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Safety Profile of Schedule III Buprenorphine and Schedule II Oral Opioids in Elderly with Chronic Low Back Pain: A Retrospective US Medicare Claims Analysis

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Abstract

Objective: This study aimed to evaluate and compare the safety of CIII buprenorphine and oral CII opioids among Medicare patients with chronic Low-Back Pain (cLBP).

Methods: The retrospective study was conducted in Merative Medicare MarketScan® database (2018-2021). The first date of CIII buprenorphine or oral CII opioid medication prescription was defined as the index date. Patients with cLBP were observed 6 months pre-index and until the end of index treatment or the end of continuous healthcare coverage. The main outcome was the incidence of serious Treatment-Emergent Adverse Events (TEAE). Primary analysis compared CIII buprenorphine (Belbuca® and transdermal patch) with oral CII opioids, while sub-analyses compared Belbuca® to CII opioids and buprenorphine patches. Incidence Rate Ratios (IRR) and Incidence Rate Differences (IRD) (per 1,000 person-years) were reported. Propensity-Score Matching (PSM) was performed to balance differences in patients' characteristics.

Results: CIII buprenorphine treatment (n=545 patients) was associated with significantly lower rates ($p<0.050$) of serious confusion (IRR=0.07), syncope (IRR=0.08), headache (IRR=0.11), urinary discomfort (IRR=0.16), constipation (IRR=0.17), cerebrovascular accident (IRR=0.18), atrial fibrillation (IRR=0.19), osteoarthritis (IRR=0.28), cellulitis (IRR=0.29), pneumonia (IRR=0.34), abdominal pain (IRR=0.45), sleep disturbances (IRD=-91.85), and hypotension (IRD=-30.62). The buprenorphine cohort (n=951 patients) more frequently experienced serious bone fractures (IRR=5.90).

Belbuca® (n=124 patients) showed significantly lower rates of serious TEAEs including fatigue (IRR=0.20), constipation (IRR=0.12), osteoarthritis (IRD=-340.08), and urinary discomfort (IRD=-194.33) than CII opioids (n=297 patients). Belbuca® had significantly lower incidence of serious dehydration (IRR=0.08), pneumonia (IRR=0.12), opioid abuse/dependence (IRD=-806.84), abdominal pain (IRD=-496.52), and appetite loss (IRD=-372.39) than patches (n=62 patients per cohort), while patches had significantly lower rates of serious osteoarthritis (IRD=867.30) and confusion (IRD=462.56).

Conclusion: Based on this retrospective claims analysis, CIII buprenorphine may have a milder safety profile than oral CII opioids for cLBP treatment. Belbuca® seems to be better tolerated than CII opioids and buprenorphine patch, based on this study.

Keywords: Chronic pain; Insurance claims; Buprenorphine buccal film; Buprenorphine patch; Opioids; Safety; Adverse events

Introduction

According to the World Health Organization (WHO), chronic Low Back Pain (cLBP) affects over six hundred million people worldwide, representing one of the leading causes of disability globally [1]. Most people experience chronic back pain at least once over their course of life [1,2]. The prevalence of cLBP increases with age, affecting 20-25% of the population aged 65 or older [1,3,4]. In older individuals, cLBP is characterized by more frequent and longer pain episodes that require continuous monitoring [4]. Persisting pain reduces the ability to participate in family, social, and routine daily activities, negatively impacting overall well-being and mental health [1,4]. Clinical management of cLBP requires substantial resources, particularly in the geriatric population. The estimated economic burden of cLBP in the United States is over $100 billion annually and is expected to rise with the fast-growing aging population [4].

Management of cLBP in older adults is challenging due to the high prevalence of comorbidities, multiple medication regimens, slower metabolism, and increased fall risk [5]. The current WHO guideline for treating older adults with cLBP recommends a risk-stratified approach, predominantly based on multimodal non-pharmacological strategies, such as education programs, exercises, and physical and psychological therapies [6]. Still, pharmacological treatment remains an essential part of pain management, though it is important to consider medication pharmacokinetic, safety profiles, and individual comorbidity when selecting the appropriate treatment regimen. Pharmacotherapy for cLBP in older patients employs lower therapeutic doses considering the frequency of polypharmacy, co-morbid medical disorders, and potentially decreased renal and hepatic metabolism. Although used judiciously in elderly due to the increased morbidity and mortality

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risk, opioids remain a mainstay in persistent refractory severe cLBP treatment [5]. The rate of opioid prescribing in the elderly population is high; with one in four Americans aged 65 and older prescribed at least one opioid in 2017, according to the Centers for Disease Control and Prevention [7]. Common side effects of opioid use in the elderly population include constipation, urinary retention, and cardiovascular and endocrine disorders [8], while central nervous system adverse events and respiratory depression represent the most serious conditions that may lead to a higher risk of death in this population [9]. Older patients with chronic pain are at an increased risk of opioid use overdose and abuse. According to the Centers for Medicare and Medicaid Services, more than 6 of every 1,000 Medicare beneficiaries were diagnosed with opioid use disorder [9], with considerable opioid-related mortality [10].

Buprenorphine represents a valuable therapeutic alternative for elderly patients with cLBP due to the potent and sustained analgesia, resulting from a very high binding affinity and partial agonism at the μ-opioid receptor, as well as the prolonged pharmacokinetic characteristics of transdermal and transmucosal delivery platforms [11,12]. Buprenorphine is also considered to potentially have a milder safety profile than full μ-opioids, including lower rates and severity of constipation and urinary retention, lower risk of respiratory depression, and limited abuse potential [13]. In 2022, the United States Departments of Defense and Veterans Affairs added buprenorphine to the clinical practice guideline for the use of opioids as a first-line treatment for chronic pain due to its relatively lower risk for overdose and misuse [14]. Importantly, the pharmacokinetic and safety profile of buprenorphine is not altered by patient age due to the rapid conversion to non-active conjugates [13]. The bioavailability of orally administered buprenorphine is low, approximately 10%. However, the issue has been resolved by using the alternative routes. Transdermal patches provide approximately 15% and buccal film 46–65% bioavailability, while both formulations bypass first-pass metabolism [15].

Studies directly comparing buprenorphine to oral opioids for chronic pain in terms of their safety in the elderly population are lacking, although the topic is particularly important given the current opioid public health emergency [9, 11]. This study aimed to explore and compare Treatment-Emergent Adverse Event (TEAE) rates while using Schedule III (CIII) buprenorphine (Belbuca® and buprenorphine patch) and Schedule II (CII) oral opioids among Medicare patients with cLBP using real-world claims data. Additional sub-analyses investigated safety outcomes between Belbuca® vs. CII oral opioids and separately Belbuca® vs. buprenorphine patches.

Methodology

Data source

This retrospective cohort study used US insurance claims data from the Merative MarketScan® Medicare Supplemental and Coordination of Benefits Database. The Merative MarketScan® databases consist of deidentified, longitudinal, patient-level closed claims and specialty data for patients in the US sourced directly from a diverse pool of payers. This study focuses on retirees with employer-sponsored Medicare Supplemental and Medicare Advantage plans and includes drug information and outcomes data for healthcare services performed in both inpatient and outpatient settings [16]. The study was performed in insurance data claimed in the period from January 1, 2018, to December 31, 2021.

Study population

The study observed Medicare beneficiaries (≥ 65 years of age) with cLBP defined as at least two diagnoses of low back pain on different dates during the six-month pre-index period. The diagnoses were identified using the International Classification of Diseases – Clinical Modification (ICD-10-CM) codes (Supplement Table A1). The population of interest considered for the study were patients prescribed oral CII opioids or CIII buprenorphine (Belbuca® or buprenorphine patch). The respective drug codes were identified in the database based on the National Drug Codes (NDCs) (Supplement Table A2 and Supplement Table A3). Patients were treatment-naïve, with no CIII buprenorphine and CII oral opioids in the 6-month pre-index period. Exclusion criteria were a gap in the health plan or pharmaceutical coverage during the observational period and Belbuca® or buprenorphine patch prescriptions within the CII opioid cohort. To enable a fair comparison, CII opioid patients that received Belbuca® or buprenorphine patch prescriptions in the post-index period were excluded from the cohort. On the other hand, CIII buprenorphine patients were allowed to have concomitant CII opioid use during the post-index period. This way, the study ensured that potential selection bias is conservative, with possibly overestimated rates of adverse events in CIII buprenorphine cohort.

Study design

The index date was defined as the first date of buprenorphine or oral CII opioid treatment. The analysis observed 6-month pre-index period and the post-index period lasted until the end of continuous healthcare and pharmaceutical coverage. Clinical characteristics were evaluated in the pre-index period, while demographic characteristics were assessed on the index date. Patients were classified into cohorts based on the index prescription. The primary analysis compared CIII buprenorphine (prescribed Belbuca® or buprenorphine patch) and oral CII opioid patients (short-acting [SAO] and long-acting [LAO]), while sub-analyses considered the comparison of Belbuca® vs. CII oral opioids and Belbuca® vs. buprenorphine patch patients. The study design is presented in Figure 1.

Outcome measures

The main study outcome was the incidence of TEAEs. The list of relevant adverse events was comprised based on the published literature sources including the most common adverse events (≥5% rate), serious adverse events, adverse events leading to treatment discontinuation, and opioid-related adverse events [17-26]. Finally, the list comprised 44 relevant TEAEs reported in Table 1.

Diagnoses of TEAEs were identified in the database based on the ICD-10-CM codes (Supplement Table A4). The diagnosis was considered as TEAE if occurred during the treatment period with index medication and only among patients without a history of investigated TEAE during the pre-index period. The treatment period was calculated by summing up the drug supply periods for the index medication, excluding treatment gaps and extracting the days of prescription overlaps. In the CIII buprenorphine cohort, only buprenorphine prescription claims were considered when defining the treatment period although patients were allowed to use oral CII opioid concomitantly. The scheme of treatment period definition is presented in Figure 2. Repeated events experienced by a patient during the post-index period were counted as separate events. All-grade TEAEs were all relevant diagnoses observed within treatment periods, while serious TEAEs were defined as events claimed in inpatient or Emergency Department (ED) settings. TEAE rates were reported per 1,000 person-years. The comparison between the cohorts was performed using absolute Incidence Rate Difference (IRD) and Incidence Rate Ratio (IRR). The IRD is calculated as a crude difference of the observed

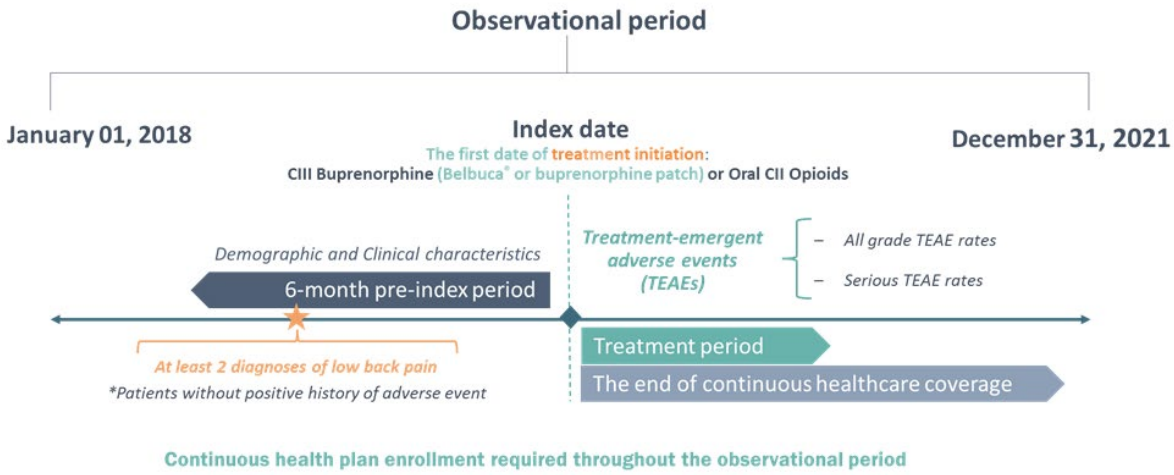

Figure 1: Study design.

Table 1: List of captured adverse events of interest.

Cardiovascular	QT prolongation, hypotension, arial fibrillation, coronary artery disease, hypertension
Central Nervous System (CNS)	Dizziness, somnolence, confusion, seizures, syncope, cerebrovascular accident, nervousness, visual discomfort, suicidal ideation, sleep disturbances
Opioid Use Disorder (OUD)	Opioid abuse, opioid dependence, opioid poisoning
Hormonal	Adrenal insufficiency
Musculoskeletal	Bone fractures, osteoarthritis
Respiratory	Respiratory depression, pneumonia
General	Headache, fatigue, allergic reactions, dehydration, dry mouth, xerostomia, sweating, hot flushes, sinusitis
Gastrointestinal (GIT)	Nausea/vomiting, constipation, hepatotoxicity, cholecystitis, abdominal pain, diarrhea, anorexia/loss of appetite
Skin Toxicities	Cellulitis, pruritus, erythema, rash, skin irritation
Urinary	Urinary discomfort

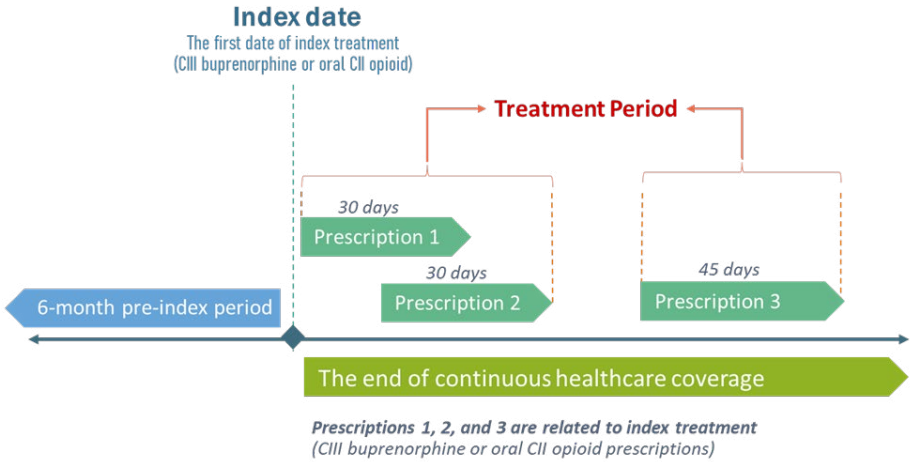

Figure 2: Treatment period definition scheme.

incidence rates (i.e., cohort I incidence rate minus cohort II incidence rate), while IRR represents a relative difference measure calculated as a quotient of incidence rates (i.e., cohort I incidence rate divided by cohort II incidence rate).

Sub-analyses

The primary analysis compared study outcomes between CIII buprenorphine (Belbuca® and buprenorphine patch) vs. oral CII opioid (SAO and LAO) cohorts. Sub-analyses aimed to assess the outcomes in more granularly stratified populations. Sub-analysis #1 compared TEAE rates between Belbuca® vs. CII oral opioid cohorts, while sub-analysis #2 compared Belbuca® vs. buprenorphine patches.

