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Comparison of the Risks of Opioid Abuse or Dependence Between Tapentadol and Oxycodone: Results From a Cohort Study

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Abstract: **Tapentadol may have a lower abuse risk than other opioids because it has a relatively low affinity for the mu-opioid receptor. The aim of this retrospective cohort study was to compare the risk of opioid abuse between tapentadol immediate release (IR) and oxycodone IR using 2 claims databases (Optum and MarketScan). Subjects with no recent opioid use exposed to tapentadol IR or oxycodone IR in 2010 were followed for 1 year. The outcome was the proportion of subjects who developed opioid abuse, defined as subjects with *International Classification of Diseases, 9th revision*, codes for opioid abuse, addiction, or dependence. The relative odds of abuse were estimated using a logistic regression model with propensity-score stratification. The estimates from the 2 databases were pooled using a random effects model. There were 13,814 subjects in Optum (11,378 exposed to oxycodone, 2,436 exposed to tapentadol) and 25,553 in MarketScan (21,728 exposed to oxycodone, 3,825 exposed to tapentadol). The risk of abuse was higher in the oxycodone group than in the tapentadol group in each database. The pooled adjusted estimate for the odds of abuse was 65% lower with tapentadol than with oxycodone (odds ratio = .35, 95% confidence interval = .21–.58). The risk of receiving an abuse diagnosis with tapentadol was lower than the risk with oxycodone. Continued monitoring is warranted because opioid desirability can change over time.**

***Perspective:** This study compared the risk of receiving an opioid abuse diagnosis between tapentadol and oxycodone in 2 U.S. claims databases. The risk of receiving an abuse diagnosis was lower with tapentadol during the year of follow-up. Opioid prescribers and patients must be aware of the risk of abuse associated with all opioids.*

Key words: *Opioids, tapentadol, oxycodone, opioid abuse, opioid dependence, cohort studies.*

The burden of pain is a significant public health problem. The Institute of Medicine reported in 2011 that chronic pain affects millions of adults in the United States, more than the total affected by heart disease, cancer, and diabetes combined,[17] and that uncontrolled pain substantially reduces quality of life and productivity.[17] Opioids are increasingly prescribed for the treatment of painful chronic conditions,[20] but there is growing concern about the risk of opioid abuse, diversion,[10,20] overdose, and death.[3,32,36,40]

The mechanism of action of an opioid could influence its risk of abuse.[21,43,44] Tapentadol is an opioid with 2 mechanisms of action; it activates opioid receptors and inhibits the reuptake of norepinephrine.[19] Tapentadol has an 18-fold lower affinity for the mu-opioid receptor than morphine.[39] Because the activation of the mu-opioid receptor is responsible for the mood alterations and the euphoria associated with opioids, the risk of abuse associated with tapentadol may be expected to be lower than with other opioids. Limited evidence from population-based studies also suggests that the risk of abuse of tapentadol may be lower than other opioids. Opioid doctor shopping, that is, obtaining opioid prescriptions from multiple prescribers,[7,8] which is a way in which opioids may be abused and their use diverted,[3,26,35] is much less commonly observed in opioid-naïve subjects initially exposed to tapentadol than in opioid-naïve subjects initially exposed to oxycodone.[9] Similarly, data from internet monitoring, surveillance of addiction treatment centers, pharmacovigilance efforts, and surveys of college students suggest that the risk of abuse of tapentadol is lower than that of other Schedule II opioids.[11,12] However, there are no studies that explicitly compare the risk of opioid abuse and addiction in subjects prescribed

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tapentadol versus oxycodone. Therefore, we sought to compare the risk of opioid abuse between tapentadol immediate release (IR) and oxycodone IR.

Methods

We conducted a retrospective cohort study using 2 U.S. claims databases (Optum and MarketScan), which are commonly used for pharmacoepidemiologic research. The Optum Clinformatics database represents a privately insured population and captures administrative claims primarily from the UnitedHealth Group; it has at least 36 million members with both medical and pharmacy benefits. The MarketScan Commercial Claims and Encounters database represents a privately insured population and captures administrative claims from inpatient and outpatient visits and pharmacy claims of large employers and multiple insurance plans. The data set used for this study contains more than 90 million individuals with medical and pharmacy coverage from January 2000 to January 2012.

