HCL	SUPP.RECT
HYDROMORPHONE HCL	HYDROMORPHONE HCL	TABLET
IBUPROFEN/OXYCODONE HCL	OXYCODONE HCL-IBUPROFEN	TABLET
LEVORPHANOL TARTRATE	LEVORPHANOL TARTRATE	TABLET
MEPERIDINE HCL	DEMEROL	TABLET
MEPERIDINE HCL	MEPERIDINE HCL	SOLUTION
MEPERIDINE HCL	MEPERIDINE HCL	TABLET
METHADONE HCL	DISKETS	TABLET SOL
METHADONE HCL	DOLOPHINE HCL	TABLET
METHADONE HCL	METHADONE HCL	ORAL CONC
METHADONE HCL	METHADONE HCL	SOLUTION
METHADONE HCL	METHADONE HCL	TABLET
METHADONE HCL	METHADONE HCL	TABLET SOL
METHADONE HCL	METHADONE INTENSOL	ORAL CONC
METHADONE HCL	METHADOSE	ORAL CONC
METHADONE HCL	METHADOSE	TABLET SOL
MORPHINE SULFATE	ARYMO ER	TAB PO ER
MORPHINE SULFATE	KADIAN	CAP ER PEL
MORPHINE SULFATE	MORPHINE SULFATE	SOLUTION
MORPHINE SULFATE	MORPHINE SULFATE	SUPP.RECT
MORPHINE SULFATE	MORPHINE SULFATE	SYRINGE
MORPHINE SULFATE	MORPHINE SULFATE	TABLET
MORPHINE SULFATE	MORPHINE SULFATE ER	CAP ER PEL
MORPHINE SULFATE	MORPHINE SULFATE ER	CPMP 24HR
MORPHINE SULFATE	MORPHINE SULFATE ER	TABLET ER
MORPHINE SULFATE	MS CONTIN	TABLET ER
MORPHINE SULFATE/NALTREXONE	EMBEDA	CAP ER PO
OPIUM/BELLADONNA ALKALOIDS	BELLADONNA-OPIUM	SUPP.RECT
OXYCODONE HCL	OXAYDO	TABLET ORL
OXYCODONE HCL	OXYCODONE HCL	CAPSULE
OXYCODONE HCL	OXYCODONE HCL	ORAL CONC
OXYCODONE HCL	OXYCODONE HCL	SOLUTION
OXYCODONE HCL	OXYCODONE HCL	SYRINGE
OXYCODONE HCL	OXYCODONE HCL	TABLET
OXYCODONE HCL	OXYCODONE HCL ER	TAB ER 12H
OXYCODONE HCL	OXYCONTIN	TAB ER 12H
OXYCODONE HCL	ROXICODONE	TABLET
OXYCODONE HCL/ACETAMINOPHEN	ENDOCET	TABLET
OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	SOLUTION
OXYCODONE HCL/ACETAMINOPHEN	OXYCODONE-ACETAMINOPHEN	TABLET
OXYCODONE HCL/ACETAMINOPHEN	PERCOCET	TABLET
OXYCODONE HCL/ACETAMINOPHEN	PRIMLEV	TABLET
OXYCODONE HCL/ASPIRIN	OXYCODONE HCL-ASPIRIN	TABLET

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OXYCODONE MYRISTATE	XTAMPZA ER	CAP SPR 12
OXYMORPHONE HCL	OPANA	TABLET
OXYMORPHONE HCL	OPANA ER	TAB ER 12H
OXYMORPHONE HCL	OXYMORPHONE HCL	TABLET
OXYMORPHONE HCL	OXYMORPHONE HCL ER	TAB ER 12H
PENTAZOCINE HCL/NALOXONE HCL	PENTAZOCINE-NALOXONE HCL	TABLET
PROPOXYPHENE HCL	PROPOXYPHENE HCL	CAPSULE
PROPOXYPHENE HCL/ACETAMINOPHEN	PROPOXYPHENE HCL-ACETAMINOPHEN	TABLET
TAPENTADOL HCL	NUCYNTA	TABLET
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H

TRAMADOL HCL	CONZIP	CPBP 17-83
TRAMADOL HCL	CONZIP	CPBP 25-75
TRAMADOL HCL	TRAMADOL HCL	TABLET
TRAMADOL HCL	TRAMADOL HCL ER	CPBP 17-83
TRAMADOL HCL	TRAMADOL HCL ER	CPBP 25-75
TRAMADOL HCL	TRAMADOL HCL ER	TAB ER 24H
TRAMADOL HCL	TRAMADOL HCL ER	TBMP 24HR
TRAMADOL HCL	ULTRAM	TABLET
TRAMADOL HCL/ACETAMINOPHEN	TRAMADOL HCL-ACETAMINOPHEN	TABLET
TRAMADOL HCL/ACETAMINOPHEN	ULTRACET	TABLET

Appendix 4. 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