Statistical analysis

Descriptive statistics was reported summarizing continuous variables as means with standard deviations and categorical variables

as numbers with proportions of the sample. The independent t-test was performed to test the difference between the compared cohorts for continuous variables, while chi-square test of independence was used for categorical variables. P-values lower than 0.05 were considered statistically significant.

All TEAE rates and IRD values were reported per 1,000 person-years, while IRR was reported as a rate ratio with 95% confidence intervals (95% CI). The incidence rate ratio test computed IRD and IRR and explored the statistical significance of TEAE rate differences between study cohorts. If TEAE occurred in only one cohort, the P-value was reported for IRD, otherwise it refers to the statistical difference between the cohorts in IRR Negative IRD values and IRR less than 1 imply that the TEAE rate was lower in the referent cohort (CIII buprenorphine in primary analysis and Belbuca® in sub-analyses).

To control for confounders and minimize the selection bias, the Propensity-Score Matching (PSM) analysis was performed applying the nearest-neighbour matching algorithm. Demographic and clinical characteristics of patients were used as covariates in the matching process.

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS®) and MedCalc® statistical software.

Results

The final sample of patients before PSM consisted of 26,995 patients (1,020 in CIII buprenorphine cohort and 25,975 in CII opioid cohort). The CIII buprenorphine cohort was composed of 203 patients treated with Belbuca® and 817 patients on buprenorphine patch. In the sample of 1,496 matched patients, 545 patients were treated with CIII buprenorphine and 951 patients with CII opioids. The subgroup analyses considered 421 patients (124 Belbuca® matched to 297 CII opioid patients) and 124 patients (62 patients in both Belbuca® and buprenorphine patch cohorts). The flow diagram depicting patient selection process is shown in Figure 3.

Primary analysis: CIII buprenorphine vs. CII opioids

Non-matched population: Demographic characteristics of the total sample of 26,995 patients with cLBP stratified in the treatment cohorts are presented in Table 2. Medicare beneficiaries with cLBP were approximately 75 years old and predominantly females. A higher proportion of males was observed in the CII opioid cohort (34.4% vs. 43.8%, p<0.001). The majority of patients were covered by the Preferred Provider Organization (43.4% vs. 47.5%, p=0.011 in CIII buprenorphine vs. CII opioids). A higher proportion of CIII buprenorphine patients were covered by the Comprehensive plan (33.3% vs. 24.5%, p<0.001), while CII opioid patients were more commonly covered by the Health Maintenance Organization plan (17.2% vs. 20.9%, p=0.004). CII opioid-treated patients mostly resided in the North East region, while the majority of CIII buprenorphine patients were located in the North Central and South regions (p<0.001, respectively). Observing the comorbidity burden, CIII buprenorphine patients had a higher Charlson Comorbidity Index (CCI) than CII opioid patients (2.3 vs. 1.9, p<0.001), with a significantly higher proportion of patients in CCI category 4+ (24.8% vs. 18.0%, p<0.001), while more patients in CII opioid cohort were noted in CCI=0 category (26.7% vs. 35.2%, p<0.001). There were significant differences between study cohorts in almost all CCI components (except moderate or severe liver disease, hemiplegia or paraplegia, metastatic solid tumors, and AIDS/HIV), as well as all mental health disorders and other chronic pain comorbidities (p<0.05), except spine disorders. The list of clinical characteristics is presented in Table 3.

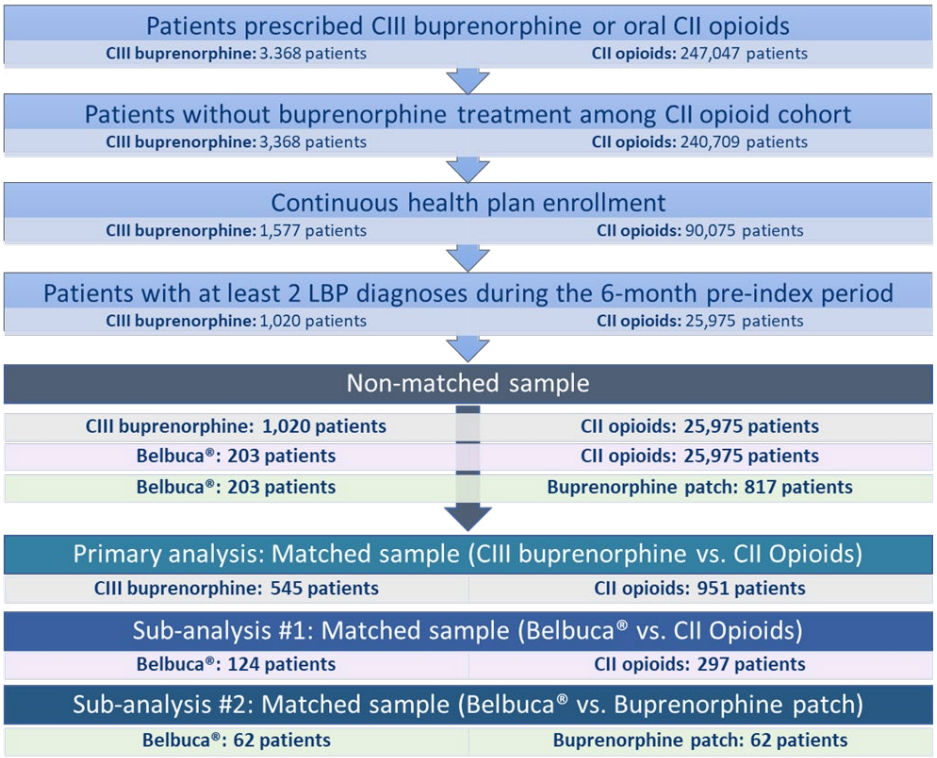

Figure 3: Patient selection flow diagram.

Table 2: Demographic characteristics of non-matched patients.

	CIII Buprenorphine (N=1,020)	CII Opioids (N=25,975)	P-value*
Age, mean (SD)	74.9 (8.0)	74.5 (7.2)	0.154
Gender, n (%)			
Male	351 (34.4)	11,372 (43.8)	**<0.001**
Female	669 (65.6)	14,603 (56.2)	**<0.001**
Health Plan, n (%)			
Basic/major medical	0 (0.0)	0 (0.0)	-
Comprehensive	340 (33.3)	6,372 (24.5)	**<0.001**
Exclusive Provider Organization	4 (0.4)	133 (0.5)	0.821
Health Maintenance Organization	175 (17.2)	5,418 (20.9)	**0.004**
Non-Capitated Point-of-Service	4 (0.4)	121 (0.5)	1.000
POS with capitation	13 (1.3)	433 (1.7)	0.335
Preferred Provider Organization	443 (43.4)	12,331 (47.5)	**0.011**
Consumer-Driven Health Plan	3 (0.3)	155 (0.6)	0.293
High Deductible Health Plan	5 (0.5)	178 (0.7)	0.563
Unknown	33 (3.2)	834 (3.2)	0.965
Region, n (%)			
North East	88 (8.6)	4,691 (18.1)	**<0.001**
North Central	468 (45.9)	10,905 (42.0)	**0.013**
South	360 (35.3)	7,609 (29.3)	**<0.001**
West	103 (10.1)	2,742 (10.6)	0.640
Unknown	1 (0.1)	28 (0.1)	1.000

*Chi-square test was performed for categorical variables and independent T-test for continuous variables

Matched population: The sample of matched patients consisted of 1,496 patients (545 patients in CIII buprenorphine cohort and 951 patients in CII opioid cohort). Patients were well-balanced between the study cohorts and there were no differences in demographic and clinical characteristics that could impact study outcome measures (Supplement Tables A5 and Supplement A6).

The rate of serious hypertension was significantly higher (IRR 0.23, p=0.036) in CII opioid cohort, while other cardiovascular TEAEs were occurred with similar incidence in both cohorts (Table 4). Out of all-grade CNS-related TEAEs, the rates of all-grade confusion, syncope, cerebrovascular accident, and sleep disturbances more commonly occurred in the CII opioid cohort (IRR 0.15, 0.35, 0.42, and 0.31, p<0.050, respectively). The rate of all-grade headache, fatigue and dehydration was significantly higher among CII opioid patients (IRR 0.18, 0.71, and 0.52, p<0.050). The rate of all-grade constipation was significantly higher in the CII opioid cohort (IRR 0.41, p=0.041), while all-grade anorexia/loss of appetite was more frequent in CIII buprenorphine cohort (IRR 2.12, p=0.032). The rates of all-grade osteoarthritis (IRR 0.34, p<0.001), pneumonia (IRR 0.26, p<0.001), cellulitis (IRR 0.52, p=0.026), and urinary discomfort (IRR 0.45, p=0.002) were significantly higher in CII opioid patients.

The reported rates of serious hypotension (IRD -30.62 per 1,000 person-years, p=0.036) and atrial fibrillation (IRR 0.19, p=0.001) were significantly lower in the CIII buprenorphine cohort (Table 5). From all investigated serious CNS-related TEAEs, the rates of serous confusion (IRR 0.07, p<0.001), syncope (IRR 0.08, p<0.001), cerebrovascular accident (IRR 0.18, p=0.003), and sleep disturbances (IRD -91.85 per 1,000 person-years, p<0.001) were significantly higher among CII opioid-treated patients. The rate of serious headache was also significantly more frequent among CII opioid patients (IRR 0.11, p=0.002). Out of GIT-related TEAEs, serious constipation and abdominal pain more commonly occurred among CII opioid patients compared to the CIII buprenorphine cohort (IRR 0.17 and 0.45, respectively, p<0.05). Serious bone fractures were more frequent among CIII buprenorphine patients (IRR 5.90, p=0.044), while serious osteoarthritis occurred more commonly in oral CII opioid-treated patients (IRR 0.28, p=0.029). The rates of serious pneumonia, cellulitis, and urinary discomfort appeared to be significantly higher among CII opioid cohort (IRR 0.34, 0.29, and 0.16, respectively, p<0.05).

Sub-analysis #1: belbuca® vs. CII opioids

Non-matched population: Demographic and clinical characteristics of 26,178 patients treated with Belbuca® (203 patients) and CII Opioids (25,976 patients) before the PSM are provided in the Supplement (Supplement Table A7 and Supplement Table A8).

Matched population: A total number of 421 patients were identified in the final sample of matched patients (124 patients in Belbuca® cohort and 297 patients in CII opioid cohort). As the demographic and clinical characteristics were used as a basis for PSM analysis, there were no statistical differences in these measures implying the cohorts were well-balanced. The list of demographic and clinical characteristics is shown in the Supplement (Supplement Table A9 and Supplement Table A10).

There was no observed all-grade TEAEs with significantly higher rates in Belbuca® compared to CII opioid-treated Medicare patients diagnosed with cLBP. Otherwise, it was demonstrated that all-grade atrial fibrillation (IRD -194.33, p=0.010), confusion (IRD -194.33, p=0.010), headache (IRR 0.12, p=0.035), constipation (IRR 0.15, p=0.001), cellulitis (IRD -242.92, p=0.004), and urinary discomfort (IRR 0.11, p<0.001) occurred more frequently in CII opioid cohort. The list of all-grade TEAE rates in sub-analysis #1 matched sample is provided in Table 6.

There were no serious TEAEs that occurred significantly more in Belbuca®- vs. CII opioid-treated Medicare patients diagnosed with cLBP. Significantly lower rates of fatigue (IRR 0.20, p=0.43), constipation (IRR 0.12, p=0.035), osteoarthritis (IRD -340.08, p<0.001), and urinary discomfort (IRD -194.33, p=0.010). All serious TEAE rates among sub-analysis #1 matched sample are listed in Table 7.

Table 3: Clinical characteristics of non-matched patients.

	CIII Buprenorphine (N=1,020)	CII Opioids (N=25,975)	P-value*
Charlson Comorbidity Index			
0	272 (26.7)	9,146 (35.2)	**<0.001**
1	215 (21.1)	5,472 (21.1)	0.993
2	156 (15.3)	3,842 (14.8)	0.657
3	124 (12.2)	2,833 (10.9)	0.210
4+	253 (24.8)	4,682 (18.0)	**<0.001**
Charlson Comorbidity Index, mean (SD)	2.3 (2.4)	1.9 (2.3)	**<0.001**
Charlson Comorbidity Index Components			
Myocardial infarction	44 (4.3)	811 (3.1)	**0.033**
Congestive heart failure	159 (15.6)	2,680 (10.3)	**<0.001**
Peripheral vascular disease	166 (16.3)	3,612 (13.9)	**0.032**
Cerebrovascular disease	129 (12.6)	2,755 (10.6)	**0.038**
Dementia	51 (5.0)	935 (3.6)	**0.019**
Chronic pulmonary disease	269 (26.4)	4,535 (17.5)	**<0.001**
Rheumatic disease	76 (7.5)	1,160 (4.5)	**<0.001**
Peptic ulcer disease	18 (1.8)	284 (1.1)	**0.046**
Mild liver disease	56 (5.5)	868 (3.3)	**<0.001**
Moderate or severe liver disease	3 (0.3)	29 (0.1)	0.119
Diabetes without chronic complication	294 (28.8)	6,552 (25.2)	**0.010**
Diabetes with chronic complication	221 (21.7)	3,734 (14.4)	**<0.001**
Hemiplegia or paraplegia	12 (1.2)	286 (1.1)	0.821
Renal disease	142 (13.9)	2,631 (10.1)	**<0.001**
Malignancy	111 (10.9)	3,760 (14.5)	**0.001**
Metastatic solid tumor	17 (1.7)	654 (2.5)	0.087
AIDS/HIV	0 (0.0)	20 (0.1)	1.000
Mental Disorders			
Anxiety	240 (23.5)	3,285 (12.6)	**<0.001**
Bipolar disorder	25 (2.5)	209 (0.8)	**<0.001**
Depression	281 (27.5)	3,344 (12.9)	**<0.001**
Sleep disorder	182 (17.8)	2,515 (9.7)	**<0.001**
Psychosis	15 (1.5)	182 (0.7)	**0.005**
Post-traumatic stress syndrome	15 (1.5)	132 (0.5)	**<0.001**
Chronic Pain Specific Comorbidities			
Joint pain	308 (30.2)	4,885 (18.8)	**<0.001**
Musculoskeletal disorders	764 (74.9)	15,886 (61.2)	**<0.001**
Diabetic neuropathy	196 (19.2)	3,257 (12.5)	**<0.001**
Other neuropathies	659 (64.6)	12,185 (46.9)	**<0.001**
Spine disorders	1,015 (99.5)	25,787 (99.3)	0.566
Fibromyalgia	104 (10.2)	1,262 (4.9)	**<0.001**

*Chi-square test was performed for categorical variables and independent T-test for continuous variables

Sub-analysis #2: Belbuca® vs. Buprenorphine patches

Non-matched population: Demographic and clinical characteristics of 1,020 patients before the PSM, including 203 patients initially prescribed Belbuca® and 817 patients initially prescribed buprenorphine patches, are provided in the Supplement (Supplement Table A11 and Supplement Table A12).

Matched population: The sample of matched patients included 62 patients in each of the compared cohorts. Patient demographic and clinical characteristics were well-balanced with no remaining statistical differences between the cohorts (Supplement Table A13 and Supplement Table A14).

There were differences observed between study cohorts in 7/44 all-grade TEAEs. Belbuca® treatment was associated with lower rates of all-grade cerebrovascular accident (IRD -248.26 per 1,000 person-years, p=0.038), and opioid abuse and dependence (IRR 0.07, p<0.001), dehydration (IRR 0.08, p=0.002), and nausea and vomiting (IRR 0.25, p=0.025). Contrary, all-grade confusion (IRD 520.38, p=0.004), fatigue (IRR 2.68, p=0.012), and osteoarthritis (IRR 10.71, p<0.001) more commonly occurred in Belbuca® cohort. The list of all-grade TEAE rates in sub-analysis #2 matched sample is reported in Table 8.

Serious confusion and osteoarthritis occurred only in the Belbuca® cohort (IRDs 462.56 [p=0.006] and 867.30 [p<0.001] per 1,000 person-years, respectively). However, the rates of serious opioid abuse and dependence (IRD -806.84 per 1,000 person-years, p<0.001), dehydration (IRR 0.08, p=0.002), abdominal pain (IRD -496.52, p=0.003), anorexia/loss of appetite (IRD -372.39, p=0.011), and pneumonia (IRR 0.112, p=0.016) were significantly higher in the

Table 4: All-grade TEAE rates (per 1,000 person-years) during the CIII buprenorphine and CII opioid treatment among matched sample in the primary analysis.

	CIII Buprenorphine (N=545)	CII Opioids (N=951)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)	P-value*
Cardiac Adverse Events					
QT prolongation	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Hypotension	13.89	30.62	-16.73 (-57.14 - 23.70)	0.45 (0.03 - 6.26)	0.463
Atrial Fibrillation	173.67	290.85	-117.18 (-251.20 - 16.90)	0.60 (0.32 - 1.15)	0.096
Coronary Artery Disease	173.67	122.46	51.21 (-64.89 - 167.32)	1.42 (0.62 - 3.64)	0.399
Hypertension	20.84	91.85	-71.01 (-131.63 - (-10.37))	0.23 (0.04 - 1.06)	**0.036**
Central Nervous System-related Adverse Events					
Dizziness	180.62	199.00	-18.38 (-144.59 - 107.85)	0.91 (0.45 - 1.92)	0.764
Somnolence	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Confusion	69.47	474.55	-405.08 (-534.50 - (-275.60))	0.15 (0.06 - 0.31)	**<0.001**
Seizures	20.84	45.92	-25.08 (-74.59 - 24.43)	0.45 (0.36 - 3.39)	0.359
Syncope	145.89	413.32	-267.43 (-407.40 - (-127.40))	0.35 (0.19 - 0.65)	**<0.001**
Cerebrovascular Accident	90.31	214.31	-124.00 (-229.00 - (-19.00))	0.42 (0.18 - 0.97)	**0.028**
Nervousness	0.00	0.00	-	-	-
Visual Discomfort	41.68	30.62	11.06 (-46.10 - 68.23)	1.36 (0.24 - 13.79)	0.753
Suicidal Ideation	0.00	15.31	-15.31 (-35.52 - 4.90)	0.00 (0.00 - 17.70)	0.138
Sleep Disturbances	187.57	597.01	-409.44 (-573.60 - (245.20))	0.31 (0.19 - 0.53)	**<0.001**
Opioid Use Disorder-related Adverse Events					
OAD	194.51	183.70	10.81 (-117.00 - 138.65)	1.06 (0.52 - 2.29)	0.886
Opioid Poisoning	48.63	15.31	33.32 (-23.84 - 90.49)	3.18 (0.41 - 143.2)	0.282
General Adverse Events					
Headache	55.58	306.16	250.58 (-357.50 - (-143.60))	0.18 (0.07 - 0.43)	**<0.001**
Fatigue	639.12	903.17	-264.05 (-512.40 - (-15.60))	0.71 (0.50 - 1.00)	**0.041**
Allergic Reactions	13.89	45.92	-32.03 (-77.22 - 13.17)	0.30 (0.03 - 2.64)	0.215
Dehydration	166.73	321.47	-154.74 (-290.30 - (-19.10))	0.52 (0.28 - 0.98)	**0.031**
Dry Mouth	0.00	15.31	-15.31 (-35.52 - 4.90)	0.00 (0.00 - 17.70)	0.138
Xerostomia	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Sweating	13.89	15.31	-1.42 (-36.42 - 33.59)	0.91 (0.05 - 53.55)	0.906
Hot Flushes	0.00	0.00	-	-	-
Sinusitis	90.31	30.62	59.69 (-18.58 - 137.97)	2.95 (0.67 - 26.93)	0.136
Gastrointestinal Adverse Events					
Nausea and Vomiting	361.24	382.70	-21.46 (-198.79 - 155.91)	0.94 (0.58 - 1.59)	0.803
Constipation	180.62	443.93	-263.31 (-413.20 - (-113.40))	0.41 (0.23 - 0.72)	**0.001**
Hepatotoxicity	0.00	0.00	-	-	-
Cholecystitis	55.58	61.23	-5.65 (-75.67 - 64.36)	0.91 (0.24 - 4.12)	0.854
Abdominal Pain	527.97	612.32	-84.35 (-301.99 - 133.36)	0.86 (0.58 - 1.30)	0.447
Diarrhea	145.89	91.85	54.04 (-50.98 - 159.06)	1.59 (0.62 - 4.81)	0.324
Anorexia/Loss of Appetite	291.77	137.77	154.00 (9.70 - 298.30)	2.12 (1.02 - 4.95)	**0.032**
Hormonal Adverse Events					
Adrenal Insufficiency	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Musculoskeletal Adverse Events					
Bone Fractures	90.31	122.46	-32.15 (-124.76 - 60.47)	0.74 (0.28 - 2.05)	0.499
Osteoarthritis	361.24	1,056.26	-695.02 (-917.30 - (472.60))	0.34 (0.23 - 0.50)	**<0.001**
Respiratory Adverse Events					
Respiratory Depression	312.61	489.86	-177.25 (-354.60 - 0.10)	0.64 (0.40 - 1.04)	0.056
Pneumonia	159.78	612.32	-452.54 (-612.90 - (-292.10))	0.26 (0.15 - 0.45)	**<0.001**
Skin-related Adverse Events					
Cellulitis	173.67	336.78	-163.11 (-301.60 - (-24.50))	0.52 (0.28 - 0.96)	**0.026**
Pruritus	48.63	30.62	18.01 (-42.62 - 78.65)	1.59 (0.30 - 15.67)	0.606
Erythema	48.63	15.31	33.32 (-23.84 - 90.49)	3.18 (0.41 - 143.18)	0.282
Rash	34.73	45.92	-11.19 (-68.35 - 45.98)	0.76 (0.15 - 4.87)	0.696
Skin Irritation	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Urinary Adverse Events					
Urinary Discomfort	215.36	474.55	-259.19 (-418.30 - (-100.00))	0.45 (0.27 - 0.77)	**0.002**

*Incidence rate ratio test was performed to assess statistical differences between study cohorts. If the rate of adverse event was zero in one of the cohorts, p-value reflects the difference between study cohorts in the absolute incidence rate difference

Abbreviations: OAD: Opioid abuse/dependence; CI: Confidence interval

Table 5: Serious TEAE rates (per 1,000 person-years) during the CIII buprenorphine and CII opioid treatment in the primary analysis.

	CIII Buprenorphine (N=545)	CII Opioids (N=951)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)	P-value*
Cardiac Adverse Events					
QT prolongation	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Hypotension	0.00	30.62	-30.62 (-5.92 - (-2.03))	0.00 (0.00 - 2.42)	**0.036**
Atrial Fibrillation	34.73	183.70	-148.97 (-232.30 - (-6.56))	0.19 (0.05 - 0.58)	**0.001**
Coronary Artery Disease	111.15	45.92	65.23 (-22.87 - 153.33)	2.42 (0.69 - 12.96)	0.147
Hypertension	13.89	61.23	-47.34 (-96.84 - 2.17)	0.23 (0.02 - 1.58)	0.094
Central Nervous System-related Adverse Events					
Dizziness	69.47	122.46	-52.99 (-138.73 - 32.76)	0.57 (0.20 - 1.65)	0.243
Somnolence	0.00	0.00	-	-	-
Confusion	27.79	398.01	-370.22 (-480.90 - (-259.50))	0.07 (0.02 - 0.20)	**<0.001**
Seizures	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Syncope	20.84	275.54	-254.70 (-347.30 - (-162.10))	0.08 (0.01 - 0.26)	**<0.001**
Cerebrovascular Accident	27.79	153.08	-125.29 (-200.90 - (-49.70))	0.18 (0.04 - 0.63)	**0.003**
Nervousness	0.00	0.00	-	-	-
Visual Discomfort	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Suicidal Ideation	0.00	15.31	-15.31 (-35.52 - 4.90)	0.00 (0.00 - 17.70)	0.138
Sleep Disturbances	0.00	91.85	-91.85 (-141.35 - (-42.33))	0.00 (0.00 - 0.39)	**<0.001**
Opioid Use Disorder-related Adverse Events					
OAD	13.89	0.00	13.89 (-14.69 - 42.48)	-	0.341
Opioid Poisoning	41.68	15.31	26.37 (-27.10 - 79.85)	2.72 (0.33 - 125.25)	0.377
General Adverse Events					
Headache	13.89	122.46	-108.57 (-172.50 - (-44.60))	0.11 (0.01 - 0.57)	**0.002**
Fatigue	145.89	168.39	-22.49 (-136.82 - 91.84)	0.87 (0.40 - 1.99)	0.691
Allergic Reactions	6.95	15.31	-8.36 (-36.94 - 20.22)	0.45 (0.01 - 35.63)	0.624
Dehydration	145.89	199.00	-53.11 (-170.95 - 64.74)	0.73 (0.35 - 1.59)	0.382
Dry Mouth	0.00	0.00	-	-	-
Xerostomia	0.00	0.00	-	-	-
Sweating	0.00	0.00	-	-	-
Hot Flushes	0.00	0.00	-	-	-
Sinusitis	0.00	0.00	-	-	-
Gastrointestinal Adverse Events					
Nausea and Vomiting	138.94	168.39	-29.45 (-141.97 - 83.09)	0.83 (0.38 - 1.91)	0.603
Constipation	41.68	244.93	-203.25 (-298.00 - (-108.40))	0.17 (0.05 - 0.46)	**<0.001**
Hepatotoxicity	0.00	0.00	-	-	-
Cholecystitis	55.58	30.62	24.96 (-38.95 - 88.87)	1.82 (0.36 - 17.55)	0.482
Abdominal Pain	111.15	244.93	-133.78 (-248.10 - (19.40))	0.45 (0.21 - 0.97)	**0.029**
Diarrhea	6.95	15.31	-8.36 (-36.94 - 20.22)	0.45 (0.01 - 35.63)	0.624
Anorexia/Loss of Appetite	13.89	0.00	13.89 (-14.69 - 42.48)	-	0.341
Hormonal Adverse Events					
Adrenal Insufficiency	0.00	0.00	-	-	-
Musculoskeletal Adverse Events					
Bone Fractures	90.31	15.31	75.00 (-0.62 - 150.62)	5.90 (0.89 - 250.73)	**0.044**
Osteoarthritis	34.73	122.46	-87.73 (-160.59 - (14.85))	0.28 (0.07 - 0.98)	**0.029**
Respiratory Adverse Events					
Respiratory Depression	284.83	398.01	-113.18 (-278.60 - 52.30)	0.72 (0.43 - 1.22)	0.187
Pneumonia	125.05	367.39	-242.34 (-373.30 - (-111.30))	0.34 (0.17 - 0.65)	**0.001**
Skin-related Adverse Events					
Cellulitis	62.52	214.31	-151.79 (-248.70 - (-54.80))	0.29 (0.11 - 0.72)	**0.004**
Pruritus	0.00	0.00	-	-	-
Erythema	6.95	0.00	6.95 (-13.26 - 27.16)	-	0.501
Rash	0.00	15.31	-15.31 (-35.52 - 4.90)	0.00 (0.00 - 17.70)	0.138
Skin Irritation	0.00	0.00	-	-	-
Urinary Adverse Events					
Urinary Discomfort	34.73	214.31	-179.58 (-267.70 - (91.50))	0.16 (0.05 - 0.48)	**<0.001**

*Incidence rate ratio test was performed to assess statistical differences between study cohorts. If the rate of adverse event was zero in one of the cohorts, p-value reflects the difference between study cohorts in the absolute incidence rate difference

Abbreviations: OAD: Opioid abuse/dependence; CI: Confidence interval

Table 6: All-grade TEAE rates (per 1,000 person-years) during the Belbuca® and CII opioid treatment among matched sample in sub-analysis #1

	Belbuca® (N=124)	CII Opioids (N=297)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)	P-value*
Cardiac Adverse Events					
QT prolongation	0.00	0.00	-	-	-
Hypotension	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Atrial Fibrillation	0.00	194.33	-194.33 (-342.80 - (-45.90))	0.00 (0.00 - 0.92)	**0.010**
Coronary Artery Disease	0.00	97.17	-97.17 (-202.15 - 7.79)	0.00 (0.00 - 3.23)	0.070
Hypertension	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Central Nervous System-related Adverse Events					
Dizziness	88.56	0.00	88.56 (-40.01 - 217.11)	-	0.177
Somnolence	59.04	0.00	59.04 (-45.94 - 164.00)	-	0.270
Confusion	0.00	194.33	-194.33 (-342.80 - (-45.90))	0.00 (0.00 - 0.92)	**0.010**
Seizures	59.04	0.00	59.04 (-45.94 - 164.00)	-	0.270
Syncope	29.52	194.33	-164.81 (-330.80 - 1.10)	0.15 (0.00 - 1.53)	0.079
Cerebrovascular Accident	236.16	97.17	138.89 (11.77 - 351.05)	2.43 (0.48 - 23.49)	0.267
Nervousness	0.00	0.00	-	-	-
Visual Discomfort	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Suicidal Ideation	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Sleep Disturbances	236.16	388.67	-152.51 (-449.50 - 144.30)	0.61 (0.20 - 1.86)	0.329
Opioid Use Disorder-related Adverse Events					
OAD	177.12	97.17	79.95 (-130.03 - 289.86)	1.82 (0.33 - 18.46)	0.495
Opioid Poisoning	0.00	0.00	-	-	-
General Adverse Events					
Headache	29.52	242.92	-213.40 (-395.30 - (-31.60))	0.12 (0.00 - 1.09)	**0.035**
Fatigue	944.64	825.92	118.72 (-401.10 - 638.00)	1.14 (0.62 - 2.20)	0.666
Allergic Reactions	0.00	0.00	-	-	-
Dehydration	118.08	145.75	-27.67 (-224.09 - 168.67)	0.81 (0.14 - 5.53)	0.779
Dry Mouth	0.00	0.00	-	-	-
Xerostomia	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Sweating	0.00	0.00	-	-	-
Hot Flushes	0.00	0.00	-	-	-
Sinusitis	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Gastrointestinal Adverse Events					
Nausea and Vomiting	147.60	388.67	-241.07 (-508.80 - 26.50)	0.38 (0.10 - 1.32)	0.093
Constipation	88.56	583.00	-495.44 (-782.00 - (-207.10))	0.15 (0.03 - 0.56)	**0.001**
Hepatotoxicity	0.00	0.00	-	-	-
Cholecystitis	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Abdominal Pain	442.80	437.25	5.55 (-358.21 - 369.05)	1.01 (0.42 - 2.62)	0.990
Diarrhea	88.56	145.75	-57.19 (-239.04 - 124.59)	0.61 (0.08 - 4.54)	0.560
Anorexia/Loss of Appetite	383.76	534.42	-150.66 (-514.40 - 212.80)	0.72 (0.30 - 1.77)	0.423
Hormonal Adverse Events					
Adrenal Insufficiency	0.00	0.00	-	-	-
Musculoskeletal Adverse Events					
Bone Fractures	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Osteoarthritis	442.80	534.42	-91.62 (-470.24 - 286.72)	0.83 (0.36 - 1.99)	0.633
Respiratory Adverse Events					
Respiratory Depression	0.00	97.17	-97.17 (-202.15 - 7.79)	0.00 (0.00 - 3.23)	0.070
Pneumonia	295.20	194.33	100.87 (-176.90 - 378.50)	1.52 (0.44 - 6.63)	0.502
Skin-related Adverse Events					
Cellulitis	0.00	242.92	-242.92 (-408.90 - (-77.00))	0.00 (0.00 - 0.66)	**0.004**
Pruritus	0.00	97.17	-97.17 (-202.15 - 7.79)	0.00 (0.00 - 3.23)	0.070
Erythema	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Rash	88.56	0.00	88.56 (-40.01 - 217.11)	-	0.177
Skin Irritation	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Urinary Adverse Events					
Urinary Discomfort	88.56	825.92	-737.36 (-1,069.40 - (-405.50))	0.11 (0.02 - 0.37)	**<0.001**

*Incidence rate ratio test was performed to assess statistical differences between study cohorts. If the rate of adverse event was zero in one of the cohorts, p-value reflects the difference between study cohorts in the absolute incidence rate difference

Abbreviations: OAD: Opioid abuse/dependence; CI: Confidence interval

Table 7: Serious TEAE rates (per 1,000 person-years) during the Belbuca® and CII opioid treatment among matched sample in sub-analysis #1.

	Belbuca® (N=124)	CII Opioids (N=297)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)	P-value*
Cardiac Adverse Events					
QT prolongation	0.00	0.00	-	-	-
Hypotension	0.00	0.00	-	-	-
Atrial Fibrillation	0.00	0.00	-	-	-
Coronary Artery Disease	0.00	0.00	-	-	-
Hypertension	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Central Nervous System-related Adverse Events					
Dizziness	0.00	0.00	-	-	-
Somnolence	0.00	0.00	-	-	-
Confusion	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Seizures	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Syncope	0.00	0.00	-	-	-
Cerebrovascular Accident	236.16	48.58	187.42 (-35.10 - 410.20)	4.86 (0.65 - 216.63)	0.104
Nervousness	0.00	0.00	-	-	-
Visual Discomfort	0.00	0.00	-	-	-
Suicidal Ideation	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Sleep Disturbances	0.00	0.00	-	-	-
Opioid Use Disorder-related Adverse Events					
OAD	0.00	0.00	-	-	-
Opioid Poisoning	0.00	0.00	-	-	-
General Adverse Events					
Headache	29.52	48.58	-19.06 (-124.05 - 85.90)	0.61 (0.01 - 47.68)	0.756
Fatigue	59.04	291.50	-232.46 (-442.50 - (-22.60))	0.20 (0.02 - 1.13)	**0.043**
Allergic Reactions	0.00	0.00	-	-	-
Dehydration	88.56	145.75	-57.19 (-239.04 - 124.59)	0.61 (0.08 - 4.54)	0.560
Dry Mouth	0.00	0.00	-	-	-
Xerostomia	0.00	0.00	-	-	-
Sweating	0.00	0.00	-	-	-
Hot Flushes	0.00	0.00	-	-	-
Sinusitis	0.00	0.00	-	-	-
Gastrointestinal Adverse Events					
Nausea and Vomiting	29.52	48.58	-19.07 (-124.05 - 85.90)	0.61 (0.01 - 47.68)	0.756
Constipation	29.52	242.92	-213.40 (-395.30 - (-31.60))	0.12 (0.00 - 1.09)	**0.035**
Hepatotoxicity	0.00	0.00	-	-	-
Cholecystitis	0.00	0.00	-	-	-
Abdominal Pain	118.08	291.50	-173.42 (-408.20 - 61.20)	0.41 (0.08 - 1.71)	0.172
Diarrhea	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Anorexia/Loss of Appetite	0.00	97.17	-97.17 (-202.15 - 7.79)	0.00 (0.00 - 3.23)	0.070
Hormonal Adverse Events					
Adrenal Insufficiency	0.00	0.00	0.00 (0.00 - 0.00)	-	-
Musculoskeletal Adverse Events					
Bone Fractures	0.00	48.58	-48.58 (-122.82 - 25.63)	0.00 (0.00 - 23.69)	0.200
Osteoarthritis	0.00	340.08	-340.08 (-536.50 - (-143.80))	0.00 (0.00 - 0.42)	**0.001**
Respiratory Adverse Events					
Respiratory Depression	0.00	97.17	-97.17 (-202.15 - 7.79)	0.00 (0.00 - 3.23)	0.070
Pneumonia	206.64	145.75	60.91 (-173.88 - 295.56)	1.42 (0.32 - 8.49)	0.645
Skin-related Adverse Events					
Cellulitis	0.00	0.00	-	-	-
Pruritus	0.00	0.00	-	-	-
Erythema	0.00	0.00	-	-	-
Rash	29.52	0.00	29.52 (-44.71 - 103.74)	-	0.436
Skin Irritation	0.00	0.00	-	-	-
Urinary Adverse Events					
Urinary Discomfort	0.00	194.33	-194.33 (-342.80 - (-45.90))	0.00 (0.00 - 0.92)	**0.010**

*Incidence rate ratio test was performed to assess statistical differences between study cohorts. If the rate of adverse event was zero in one of the cohorts, p-value reflects the difference between study cohorts in the absolute incidence rate difference

Abbreviations: OAD: Opioid abuse/dependence; CI: Confidence interval

Table 8: All-grade TEAE rates (per 1,000 person-years) during the Belbuca® and buprenorphine patch treatment among matched sample in the sub-analysis #2.

	Belbuca® (N=62)	Bup. patch (N=62)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)	P-value*
Cardiac Adverse Events					
QT prolongation	0.00	0.00	-	-	-
Hypotension	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Atrial Fibrillation	0.00	0.00	-	-	-
Coronary Artery Disease	0.00	0.00	-	-	-
Hypertension	0.00	124.13	-124.13 (-290.20 - 41.90)	0.00 (0.00 - 4.96)	0.143
Central Nervous System-related Adverse Events					
Dizziness	404.74	124.13	280.61 (-71.70 - 632.70)	3.26 (0.62 - 32.16)	0.134
Somnolence	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Confusion	520.38	0.00	520.38 (168.00 - 872.40)	-	**0.004**
Seizures	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Syncope	0.00	62.06	-62.06 (-179.48 - 55.33)	0.00 (0.00 - 36.32)	0.300
Cerebrovascular Accident	0.00	248.26	-248.26 (-483.10 - (-13.50))	0.00 (0.00 - 1.41)	**0.038**
Nervousness	0.00	0.00	-	-	-
Visual Discomfort	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Suicidal Ideation	0.00	0.00	-	-	-
Sleep Disturbances	173.46	372.39	-199.07 (-551.20 - 153.20)	0.47 (0.08 - 2.18)	0.294
Opioid Use Disorder-related Adverse Events					
OAD	115.64	1,551.61	-1,436.17 (-2,046.30 - (-826.20))	0.07 (0.01 - 0.30)	**<0.001**
Opioid Poisoning	0.00	0.00	-	-	-
General Adverse Events					
Headache	57.82	62.06	-4.24 (-170.30 - 161.76)	0.93 (0.01 - 73.10)	0.964
Fatigue	1,329.86	496.52	832.86 (179.20 - 1,486.60)	2.68 (1.16 - 6.92)	**0.012**
Allergic Reactions	0.00	0.00	-	-	-
Dehydration	57.82	682.71	-625.11 (-1,031.70 - (218.30))	0.08 (0.00 - 0.58)	**0.002**
Dry Mouth	0.00	0.00	-	-	-
Xerostomia	0.00	0.00	-	-	-
Sweating	0.00	0.00	-	-	-
Hot Flushes	0.00	0.00	-	-	-
Sinusitis	57.82	124.13	-66.31 (-269.69 - 137.00)	0.47 (0.01 - 8.94)	0.585
Gastrointestinal Adverse Events					
Nausea and Vomiting	173.46	682.71	-509.25 (-948.70 - (-70.10))	0.25 (0.05 - 0.96)	**0.025**
Constipation	289.10	310.32	-21.22 (-392.61 - 349.91)	0.93 (0.21 - 4.05)	0.913
Hepatotoxicity	0.00	0.00	-	-	-
Cholecystitis	0.00	0.00	-	-	-
Abdominal Pain	404.74	806.84	-402.30 (-927.40 - 122.70)	0.50 (0.17 - 1.35)	0.142
Diarrhea	115.64	0.00	115.64 (-50.40 - 281.60)	-	0.172
Anorexia/Loss of Appetite	693.84	434.45	259.39 (-252.60 - 770.90)	1.60 (0.58 - 4.79)	0.334
Hormonal Adverse Events					
Adrenal Insufficiency	0.00	0.00	-	-	-
Musculoskeletal Adverse Events					
Bone Fractures	0.00	0.00	-	-	-
Osteoarthritis	1,329.86	124.13	1,205.73 (618.30 - 1,792.30)	10.71 (2.65 - 93.71)	**<0.001**
Respiratory Adverse Events					
Respiratory Depression	0.00	0.00	-	-	-
Pneumonia	231.28	496.52	-265.24 (-672.10 - 141.30)	0.47 (0.10 - 1.74)	0.219
Skin-related Adverse Events					
Cellulitis	462.56	310.32	152.14 (-271.20 - 575.40)	1.49 (0.43 - 5.79)	0.500
Pruritus	0.00	0.00	-	-	-
Erythema	0.00	0.00	-	-	-
Rash	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Skin Irritation	115.64	0.00	115.64 (-50.40 - 281.60)	-	0.172
Urinary Adverse Events					
Urinary Discomfort	115.64	62.06	53.58 (-149.81 - 256.88)	1.86 (0.10 - 109.88)	0.666

*Incidence rate ratio test was performed to assess statistical differences between study cohorts. If the rate of adverse event was zero in one of the cohorts, p-value reflects the difference between study cohorts in the absolute incidence rate difference

Abbreviations: OAD: Opioid abuse/dependence; CI: Confidence interval

Table 9: Serious TEAE rates (per 1,000 person-years) during the Belbuca® and buprenorphine patch treatment among matched sample in the sub-analysis #2.

	Belbuca® (N=62)	Bup. patch (N=62)	Incidence Rate Difference (95% CI)	Incidence Rate Ratio (95% CI)	P-value*
Cardiac Adverse Events					
QT prolongation	0.00	0.00	-	-	-
Hypotension	0.00	0.00	-	-	-
Atrial Fibrillation	0.00	0.00	-	-	-
Coronary Artery Disease	0.00	0.00	-	-	-
Hypertension	0.00	124.13	-124.13 (-290.20 - 41.90)	0.00 (0.00 - 4.96)	0.143
Central Nervous System-related Adverse Events					
Dizziness	57.82	124.13	-66.31 (-269.69 - 137.00)	0.47 (0.01 - 8.94)	0.585
Somnolence	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Confusion	462.56	0.00	462.56 (130.40 - 794.50)	-	**0.006**
Seizures	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Syncope	0.00	62.06	-62.06 (-179.48 - 55.33)	0.00 (0.00 - 36.32)	0.300
Cerebrovascular Accident	0.00	62.06	-62.06 (-179.48 - 55.33)	0.00 (0.00 - 36.32)	0.300
Nervousness	0.00	0.00	-	-	-
Visual Discomfort	0.00	0.00	-	-	-
Suicidal Ideation	0.00	0.00	-	-	-
Sleep Disturbances	0.00	0.00	-	-	-
Opioid Use Disorder-related Adverse Events					
OAD	0.00	806.84	-806.84 (-1,230.30 - (-383.70))	0.00 (0.00 - 0.31)	**<0.001**
Opioid Poisoning	0.00	0.00	-	-	-
General Adverse Events					
Headache	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Fatigue	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Allergic Reactions	0.00	0.00	-	-	-
Dehydration	57.82	682.71	-624.89 (-1,031.70 - (-218.30))	0.08 (0.00 - 0.58)	**0.002**
Dry Mouth	0.00	0.00	-	-	-
Xerostomia	0.00	0.00	-	-	-
Sweating	0.00	0.00	-	-	-
Hot Flushes	0.00	0.00	-	-	-
Sinusitis	0.00	0.00	-	-	-
Gastrointestinal Adverse Events					
Nausea and Vomiting	115.64	496.52	-380.88 (-752.20 - (-9.70))	0.23 (0.02 - 1.17)	0.051
Constipation	57.82	124.13	-66.31 (-269.69 - 137.00)	0.47 (0.01 - 8.94)	0.585
Hepatotoxicity	0.00	0.00	-	-	-
Cholecystitis	0.00	0.00	-	-	-
Abdominal Pain	0.00	496.52	-496.52 (-828.70 - (-164.50))	0.00 (0.00 - 0.55)	**0.003**
Diarrhea	57.82	0.00	57.82 (-59.60 - 175.21)	-	0.335
Anorexia/Loss of Appetite	0.00	372.39	-372.39 (-660.00 - (-84.90))	0.00 (0.00 - 0.79)	**0.011**
Hormonal Adverse Events					
Adrenal Insufficiency	0.00	0.00	-	-	-
Musculoskeletal Adverse Events					
Bone Fractures	0.00	0.00	-	-	-
Osteoarthritis	867.30	0.00	867.30 (412.40 - 1,321.70)	-	**<0.001**
Respiratory Adverse Events					
Respiratory Depression	0.00	0.00	-	-	-
Pneumonia	57.82	496.52	-438.70 (-791.00 - (-86.60))	0.12 (0.00 - 0.87)	**0.016**
Skin-related Adverse Events					
Cellulitis	0.00	186.19	-186.19 (-389.60 - 17.10)	0.00 (0.00 - 2.25)	0.073
Pruritus	0.00	0.00	-	-	-
Erythema	0.00	0.00	-	-	-
Rash	0.00	0.00	-	-	-
Skin Irritation	0.00	0.00	-	-	-
Urinary Adverse Events					
Urinary Discomfort	0.00	0.00	-	-	-

*Incidence rate ratio test was performed to assess statistical differences between study cohorts. If the rate of adverse event was zero in one of the cohorts, p-value reflects the difference between study cohorts in the absolute incidence rate difference

Abbreviations: OAD: Opioid abuse/dependence; CI: Confidence interval

buprenorphine patch cohort. All serious TEAE rates in sub-analysis #2 matched samples are reported in Table 9.

Discussion

This retrospective study indicates to a more favourable safety and tolerability profile of CIII buprenorphine compared to oral CII opioids in the population of Medicare patients with cLBP based on reporting TEAEs. Out of more than 40 serious TEAEs that were tracked during the treatment, CIII buprenorphine had significantly lower rates of 13 events. Among those, serious hypotension and sleep disturbances occurred only in oral CII opioid patients. On the contrary, only a higher rate of serious bone fractures was reported in the CIII buprenorphine cohort. Results of sub-analysis #1 that compared TEAE rates between Belbuca® and oral CII opioid cohorts were in line with the findings reported in the primary analysis. Belbuca® showed significantly lower rates of 4 out of 44 serious TEAEs, and none of the 44 serious TEAEs occurred more frequently in the Belbuca® cohort. In sub-analysis #2, safety outcomes were compared between different buprenorphine formulations – buccal film (Belbuca®) and transdermal patches. Results were mostly similar between the cohorts, but Belbuca®-treated patients yielded a slightly better safety profile with a significantly lower rate of 5 out of 44 serious TEAEs. Serious opioid abuse and dependence, abdominal pain, and anorexia/loss of appetite occurred only in the buprenorphine patch cohort. On the other hand, confusion and osteoarthritis were serious TEAEs with higher rates in the Belbuca® cohort. This analysis also explored all-grade TEAE rates in the primary analysis and sub-analyses. Still, all-grade TEAE outcomes were considered less reliable than those occurring in the ED or requiring hospitalization, as they may indicate comorbid conditions or coinciding events. Also, all-grade TEAEs were considered less significant for reimbursement purposes from the payer's perspective.

A recently published study evaluated the safety of CIII buprenorphine compared to CII oral opioids in a younger population of commercially insured adults with cLBP [27]. The study identified more common occurrences of opioid poisoning, constipation, nausea/vomiting, seizures, and coronary artery disease in patients treated with CII oral opioids. Still, significantly greater rates of dizziness, cholecystitis, and, unexpectedly, opioid abuse/dependence were seen among CIII buprenorphine patients. The authors noted that all opioid abuse/dependence events occurred among patients treated with the buprenorphine patch rather than Belbuca®. In this retrospective study, Belbuca® patients experienced a milder safety profile than CII opioids, with lower rates of respiratory depression, seizures, osteoarthritis, and atrial fibrillation in patients using the buccal film [27]. A Systematic Literature Review (SLR) evaluated the safety and efficacy of the CIII buprenorphine for chronic pain treatment based on randomized controlled trials [15]. Based on over 30 studies, including four on buprenorphine buccal film and two assessing specifically an elderly population, buprenorphine demonstrated efficacy in pain relief and was generally well tolerated. Based on SLR study results, when juxtaposed with safety data for full μ-opioid receptor agonists, buprenorphine exhibited favourable safety. As the study concluded, the buccal film seemed to confer additional safety advantages compared with the transdermal patch, with lower reported rates of nausea, vomiting, constipation, headache, dizziness, and somnolence [15]. A case series report retrospectively observed cases of clinically significant buprenorphine toxicity in the intensive care, high-dependency unit, and acute pain service databases of an academic hospital in Australia [28]. The study described six cases of buprenorphine-related respiratory and neurological depression among opioid-naïve elderly hospitalized patients with additional risk factors such as concurrent comorbidities and ingestion of other central nervous system depressants. In all six patients, buprenorphine was used for the treatment of acute pain and administered sublingually, with the addition of a transdermal patch for one patient. The study highlights the need for caution when buprenorphine is used in patients with reduced respiratory or neurological reserve and risk factors. While these findings are concerning, it should also be considered that the hospital units manage about 5 thousand patients each year [28], so the fact that six patients with serious buprenorphine-related toxicity were seen over two years suggests the relative rare incidence and the safety profile of buprenorphine. It should also be noted that sublingual forms of buprenorphine are not approved for pain management by the US Food and Drug Administration and the doses in the products are much higher than buprenorphine products approved for use in pain management [29]. Several well-sourced narrative reviews emphasized the suitability of buprenorphine as the preferred treatment for chronic pain in older patients requiring around-the-clock analgesia [11,12,29-31]. The reports based their recommendation on favourable pharmacokinetic characteristics and fast clearance that is not affected by patient age, renal failure, or liver impairment. An open-label single-arm study assessed the long-term safety and efficacy of buprenorphine buccal film in patients with moderate to severe chronic pain [32]. Treatment with the buccal film occurred for 48 weeks after the after rollover subjects completed a 12-week clinical trial. Buprenorphine buccal film was well tolerated during the study, with treatment-related adverse events seen in 23% of patients during the titration phase and 14% of patients during the long-term treatment phase. Adverse events led to treatment discontinuation in 3% of patients in both phases. The principal adverse events were nausea, constipation, and headache. No adverse events related to respiratory depression were observed during the study [32]. Finally, the consensus statement of an International Expert Panel on opioids in the management of chronic severe pain identifies buprenorphine as "the top-line choice for opioid treatment in the elderly" based on the distinct benefits in the treatment of cancer pain, non-cancer-related pain, neuropathic pain, its use in patients with renal and hepatic impairment and immunocompromised patient, but also its cost and availability [33].

Strengths and limitations

To our knowledge, this is the first real-world evidence analysis in the US healthcare setting that explored a wide spectrum of TEAEs and compared their rates in the elderly Medicare beneficiaries with cLBP between CIII buprenorphine and oral CII opioids. From a standpoint of the current opioid crisis and the lack of effective approaches to combat ever-rising OUD rates, this study attempts to fill some of the existing knowledge gaps, provides important insights into real-world clinical practice and evidence on the safety of commonly used treatment options, and may serve as a basis for further research and prospective clinical studies. The comprehensive analysis explored safety outcomes in patients treated with particular buprenorphine formulations, Belbuca® vs. oral CII opioids and Belbuca® vs. buprenorphine transdermal patches. The criteria applied during the patient selection process and statistical analyses aimed to minimize the research bias and provide reliable comparison between the study cohorts. Patients were required to have continuous insurance coverage in order to minimize the bias due to missing data in retrospective claims. The PSM was used to adjust for the covariates between studied cohorts and minimize their impact on the safety outcomes. Moreover, for patients with a positive history of explored events in the pre-index period, the events occurring during the treatment period were not classified as TEAEs and were not

taken into account when reporting the safety outcomes. In this way, more reliable association between the index treatment and TEAEs was established.

However, several study limitations should be considered when interpreting the results. The main limitation is related the nature and characteristics of real-world insurance claims and related restrictions of coding systems. These data are primarily collected for administrative purposes, with possible data entry errors such as miscoding or duplicate claims. The impact of this limitation has been reduced by performing thorough data cleaning, a careful patient selection process, and bias-controlling methods such as PSM. Additionally, the chronicity of low back pain could not be determined based on the diagnostic claims and was assumed in patients who had low back pain diagnosis at two separate claims during the pre-index period. The study findings' generalizability should be also considered. This retrospective analysis was performed on the Medicare population and results may not be applicable to patients with other types of insurance. Furthermore, the sub-analyses that compared the occurrence of TEAEs within Belbuca®-vs. CII opioids-, and vs. buprenorphine patch-treated patients yielded statistical significance between cohorts, but they were conducted on small samples of Medicare patients with cLBP (sub-analysis #1: 124 vs. 297 patients, and sub-analysis #2: 62 vs. 62 patients) and the findings should be carefully interpreted. The authors were unable to require Medicare patients to be opioid-naïve in the pre-index period, as almost all cLBP patients in our analysis had a positive history of CII opioids utilization. Finally, although we tried to enhance the association between the treatment and TEAEs by capturing only events that occurred while supplied with the medicine and in the patients with no history of investigated TEAE during the pre-index period, we were unable to confirm that the event was caused by the treatment in the insurance claim database. Additionally, as buprenorphine patients were allowed to have concomitant CII opioid treatment, there is a possibility that some of the serious TEAEs were caused by CII opioids or their concomitant use in the buprenorphine cohort. In addition, the impact of average daily doses between CII opioids and CIII buprenorphine cohorts could not be considered since buprenorphine has no MME conversion factor value. No formal conclusions comparing safety between CII opioids and CIII buprenorphine may be drawn given no head-to-head clinical trials have been conducted.

Conclusion

This study demonstrated a higher occurrence of serious TEAEs in the CII opioid cohort vs. the buprenorphine cohort including confusion, syncope, headache, urinary discomfort, constipation, cerebrovascular accident, atrial fibrillation, osteoarthritis, cellulitis, pneumonia, abdominal pain, sleep disturbances, and hypotension. In general, CIII buprenorphine also seems better tolerated among the Medicare population than CII opioids, with the exception of the higher rate of serious bone fractures. Based on the real-world retrospective claims, Belbuca® may be indicative of better safety and tolerability than CII opioids, with lower rates of serious TEAEs including fatigue, constipation, osteoarthritis, and urinary discomfort. No serious TEAEs were significantly more common in Belbuca® than CII opioids. Finally, Belbuca® may have significantly higher rates of confusion and osteoarthritis, while significantly lower rates of serious TEAEs of opioid abuse and dependence, abdominal pain, loss of appetite, dehydration, and pneumonia compared to the buprenorphine patch.

Disclosure

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Supplementary Material

Table A1: ICD-10-CM codes related to low back pain.

ICD-10-CM	Description
M43.06	Spondylolysis lumbar region
M43.07	Spondylolysis lumbosacral region
M43.08	Spondylolysis sacral and sacrococcygeal region
M43.16	Spondylolisthesis lumbar region
M43.17	Spondylolisthesis lumbosacral region
M43.18	Spondylolisthesis sacral and sacrococcygeal region
M43.27	Fusion of spine, lumbosacral region
M43.28	Fusion of spine, sacral and sacrococcygeal region
M45.6	Ankylosing spondylitis lumbar region
M45.7	Ankylosing spondylitis of lumbosacral region
M45.8	Ankylosing spondylitis sacral and sacrococcygeal region
M46.06	Spinal enthesopathy lumbar region
M46.07	Spinal enthesopathy lumbosacral region
M46.08	Spinal enthesopathy sacral and sacrococcygeal region
M46.46	Discitis, unspecified …… lumbar region
M46.47	Discitis, unspecified …… lumbosacral region
M46.48	Discitis, unspecified …… sacral and sacrococcygeal region
M47.16	Other spondylosis with myelopathy…… lumbar region
M47.816	Spondylosis without myelopathy or radiculopathy …… lumbar region
M47.817	Spondylosis without myelopathy or radiculopathy …… lumbosacral region
M47.818	Spondylosis without myelopathy or radiculopathy …… sacral and sacrococcygeal region
M48.06	Spinal stenosis, lumbar region
M48.061	Spinal stenosis, lumbar region…… without neurogenic claudication
M48.062	Spinal stenosis, lumbar region…… with neurogenic claudication
M48.07	Spinal stenosis …… lumbosacral region
M48.08	Spinal stenosis …… sacral and sacrococcygeal region
M51.06	Intervertebral disc disorders with myelopathy, lumbar region
M51.26	Other intervertebral disc displacement, lumbar region
M51.27	Other intervertebral disc displacement, lumbosacral region
M51.36	Other intervertebral disc degeneration, lumbar region
M51.37	Other intervertebral disc degeneration, lumbosacral region
M51.46	Schmorl's nodes…… lumbar region
M51.47	Schmorl's nodes…… lumbosacral region
M51.86	Other intervertebral disc disorders, lumbar region
M51.87	Other intervertebral disc disorders, lumbosacral region
M53.2X8	Spinal instabilities…… sacral and sacrococcygeal region
M53.3	Sacrococcygeal disorders, not elsewhere classified
M54.16	Radiculopathy…… lumbar region
M54.17	Radiculopathy…… lumbosacral region
M54.30	Sciatica…… unspecified side
M54.31	Sciatica…… right side
M54.32	Sciatica…… left side
M54.40	Lumbago with sciatica…… unspecified side
M54.41	Lumbago with sciatica…… right side
M54.42	Lumbago with sciatica…… left side
M54.5	Low back pain
M54.50	…… unspecified
M54.51	Vertebrogenic low back pain
M54.59	Other low back pain
M96.1	Postlaminectomy syndrome, not elsewhere classified
M99.03	Segmental and somatic dysfunction…… of lumbar region
M99.04	Segmental and somatic dysfunction…… of sacral region
M99.13	Subluxation complex (vertebral)…… of lumbar region
M99.14	Subluxation complex (vertebral)…… of sacral region

Table A2: The relevant NDC codes related to CIII buprenorphine (Belbuca® and buprenorphine patch).

Description	NDC codes
Belbuca®	55700086760, 59385002160, 59385002260, 59385002360, 59385002401, 59385002460, 59385002501, 59385002560, 59385002601, 59385002660, 59385002760, 63481016160, 63481020760, 63481034860, 63481051960, 63481068560, 63481082060, 63481095260
Buprenorphine Patch	00093323921, 00093323940, 00093360021, 00093360040, 00093360121, 00093360140, 00093360221, 00093360240, 00093360321, 00093360340, 00093365621, 00093365640, 00093365721, 00093365740, 00093365821, 00093365840, 00093365921, 00093365940, 35356060504, 35356060604, 35356060704, 42858035340, 42858049340, 42858058640, 42858075040, 42858083940, 54569632500, 54569632600, 55700056804, 55700057904, 59011075004, 59011075104, 59011075204, 59011075704, 59011075804, 60505707505, 60505707605, 60505707705, 60505707805, 60505707905, 69238120202, 69238120302, 69238120402, 69238120502, 69238150502

Table A3: The list of relevant oral CII opioids (SAO and LAO).

Category	Medications
Oral Schedule II Opioids (SAO, LAO)	Acetaminophen/Caffeine/Dihydrocodeine Bitartrate
	Acetaminophen/Codeine Phosphate
	Acetaminophen/Hydrocodone Bitartrate
	Acetaminophen/Oxycodone Hydrochloride
	Acetaminophen/Tramadol Hydrochloride
	Acetaminophen/Butalbital/Caffeine/Codeine Phosphate
	Aspirin/Butalbital/Caffeine/Codeine Phosphate
	Hydrocodone Bitartrate
	Hydrocodone Bitartrate/Ibuprofen
	Hydromorphone Hydrochloride
	Levorphanol Tartrate
	Meperidine Hydrochloride
	Methadone Hydrochloride
	Morphine Sulfate
	Oxycodone
	Oxycodone Hydrochloride
	Oxymorphone Hydrochloride
	Tapentadol Hydrochloride
	Tramadol Hydrochloride
	Codeine Sulfate

Table A4: The list of ICD-10-CM codes related to relevant TEAEs.

Adverse Event	Codes
QT prolongation	I45.81
Severe hypotension	I95.1, I95.2
Atrial fibrillation	I48.0, I48.3, I48.4, I48.9, I48.91, I48.92
Coronary artery disease, chest pain	I20, I20.0, I20.1, I20.2, I20.8, I20.9, I21, I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I24.0, I24.8, I24.9
Hypertension	I15, I15.8, I15.9, I16, I16.0, I16.1, I16.9
Dizziness/vertigo	R42
Somnolence	R40.0
Confusion	R41.0, R41.4, R41.8, R41.82, R41.83, R41.84, R41.840, R41.841, R41.842, R41.843, R41.844, R41.89, R41.9
Seizures	G40, G40.0, G40.00, G40.001, G40.009, G40.01, G40.011, G40.019, G40.1, G40.10, G40.101, G40.109, G40.11, G40.111, G40.119, G40.2, G40.20, G40.201, G40.209, G40.21, G40.211, G40.219, G40.3, G40.30, G40.301, G40.309, G40.31, G40.311, G40.319, G40.4, G40.40, G40.401, G40.409, G40.41, G40.411, G40.419, G40.5, G40.50, G40.501, G40.509, G40.8, G40.80, G40.801, G40.802, G40.803, G40.804, G40.89, G40.9, G40.90, G40.901, G40.909, G40.91, G40.911, G40.919
Syncope	R55
Cerebrovascular accident	I60, I60.0, I60.00, I60.01, I60.02, I60.1, I60.10, I60.11, I60.12, I60.2, I60.3, I60.30, I60.31, I60.32, I60.4, I60.5, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62, I62.0, I62.00, I62.01, I62.02, I62.03, I62.1, I62.9, I63, I63.0, I63.00, I63.01, I63.011, I63.012, I63.013, I63.019, I63.02, I63.03, I63.031, I63.032, I63.033, I63.039, I63.09, I63.1, I63.10, I63.11, I63.111, I63.112, I63.113, I63.119, I63.12, I63.13, I63.131, I63.132, I63.133, I63.139, I63.19, I63.2, I63.20, I63.21, I63.211, I63.212, I63.213, I63.219, I63.22, I63.23, I63.231, I63.232, I63.233, I63.239, I63.29, I63.3, I63.30, I63.31, I63.311, I63.312, I63.313, I63.319, I63.32, I63.321, I63.322, I63.323, I63.329, I63.33, I63.331, I63.332, I63.333, I63.339, I63.34, I63.341, I63.342, I63.343, I63.349, I63.39, I63.4, I63.40, I63.41, I63.411, I63.412, I63.413, I63.419, I63.42, I63.421, I63.422, I63.423, I63.429, I63.43, I63.431, I63.432, I63.433, I63.439, I63.44, I63.441, I63.442, I63.443, I63.449, I63.49, I63.5, I63.50, I63.51, I63.511, I63.512, I63.513, I63.519, I63.52, I63.521, I63.522, I63.523, I63.529, I63.53, I63.531, I63.532, I63.533, I63.539, I63.54, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.81, I63.89, I63.9, I67, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.6, I67.7, I67.8, I67.81, I67.82, I67.83, I67.84, I67.841, I67.848, I67.89, I67.9
Nervousness	R45.0

Visual disturbances	H53, H53.0, H53.00, H53.001, H53.002, H53.003, H53.009, H53.1, H53.10, H53.11, H53.12, H53.121, H53.122, H53.123, H53.129, H53.13, H53.131, H53.132, H53.133, H53.139, H53.14, H53.141, H53.142, H53.143, H53.149, H53.15, H53.16, H53.19, H53.2, H53.3, H53.30, H53.31, H53.32, H53.33, H53.34, H53.4, H53.40, H53.41, H53.411, H53.412, H53.413, H53.419, H53.42, H53.421, H53.422, H53.423, H53.429, H53.43, H53.431, H53.432, H53.433, H53.439, H53.45, H53.451, H53.452, H53.453, H53.459, H53.46, H53.461, H53.462, H53.469, H53.47, H53.48, H53.481, H53.482, H53.483, H53.489, H53.5, H53.50, H53.51, H53.52, H53.53, H53.54, H53.55, H53.59, H53.6, H53.60, H53.61, H53.62, H53.63, H53.69, H53.7, H53.71, H53.72, H53.8, H53.9
Sleeplessness or insomnia	F519, F5102, F5109, F5101, F5103, F5109, F5119, F5111, F5112, F5119, F518, F513, G47419, G47411, G47429, G47421, G479, G4730, G4700, G4730, G4710, G4720, G478, G4730, F518, G478, Z72820
Suicide ideation	R45.85, R45.850, R45.851, T14.91, T14.91XA, T14.91XD, T14.91XS, X71, X71.0, X71.0XXA, X71.0XXD, X71.0XXS, X71.1, X71.1XXA, X71.1XXD, X71.1XXS, X71.2, X71.2XXA, X71.2XXD, X71.2XXS, X71.3, X71.3XXA, X71.3XXD, X71.3XXS, X71.8, X71.8XXA, X71.8XXD, X71.8XXS, X71.9, X71.9XXA, X71.9XXD, X71.9XXS, X72, X72.XXXA, X72.XXXD, X72.XXXS, X73, X73.0, X73.0XXA, X73.0XXD, X73.0XXS, X73.1 In, X73.1XXA, X73.1XXD, X73.1XXS, X73.2 In, X73.2XXA, X73.2XXD, X73.2XXS, X73.8 In, X73.8XXA, X73.8XXD, X73.8XXS, X73.9 In, X73.9XXA, X73.9XXD, X73.9XXS, X74, X74.0, X74.01, X74.01XA, X74.01XD, X74.01XS, X74.02, X74.02XA, X74.02XD, X74.02XS, X74.09, X74.09XA, X74.09XD, X74.09XS, X74.8, X74.8XXA, X74.8XXD, X74.8XXS, X74.9, X74.9XXA, X74.9XXD, X74.9XXS, X75, X75.XXXA, X75.XXXD, X75.XXXS, X76, X76.XXXA, X76.XXXD, X76.XXXS, X77, X77.0, X77.0XXA, X77.0XXD, X77.0XXS, X77.1, X77.1XXA, X77.1XXD, X77.1XXS, X77.2, X77.2XXA, X77.2XXD, X77.2XXS, X77.3, X77.3XXA, X77.3XXD, X77.3XXS, X77.8, X77.8XXA, X77.8XXD, X77.8XXS, X77.9, X77.9XXA, X77.9XXD, X77.9XXS, X78, X78.0, X78.0XXA, X78.0XXD, X78.0XXS, X78.1, X78.1XXA, X78.1XXD, X78.1XXS, X78.2, X78.2XXA, X78.2XXD, X78.2XXS, X78.8, X78.8XXA, X78.8XXD, X78.8XXS, X78.9, X78.9XXA, X78.9XXD, X78.9XXS, X79, X79.XXXA, X79.XXXD, X79.XXXS, X80, X80.XXXA, X80.XXXD, X80.XXXS, X81, X81.0, X81.0XXA, X81.0XXD, X81.0XXS, X81.1, X81.1XXA, X81.1XXD, X81.1XXS, X81.8, X81.8XXA, X81.8XXD, X81.8XXS, X82, X82.0, X82.0XXA, X82.0XXD, X82.0XXS, X82.1, X82.1XXA, X82.1XXD, X82.1XXS, X82.2, X82.2XXA, X82.2XXD, X82.2XXS, X82.8, X82.8XXA, X82.8XXD, X82.8XXS, X83, X83.0, X83.0XXA, X83.0XXD, X83.0XXS, X83.1, X83.1XXA, X83.1XXD, X83.1XXS, X83.2, X83.2XXA, X83.2XXD, X83.2XXS, X83.8, X83.8XXA, X83.8XXD, X83.8XXS
Opioid abuse/ dependence	F11, F11.1, F11.10, F11.11, F11.12, F11.120, F11.121, F11.122, F11.129, F11.13, F11.14, F11.15, F11.150, F11.151, F11.159, F11.18, F11.181, F11.182, F11.188, F11.19, F11.2, F11.20, F11.21, F11.22, F11.220, F11.221, F11.222, F11.229, F11.23, F11.24, F11.25, F11.250, F11.251, F11.259, F11.28, F11.281, F11.282, F11.288, F11.29, F11.9, F11.90, F11.91, F11.92, F11.920, F11.921, F11.922, F11.929, F11.93, F11.94, F11.95, F11.950, F11.951, F11.959, F11.98, F11.981, F11.982, F11.988, F11.99
Opioid poisoning	T40, T40.0, T40.0X, T40.0X1, T40.0X1A, T40.0X1D, T40.0X1S, T40.0X2, T40.0X2A, T40.0X2D, T40.0X2S, T40.0X3, T40.0X3A, T40.0X3D, T40.0X3S, T40.0X4, T40.0X4A, T40.0X4D, T40.0X4S, T40.0X5, T40.0X5A, T40.0X5D, T40.0X5S, T40.0X6, T40.0X6A, T40.0X6D, T40.0X6S, T40.2, T40.2X, T40.2X1, T40.2X1A, T40.2X1D, T40.2X1S, T40.2X2, T40.2X2A, T40.2X2D, T40.2X2S, T40.2X3, T40.2X3A, T40.2X3D, T40.2X3S, T40.2X4, T40.2X4A, T40.2X4D, T40.2X4S, T40.2X5, T40.2X5A, T40.2X5D, T40.2X5S, T40.2X6, T40.2X6A, T40.2X6D, T40.2X6S, T40.3, T40.3X, T40.3X1, T40.3X1A, T40.3X1D, T40.3X1S, T40.3X2, T40.3X2A, T40.3X2D, T40.3X2S, T40.3X3, T40.3X3A, T40.3X3D, T40.3X3S, T40.3X4, T40.3X4A, T40.3X4D, T40.3X4S, T40.3X5, T40.3X5A, T40.3X5D, T40.3X5S, T40.3X6, T40.3X6A, T40.3X6D, T40.3X6S, T40.4, T40.41, T40.411, T40.411A, T40.411D, T40.411S, T40.412, T40.412A, T40.412D, T40.412S, T40.413, T40.413A, T40.413D, T40.413S, T40.414, T40.414A, T40.414D, T40.414S, T40.415, T40.415A, T40.415D, T40.415S, T40.416, T40.416A, T40.416D, T40.416S, T40.42, T40.421, T40.421A, T40.421D, T40.421S, T40.422, T40.422A, T40.422D, T40.422S, T40.423, T40.423A, T40.423D, T40.423S, T40.424, T40.424A, T40.424D, T40.424S, T40.425, T40.425A, T40.425D, T40.425S, T40.426, T40.426A, T40.426D, T40.426S, T40.49, T40.491, T40.491A, T40.491D, T40.491S, T40.492, T40.492A, T40.492D, T40.492S, T40.493, T40.493A, T40.493D, T40.493S, T40.494, T40.494A, T40.494D, T40.494S, T40.495, T40.495A, T40.495D, T40.495S, T40.496, T40.496A, T40.496D, T40.496S, T40.6, T40.60, T40.601, T40.601A, T40.601D, T40.601S, T40.602, T40.602A, T40.602D, T40.602S, T40.603, T40.603A, T40.603D, T40.603S, T40.604, T40.604A, T40.604D, T40.604S, T40.605, T40.605A, T40.605D, T40.605S, T40.606, T40.606A, T40.606D, T40.606S, T40.69, T40.691, T40.691A, T40.691D, T40.691S, T40.692, T40.692A, T40.692D, T40.692S, T40.693, T40.693A, T40.693D, T40.693S, T40.694, T40.694A, T40.694D, T40.694S, T40.695, T40.695A, T40.695D, T40.695S, T40.696, T40.696A, T40.696D, T40.696S
Headache	R51, R51.0, R51.9, G44.4, G44.40, G44.41
Fatigue	R53, R53.1, R53.8, R53.81, R53.83
Anaphylactic/allergic reactions	T78.2, T78.2XXA, T78.2XXD, T78.2XXS, T78.3, T78.3XXA, T78.3XXD, T78.3XXS, T78.4, T78.40, T78.40XA, T78.40XD, T78.40XS, T78.49, T78.49XA, T78.49XD, T78.49XS, T88.6, T88.6XXA, T88.6XXD, T88.6XXS, T88.7, T88.7XXA, T88.7XXD, T88.7XXS, T88.8, T88.8XXA, T88.8XXD, T88.8XXS, T88.9, T88.9XXA, T88.9XXD, T88.9XXS
Dehydration	E86, E86.0, E86.1, E86.9
Dry mouth	R68.2
Xerostomia	K11.7
Sweating	R61
Hot flushes	R23.2
Sinusitis	J01, J01.0, J01.00, J01.01, J01.1, J01.10, J01.11, J01.2, J01.20, J01.21, J01.3, J01.30, J01.31, J01.4, J01.40, J01.41, J01.8, J01.80, J01.81, J01.9, J01.90, J01.91
Nausea & Vomiting	R11, R11.0, R11.1, R11.10, R11.11, R11.12, R11.13, R11.14, R11.15, R11.2
Constipation	K59.0, K59.00, K59.01, K59.02, K59.03, K59.09, K58.1
Hepatotoxicity	K71, K71.0, K71.1, K71.10, K71.11, K71.2, K71.50, K71.51, K71.6, K71.7, K71.8, K71.9
Cholecystitis	K81, K81.0, K81.2, K81.9
Abdominal pain	R10, R10.0, R10.1, R10.10, R10.11, R10.12, R10.13, R10.2, R10.3, R10.30, R10.31, R10.32, R10.33, R10.8, R10.81, R10.811, R10.812, R10.813, R10.814, R10.815, R10.816, R10.817, R10.819, R10.82, R10.821, R10.822, R10.823, R10.824, R10.825, R10.826, R10.827, R10.829, R10.83, R10.84, R10.9
Diarrhea	K59.1, R19.7, K58.0, K52.1
Loss of appetite, anorexia	F50, F50.0, F50.00, F50.01, F50.02, F50.8, F50.82, F50.89, F50.9, R63.0, R63.4, R63.6
Adrenal insufficiency	E27.2, E27.3, E27.4, E27.40, E27.49

Ankle fracture (risk of falls and fractures)	M84.3, M84.30, M84.30XA, M84.30XD, M84.30XG, M84.30XK, M84.30XP, M84.30XS, M84.31, M84.311, M84.311A, M84.311D, M84.311G, M84.311K, M84.311P, M84.311S, M84.312, M84.312A, M84.312D, M84.312G, M84.312K, M84.312P, M84.312S, M84.319, M84.319A, M84.319D, M84.319G, M84.319K, M84.319P, M84.319S, M84.32, M84.321, M84.321A, M84.321D, M84.321G, M84.321K, M84.321P, M84.321S, M84.322, M84.322A, M84.322D, M84.322G, M84.322K, M84.322P, M84.322S, M84.329, M84.329A, M84.329D, M84.329G, M84.329K, M84.329P, M84.329S, M84.33, M84.331, M84.331A, M84.331D, M84.331G, M84.331K, M84.331P, M84.331S, M84.332, M84.332A, M84.332D, M84.332G, M84.332K, M84.332P, M84.332S, M84.333, M84.333A, M84.333D, M84.333G, M84.333K, M84.333P, M84.333S, M84.334, M84.334A, M84.334D, M84.334G, M84.334K, M84.334P, M84.334S, M84.339, M84.339A, M84.339D, M84.339G, M84.339K, M84.339P, M84.339S, M84.34, M84.341, M84.341A, M84.341D, M84.341G, M84.341K, M84.341P, M84.341S, M84.342, M84.342A, M84.342D, M84.342G, M84.342K, M84.342P, M84.342S, M84.343, M84.343A, M84.343D, M84.343G, M84.343K, M84.343P, M84.343S, M84.344, M84.344A, M84.344D, M84.344G, M84.344K, M84.344P, M84.344S, M84.345, M84.345A, M84.345D, M84.345G, M84.345K, M84.345P, M84.345S, M84.346, M84.346A, M84.346D, M84.346G, M84.346K, M84.346P, M84.346S, M84.35, M84.350, M84.350A, M84.350D, M84.350G, M84.350K, M84.350P, M84.350S, M84.351, M84.351A, M84.351D, M84.351G, M84.351K, M84.351P, M84.351S, M84.352, M84.352A, M84.352D, M84.352G, M84.352K, M84.352P, M84.352S, M84.353, M84.353A, M84.353D, M84.353G, M84.353K, M84.353P, M84.353S, M84.359, M84.359A, M84.359D, M84.359G, M84.359K, M84.359P, M84.359S, M84.36, M84.361, M84.361A, M84.361D, M84.361G, M84.361K, M84.361P, M84.361S, M84.362, M84.362A, M84.362D, M84.362G, M84.362K, M84.362P, M84.362S, M84.363, M84.363A, M84.363D, M84.363G, M84.363K, M84.363P, M84.363S, M84.364, M84.364A, M84.364D, M84.364G, M84.364K, M84.364P, M84.364S, M84.369, M84.369A, M84.369D, M84.369G, M84.369K, M84.369P, M84.369S, M84.37, M84.371, M84.371A, M84.371D, M84.371G, M84.371K, M84.371P, M84.371S, M84.372, M84.372A, M84.372D, M84.372G, M84.372K, M84.372P, M84.372S, M84.373, M84.373A, M84.373D, M84.373G, M84.373K, M84.373P, M84.373S, M84.374, M84.374A, M84.374D, M84.374G, M84.374K, M84.374P, M84.374S, M84.375, M84.375A, M84.375D, M84.375G, M84.375K, M84.375P, M84.375S, M84.376, M84.376A, M84.376D, M84.376G, M84.376K, M84.376P, M84.376S, M84.377, M84.377A, M84.377D, M84.377G, M84.377K, M84.377P, M84.377S, M84.378, M84.378A, M84.378D, M84.378G, M84.378K, M84.378P, M84.378S, M84.379, M84.379A, M84.379D, M84.379G, M84.379K, M84.379P, M84.379S, M84.38, M84.38XA, M84.38XD, M84.38XG, M84.38XK, M84.38XP, M84.38XS, M84.4, M84.40, M84.40XA, M84.40XD, M84.40XG, M84.40XK, M84.40XP, M84.40XS, M84.41, M84.411, M84.411A, M84.411D, M84.411G, M84.411K, M84.411P, M84.411S, M84.412, M84.412A, M84.412D, M84.412G, M84.412K, M84.412P, M84.412S, M84.419, M84.419A, M84.419D, M84.419G, 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M84.631S, M84.632, M84.632A, M84.632D, M84.632G, M84.632K, M84.632P, M84.632S, M84.633, M84.633A, M84.633D, M84.633G, M84.633K, M84.633P, M84.633S, M84.634, M84.634A, M84.634D, M84.634G, M84.634K, M84.634P, M84.634S, M84.639, M84.639A, M84.639D, M84.639G, M84.639K, M84.639P, M84.639S, M84.64, M84.641, M84.641A, M84.641D, M84.641G, M84.641K, M84.641P, M84.641S, M84.642, M84.642A, M84.642D, M84.642G, M84.642K, M84.642P, M84.642S, M84.649, M84.649A, M84.649D, M84.649G, M84.649K, M84.649P, M84.649S, M84.65, M84.650, M84.650A, M84.650D, M84.650G, M84.650K, M84.650P, M84.650S, M84.651, M84.651A, M84.651D, M84.651G, M84.651K, M84.651P, M84.651S, M84.652, M84.652A, M84.652D, M84.652G, M84.652K, M84.652P, M84.652S, M84.653, M84.653A, M84.653D, M84.653G, M84.653K, M84.653P, M84.653S, M84.659, M84.659A, M84.659D, M84.659G, M84.659K, M84.659P, M84.659S, M84.66, M84.661, M84.661A, M84.661D, M84.661G, M84.661K, M84.661P, M84.661S, M84.662, M84.662A, M84.662D, M84.662G, M84.662K, M84.662P, M84.662S, 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Osteoarthritis	M15.3, M15.8, M15.9, M16.6, M16.7, M16.9, M17.4, M17.5, M17.9, M18.4, M18.5, M18.50, M18.51, M18.52, M18.9, M19.2, M19.21, M19.211, M19.212, M19.219, M19.22, M19.221, M19.222, M19.229, M19.23, M19.231, M19.232, M19.239, M19.24, M19.241, M19.242, M19.249, M19.27, M19.271, M19.272, M19.279, M19.29, M19.9, M19.90, M19.93,
Respiratory depression	J96.0, J96.00, J96.01, J96.02, J96.9, J96.90, J96.91, J96.92, R09.2
Pneumonia	J17, J18, J18.0, J18.1, J18.2, J18.8, J18.9, A37.91, J84.11, J84.111, J84.112, J84.113, J84.114, J84.115, J84.116, J84.117
Cellulitis	L03.01, L03.011, L03.012, L03.019, L03.03, L03.031, L03.032, L03.039, L03.1, L03.11, L03.111, L03.112, L03.113, L03.114, L03.115, L03.116, L03.119, L03.2, L03.21, L03.211, L03.213, L03.22, L03.221, L03.3, L03.31, L03.311, L03.312, L03.313, L03.314, L03.315, L03.316, L03.317, L03.319, L03.8, L03.81, L03.811, L03.818, L03.9, L03.90, H60.1, H60.10, H60.11, H60.12, H60.13, H05.01, H05.011, H05.012, H05.013, H05.019, N73.0, K12.2, N48.22
Pruritus	L29, L29.0, L29.1, L29.2, L29.3, L29.8, L29.9
Erythema	L51, L51.0, L51.1, L51.2, L51.3, L51.8, L51.9, L52, L53, L53.0, L53.1, L53.2, L53.3, L53.8, L53.9, L54
Rash	R21, D72.12
Irritation	L24, L24.4, L24.8, L24.89, L24.9
Micturition difficulty, urinary retention	R30, R30.0, R30.1, R30.9, R32, R33, R33.0, R33.8, R33.9, R34, R39, R39.1, R39.11, R39.12, R39.13, R39.14, R39.15, R39.16, R39.19, R39.191, R39.192, R39.198, R39.8, R39.81, R39.89, R39.9

Table A5: Demographic characteristics of matched patients in the primary analysis.

	CIII Buprenorphine	**CII Opioids**	**P-value***
	(N=545)	(N=951)	
Age, mean (SD)	75.6 (7.9)	75.2 (7.5)	0.259
Gender, n (%)			
Male	211 (38.7)	395 (41.5)	0.285
Female	334 (61.3)	556 (58.5)	0.285
Health Plan, n (%)			
Basic/major medical	0 (0.0)	0 (0.0)	-
Comprehensive	158 (29.0)	275 (28.9)	0.976
Exclusive Provider Organization	3 (0.6)	7 (0.7)	0.755
Health Maintenance Organization	105 (19.3)	191 (20.1)	0.702
Non-Capitated Point-of-Service	2 (0.4)	7 (0.7)	0.5
POS with capitation	11 (2.0)	17 (1.8)	0.751
Preferred Provider Organization	239 (43.9)	402 (42.3)	0.552
Consumer-Driven Health Plan	3 (0.6)	9 (0.9)	0.553
High Deductible Health Plan	4 (0.7)	8 (0.8)	1
Unknown	20 (3.7)	35 (3.7)	0.992
Region, n (%)			
North East	57 (10.5)	105 (11.0)	0.727
North Central	238 (43.7)	413 (43.4)	0.928
South	185 (33.9)	326 (34.3)	0.895
West	64 (11.7)	105 (11.0)	0.68
Unknown	1 (0.2)	2 (0.2)	1
*Chi-square test was performed for categorical variables and independent T-test for continuous variables			

Table A6: Clinical characteristics of matched patients in the primary analysis.

	CIII Buprenorphine	CII Opioids	P-value*
	(N=545)	(N=951)	
Charlson Comorbidity Index			
0	209 (38.3)	350 (36.8)	0.552
1	123 (22.6)	231 (24.3)	0.451
2	90 (16.5)	146 (15.4)	0.553
3	50 (9.2)	111 (11.7)	0.134
4+	73 (13.4)	113 (11.9)	0.394
Charlson Comorbidity Index, mean (SD)	1.6 (2.0)	1.6 (2.0)	0.788
Charlson Comorbidity Index Components			
Myocardial infarction	18 (3.3)	27 (2.8)	0.613
Congestive heart failure	56 (10.3)	98 (10.3)	0.985
Peripheral vascular disease	70 (12.8)	141 (14.8)	0.289
Cerebrovascular disease	50 (9.2)	96 (10.1)	0.564
Dementia	17 (3.1)	30 (3.2)	0.97
Chronic pulmonary disease	94 (17.2)	176 (18.5)	0.542
Rheumatic disease	27 (5.0)	42 (4.4)	0.633
Peptic ulcer disease	11 (2.0)	10 (1.1)	0.126
Mild liver disease	9 (1.7)	10 (1.1)	0.319
Moderate or severe liver disease	1 (0.2)	0 (0.0)	0.364
Diabetes without chronic complication	110 (20.2)	170 (17.9)	0.271
Diabetes with chronic complication	52 (9.5)	74 (7.8)	0.238
Hemiplegia or paraplegia	3 (0.6)	8 (0.8)	0.755
Renal disease	61 (11.2)	94 (9.9)	0.424
Malignancy	58 (10.6)	114 (12.0)	0.432
Metastatic solid tumor	8 (1.5)	23 (2.4)	0.214
AIDS/HIV	0 (0.0)	2 (0.2)	0.537
Mental Disorders			
Anxiety	68 (12.5)	124 (13.0)	0.755
Bipolar disorder	0 (0.0)	0 (0.0)	-
Depression	69 (12.7)	96 (10.1)	0.127
Sleep disorder	61 (11.2)	89 (9.4)	0.256
Psychosis	4 (0.7)	7 (0.7)	1
Post-traumatic stress syndrome	1 (0.2)	3 (0.3)	1
Chronic Pain Specific Comorbidities			
Joint pain	119 (21.8)	203 (21.3)	0.825
Musculoskeletal disorders	403 (73.9)	709 (74.6)	0.796
Diabetic neuropathy	46 (8.4)	66 (6.9)	0.289
Other neuropathies	305 (56.0)	516 (54.3)	0.524
Spine disorders	542 (99.4)	947 (99.6)	0.71
Fibromyalgia	16 (2.9)	17 (1.8)	0.146
*Chi-square test was performed for categorical variables and independent T-test for continuous variables			

Table A7: Demographic characteristics of non-matched patients in the sub-analysis #1.

	Belbuca®	CII Opioids	P-value*
	(N=203)	(N=25,975)	
Age, mean (SD)	71.3 (7.2)	74.5 (7.2)	<0.001
Gender, n (%)			
Male	75 (36.9)	11,372 (43.8)	0.051
Female	128 (63.1)	14,603 (56.2)	0.051
Health Plan, n (%)			
Basic/major medical	0 (0.0)	0 (0.0)	-
Comprehensive	90 (44.3)	6,372 (24.5)	<0.001
Exclusive Provider Organization	0 (0.0)	133 (0.5)	0.63
Health Maintenance Organization	28 (13.8)	5,418 (20.9)	0.013
Non-Capitated Point-of-Service	2 (1.0)	121 (0.5)	0.247
POS with capitation	6 (3.0)	433 (1.7)	0.154
Preferred Provider Organization	66 (32.5)	12,331 (47.5)	<0.001
Consumer-Driven Health Plan	0 (0.0)	155 (0.6)	0.637
High Deductible Health Plan	2 (1.0)	178 (0.7)	0.408
Unknown	9 (4.4)	834 (3.2)	0.326
Region, n (%)			
North East	13 (6.4)	4,691 (18.1)	<0.001
North Central	57 (28.1)	10,905 (42.0)	<0.001
South	108 (53.2)	7,609 (29.3)	<0.001
West	25 (12.3)	2,742 (10.6)	0.417
Unknown	0 (0.0)	28 (0.1)	1
*Chi-square test was performed for categorical variables and independent T-test for continuous variables			

Table A8: Clinical characteristics of non-matched patients in the sub-analysis #1.

	Belbuca®	CII Opioids	P-value*
	(N=203)	(N=25,975)	
Charlson Comorbidity Index			
0	65 (32.0)	9,146 (35.2)	0.343
1	45 (22.2)	5,472 (21.1)	0.702
2	28 (13.8)	3,842 (14.8)	0.69
3	27 (13.3)	2,833 (10.9)	0.276
4+	38 (18.7)	4,682 (18.0)	0.798
Charlson Comorbidity Index, mean (SD)	1.9 (2.1)	1.9 (2.3)	0.786
Charlson Comorbidity Index Components			
Myocardial infarction	5 (2.5)	811 (3.1)	0.838
Congestive heart failure	22 (10.8)	2,680 (10.3)	0.808
Peripheral vascular disease	26 (12.8)	3,612 (13.9)	0.652
Cerebrovascular disease	20 (9.9)	2,755 (10.6)	0.728
Dementia	6 (3.0)	935 (3.6)	0.623
Chronic pulmonary disease	56 (27.6)	4,535 (17.5)	<0.001
Rheumatic disease	13 (6.4)	1,160 (4.5)	0.184
Peptic ulcer disease	5 (2.5)	284 (1.1)	0.075
Mild liver disease	12 (5.9)	868 (3.3)	0.043
Moderate or severe liver disease	0 (0.0)	29 (0.1)	1
Diabetes without chronic complication	50 (24.6)	6,552 (25.2)	0.846
Diabetes with chronic complication	34 (16.7)	3,734 (14.4)	0.337
Hemiplegia or paraplegia	2 (1.0)	286 (1.1)	1
Renal disease	26 (12.8)	2,631 (10.1)	0.208
Malignancy	18 (8.9)	3,760 (14.5)	0.024
Metastatic solid tumor	3 (1.5)	654 (2.5)	0.497
AIDS/HIV	0 (0.0)	20 (0.1)	1
Mental Disorders			
Anxiety	62 (30.5)	3,285 (12.6)	<0.001
Bipolar disorder	4 (2.0)	209 (0.8)	0.085
Depression	71 (35.0)	3,344 (12.9)	<0.001
Sleep disorder	36 (17.7)	2,515 (9.7)	<0.001
Psychosis	3 (1.5)	182 (0.7)	0.174
Post-traumatic stress syndrome	8 (3.9)	132 (0.5)	<0.001
Chronic Pain Specific Comorbidities			
Joint pain	59 (29.1)	4,885 (18.8)	<0.001
Musculoskeletal disorders	157 (77.3)	15,886 (61.2)	<0.001
Diabetic neuropathy	36 (17.7)	3,257 (12.5)	0.026
Other neuropathies	131 (64.5)	12,185 (46.9)	<0.001
Spine disorders	201 (99.0)	25,787 (99.3)	0.661
Fibromyalgia	24 (11.8)	1,262 (4.9)	<0.001

*Chi-square test was performed for categorical variables and independent T-test for continuous variables

Table A9: Demographic characteristics of matched patients in the sub-analysis #1.

	Belbuca®	CII Opioids	P-value*
	(N=124)	(N=297)	
Age, mean (SD)	73.3 (6.4)	74.4 (7.0)	0.144
Gender, n (%)			
Male	51 (41.1)	134 (45.1)	0.452
Female	73 (58.9)	163 (54.9)	0.452
Health Plan, n (%)			
Basic/major medical	0 (0.0)	0 (0.0)	-
Comprehensive	43 (34.7)	99 (33.3)	0.79
Exclusive Provider Organization	0 (0.0)	0 (0.0)	-
Health Maintenance Organization	20 (16.1)	36 (12.1)	0.27
Non-Capitated Point-of-Service	1 (0.8)	0 (0.0)	0.295
POS with capitation	3 (2.4)	10 (3.4)	0.763
Preferred Provider Organization	50 (40.3)	127 (42.8)	0.644
Consumer-Driven Health Plan	0 (0.0)	0 (0.0)	-
High Deductible Health Plan	2 (1.6)	4 (1.3)	1
Unknown	5 (4.0)	21 (7.1)	0.275
Region, n (%)			
North East	9 (7.3)	22 (7.4)	0.957
North Central	41 (33.1)	111 (37.4)	0.401
South	57 (46.0)	129 (43.4)	0.633
West	17 (13.7)	35 (11.8)	0.584
Unknown	0 (0.0)	0 (0.0)	-

*Chi-square test was performed for categorical variables and independent T-test for continuous variables

Table A10: Clinical characteristics of matched patients in the sub-analysis #1.

	Belbuca®	CII Opioids	P-value*
	(N=124)	(N=297)	
Charlson Comorbidity Index			
0	52 (41.9)	130 (43.8)	0.729
1	26 (21.0)	59 (19.9)	0.797
2	12 (9.7)	40 (13.5)	0.281
3	16 (12.9)	29 (9.8)	0.342
4+	18 (14.5)	39 (13.1)	0.705
Charlson Comorbidity Index, mean (SD)	1.5 (1.8)	1.4 (1.8)	0.612
Charlson Comorbidity Index Components			
Myocardial infarction	4 (3.2)	6 (2.0)	0.49
Congestive heart failure	12 (9.7)	31 (10.4)	0.814
Peripheral vascular disease	14 (11.3)	30 (10.1)	0.716
Cerebrovascular disease	7 (5.6)	23 (7.7)	0.445
Dementia	5 (4.0)	10 (3.4)	0.775
Chronic pulmonary disease	21 (16.9)	37 (12.5)	0.224
Rheumatic disease	6 (4.8)	10 (3.4)	0.472
Peptic ulcer disease	4 (3.2)	2 (0.7)	0.065
Mild liver disease	6 (4.8)	9 (3.0)	0.362
Moderate or severe liver disease	0 (0.0)	0 (0.0)	-
Diabetes without chronic complication	29 (23.4)	70 (23.6)	0.968
Diabetes with chronic complication	17 (13.7)	40 (13.5)	0.947
Hemiplegia or paraplegia	0 (0.0)	2 (0.7)	1
Renal disease	15 (12.1)	38 (12.8)	0.844
Malignancy	6 (4.8)	16 (5.4)	0.818
Metastatic solid tumor	1 (0.8)	1 (0.3)	0.503
AIDS/HIV	0 (0.0)	0 (0.0)	-
Mental Disorders			
Anxiety	22 (17.7)	41 (13.8)	0.302
Bipolar disorder	1 (0.8)	3 (1.0)	1
Depression	23 (18.5)	44 (14.8)	0.34
Sleep disorder	16 (12.9)	33 (11.1)	0.601
Psychosis	1 (0.8)	0 (0.0)	0.295
Post-traumatic stress syndrome	1 (0.8)	1 (0.3)	0.503
Chronic Pain Specific Comorbidities			
Joint pain	27 (21.8)	44 (14.8)	0.082
Musculoskeletal disorders	87 (70.2)	202 (68.0)	0.665
Diabetic neuropathy	18 (14.5)	37 (12.5)	0.568
Other neuropathies	71 (57.3)	168 (56.6)	0.896
Spine disorders	122 (98.4)	295 (99.3)	0.585
Fibromyalgia	10 (8.1)	20 (6.7)	0.629

*Chi-square test was performed for categorical variables and independent T-test for continuous variables

Table A11: Demographic characteristics of non-matched patients in the sub-analysis #2.

	Belbuca®	Buprenorphine patch	P-value*
	(N=203)	(N=817)	
Age, mean (SD)	71.3 (7.2)	75.8 (7.9)	<0.001
Gender, n (%)			
Male	75 (36.9)	276 (33.8)	0.396
Female	128 (63.1)	541 (66.2)	0.396
Health Plan, n (%)			
Basic/major medical	0 (0.0)	0 (0.0)	-
Comprehensive	90 (44.3)	250 (30.6)	<0.001
Exclusive Provider Organization	0 (0.0)	4 (0.5)	1
Health Maintenance Organization	28 (13.8)	147 (18.0)	0.155
Non-Capitated Point-of-Service	2 (1.0)	2 (0.2)	0.179
POS with capitation	6 (3.0)	7 (0.9)	0.017
Preferred Provider Organization	66 (32.5)	377 (46.1)	<0.001
Consumer-Driven Health Plan	0 (0.0)	3 (0.4)	1
High Deductible Health Plan	2 (1.0)	3 (0.4)	0.261
Unknown	9 (4.4)	24 (2.9)	0.281
Region, n (%)			
North East	13 (6.4)	75 (9.2)	0.207
North Central	57 (28.1)	411 (50.3)	<0.001
South	108 (53.2)	252 (30.8)	<0.001
West	25 (12.3)	78 (9.5)	0.241
Unknown	0 (0.0)	1 (0.1)	1
*Chi-square test was performed for categorical variables and independent T-test for continuous variables			

Table A12: Clinical characteristics of non-matched patients in the sub-analysis #2.

	Belbuca®	Buprenorphine patch	P-value*
	(N=203)	(N=817)	
Charlson Comorbidity Index			
0	65 (32.0)	207 (25.3)	0.054
1	45 (22.2)	170 (20.8)	0.671
2	28 (13.8)	128 (15.7)	0.507
3	27 (13.3)	97 (11.9)	0.577
4+	38 (18.7)	215 (26.3)	0.025
Charlson Comorbidity Index, mean (SD)	1.9 (2.1)	2.4 (2.5)	0.008
Charlson Comorbidity Index Components			
Myocardial infarction	5 (2.5)	39 (4.8)	0.178
Congestive heart failure	22 (10.8)	137 (16.8)	0.037
Peripheral vascular disease	26 (12.8)	140 (17.1)	0.135
Cerebrovascular disease	20 (9.9)	109 (13.3)	0.181
Dementia	6 (3.0)	45 (5.5)	0.135
Chronic pulmonary disease	56 (27.6)	213 (26.1)	0.661
Rheumatic disease	13 (6.4)	63 (7.7)	0.526
Peptic ulcer disease	5 (2.5)	13 (1.6)	0.378
Mild liver disease	12 (5.9)	44 (5.4)	0.769
Moderate or severe liver disease	0 (0.0)	3 (0.4)	1
Diabetes without chronic complication	50 (24.6)	244 (29.9)	0.141
Diabetes with chronic complication	34 (16.7)	187 (22.9)	0.057
Hemiplegia or paraplegia	2 (1.0)	10 (1.2)	1
Renal disease	26 (12.8)	116 (14.2)	0.609
Malignancy	18 (8.9)	93 (11.4)	0.303
Metastatic solid tumor	3 (1.5)	14 (1.7)	1
AIDS/HIV	0 (0.0)	0 (0.0)	-
Mental Disorders			
Anxiety	62 (30.5)	178 (21.8)	0.008
Bipolar disorder	4 (2.0)	21 (2.6)	0.802
Depression	71 (35.0)	210 (25.7)	0.008
Sleep disorder	36 (17.7)	146 (17.9)	0.964
Psychosis	3 (1.5)	12 (1.5)	1
Post-traumatic stress syndrome	8 (3.9)	7 (0.9)	0.001
Chronic Pain Specific Comorbidities			
Joint pain	59 (29.1)	249 (30.5)	0.695
Musculoskeletal disorders	157 (77.3)	607 (74.3)	0.371
Diabetic neuropathy	36 (17.7)	160 (19.6)	0.549
Other neuropathies	131 (64.5)	528 (64.6)	0.98
Spine disorders	201 (99.0)	814 (99.6)	0.261
Fibromyalgia	24 (11.8)	80 (9.8)	0.392
*Chi-square test was performed for categorical variables and independent T-test for continuous variables			

Table A13: Demographic characteristics of matched patients in the sub-analysis #2.

	Belbuca®	Buprenorphine patch	P-value*
	(N=62)	(N=62)	
Age, mean (SD)	74.0 (6.3)	74.2 (6.3)	0.82
Gender, n (%)			
Male	27 (43.5)	20 (32.3)	0.195
Female	35 (56.5)	42 (67.7)	0.195
Health Plan, n (%)			
Basic/major medical	0 (0.0)	0 (0.0)	-
Comprehensive	23 (37.1)	21 (33.9)	0.707
Exclusive Provider Organization	0 (0.0)	0 (0.0)	-
Health Maintenance Organization	10 (16.1)	13 (21.0)	0.488
Non-Capitated Point-of-Service	0 (0.0)	0 (0.0)	-
POS with capitation	0 (0.0)	0 (0.0)	-
Preferred Provider Organization	27 (43.5)	26 (41.9)	0.856
Consumer-Driven Health Plan	0 (0.0)	0 (0.0)	-
High Deductible Health Plan	0 (0.0)	0 (0.0)	-
Unknown	2 (3.2)	2 (3.2)	1
Region, n (%)			
North East	4 (6.5)	4 (6.5)	1
North Central	33 (53.2)	31 (50.0)	0.719
South	16 (25.8)	19 (30.6)	0.549
West	9 (14.5)	8 (12.9)	0.794
Unknown	0 (0.0)	0 (0.0)	-

*Chi-square test was performed for categorical variables and independent T-test for continuous variables

Table A14: Clinical characteristics of matched patients in the sub-analysis #2.

	Belbuca®	Buprenorphine patch	P-value*
	(N=62)	(N=62)	
Charlson Comorbidity Index			
0	22 (35.5)	24 (38.7)	0.71
1	14 (22.6)	13 (21.0)	0.828
2	10 (16.1)	11 (17.7)	0.811
3	8 (12.9)	5 (8.1)	0.559
4+	8 (12.9)	9 (14.5)	0.794
Charlson Comorbidity Index, mean (SD)	1.6 (1.9)	1.6 (2.0)	1
Charlson Comorbidity Index Components			
Myocardial infarction	1 (1.6)	2 (3.2)	1
Congestive heart failure	5 (8.1)	8 (12.9)	0.559
Peripheral vascular disease	6 (9.7)	8 (12.9)	0.57
Cerebrovascular disease	3 (4.8)	3 (4.8)	1
Dementia	4 (6.5)	3 (4.8)	1
Chronic pulmonary disease	15 (24.2)	12 (19.4)	0.514
Rheumatic disease	3 (4.8)	2 (3.2)	1
Peptic ulcer disease	4 (6.5)	0 (0.0)	0.119
Mild liver disease	2 (3.2)	2 (3.2)	1
Moderate or severe liver disease	0 (0.0)	0 (0.0)	-
Diabetes without chronic complication	15 (24.2)	14 (22.6)	0.832
Diabetes with chronic complication	8 (12.9)	8 (12.9)	1
Hemiplegia or paraplegia	1 (1.6)	0 (0.0)	1
Renal disease	6 (9.7)	10 (16.1)	0.284
Malignancy	4 (6.5)	6 (9.7)	0.743
Metastatic solid tumor	1 (1.6)	0 (0.0)	1
AIDS/HIV	0 (0.0)	0 (0.0)	-
Mental Disorders			
Anxiety	14 (22.6)	10 (16.1)	0.363
Bipolar disorder	1 (1.6)	1 (1.6)	1
Depression	12 (19.4)	15 (24.2)	0.514
Sleep disorder	14 (22.6)	14 (22.6)	1
Psychosis	0 (0.0)	0 (0.0)	-
Post-traumatic stress syndrome	1 (1.6)	1 (1.6)	1
Chronic Pain Specific Comorbidities			
Joint pain	17 (27.4)	18 (29.0)	0.842
Musculoskeletal disorders	44 (71.0)	50 (80.6)	0.208
Diabetic neuropathy	8 (12.9)	7 (11.3)	0.783
Other neuropathies	39 (62.9)	40 (64.5)	0.852
Spine disorders	60 (96.8)	62 (100.0)	0.496
Fibromyalgia	5 (8.1)	6 (9.7)	1

*Chi-square test was performed for categorical variables and independent T-test for continuous variables