Inclusion Criteria

Subjects with no recent opioid use whose first opioid exposure was to tapentadol IR or oxycodone IR in 2010 were included and observed for 1 year. Subjects with no recent opioid use were those with no opioid dispensing during the 3 months before the index date. The index date was the date of the first dispensing of tapentadol or oxycodone. Subjects were required to have been in the database for at least 3 months prior to their index date and for at least 12 months after. The codes used to identify tapentadol IR and oxycodone IR are listed in Appendix 1.

One year of follow-up was selected because studies assessing shopping behavior suggest that 75% of the subjects who developed shopping behavior had the first event ≤261 days after first exposure with a median of 234 days.[8]

Exclusion Criteria

Subjects with a history of opioid abuse, opioid addiction, or opioid dependence at any time before the index date, as well as subjects who filled a prescription for an opioid other than the indexed opioid before the index date or within the next 3 days, were excluded.

Outcome

The outcome of interest was incident reported diagnosis of opioid abuse, opioid addiction, or opioid dependence after the index date. The list of the *International Classification of Diseases, 9th revision* (ICD-9), Healthcare Common Procedure Coding System, and Current Procedural Terminology codes used is found in Table 1.

Confounders

To control for the effect of baseline differences between the subjects exposed to tapentadol and those exposed to oxycodone, propensity score stratification was used. Propensity score is the conditional probability of a subject's receiving a particular exposure, in this case, initial exposure to tapentadol versus oxycodone, given a set of confounders. To calculate the propensity score, the confounders were included in a logistic regression model to predict the exposure, without including the outcome.[5,6] As a result, the collection of confounders was collapsed into a single variable, the probability (propensity) of being initially exposed to tapentadol versus oxycodone. Subjects initially exposed to tapentadol and subjects initially exposed to oxycodone who have the same value of propensity score (regardless of the treatment they actually received) will have the same probability of receiving one initial treatment or the other.

Table 1. Codes Used to Identify Opioid Abuse, Dependence, and Addiction

Code	Description
305.50	Opioid abuse, unspecified use
305.51	Opioid abuse, continuous use
305.52	Opioid abuse, episodic use
304.00	Opioid type dependence, unspecified use
304.01	Opioid type dependence, continuous use
304.02	Opioid type dependence, episodic use
304.70	Combinations of opioid type drug with any other drug dependence, unspecified use
304.71	Combinations of opioid type drug with any other drug dependence, continuous use
304.72	Combinations of opioid type drug with any other drug dependence, episodic use
4306 F	Patient counseled regarding psychosocial AND pharmacologic treatment options for opioid addiction

Propensity Score

It has been shown that models that automatically select the variables to calculate the propensity score can reduce bias relative to the models that use only a predefined group of variables.[24,27,30] Therefore, we supplemented a defined set of a priori confounders with additional covariates for all medical conditions and drugs. The known confounders were age, gender, state, quarter of the year of the index date, year, time in the database before the index date, major depression, mood disorders, anxiety disorders, abuse of nonopioid medications (such as alcohol or tobacco), and use of benzodiazepines. The ICD-9 codes used to define these conditions are listed in Appendix 2. In addition, binary covariates were added for each medical condition, based on a diagnosis of the condition in the prior 3 months, as represented by the 227 unique high level group terms with the Medical Dictionary for Regulatory Activities (MedDRA) vocabulary (eg, coronary artery disorders). Eighty-two covariates were also included for each drug class, as represented by 2-digit codes within the Anatomical Therapeutic Chemical classification system (eg, diuretics) if any drug within the class was dispensing during the 3 months prior to the index date. The Observational Medical Outcomes Partnership vocabulary was used to map ICD-9 codes to MedDRA high level group terms and National Drug Codes into Anatomical Therapeutic Chemical classification.[14,28,34]

Major depression, mood and anxiety disorders, and abuse of nonopioid medications, such as alcohol or tobacco, and pain-related diagnoses were not mapped to MedDRA concepts to allow for more specificity. Pain diagnoses were included as arthritis, back pain, fractures, headache, malignancies, musculoskeletal pain, neuropathic pain, other, reproductive system pain, visceral pain, and wound/injury using published ICD-9 groupings.[31]

The propensity score was estimated using Bayesian logistic regression.[18] We used a Laplace distribution for the prior and cross validation to obtain the variance.

Checking Balancing Properties of the Propensity Score

To check the balancing properties of the propensity score, we tabulated the pain-related conditions and the other variables known to be associated with opioid abuse in each treatment group and calculated standardized differences of means or proportions in each of the quintiles of the propensity scores and overall. To calculate the overall standardized difference for each potential confounder, we averaged the standardized differences of the propensity score quintiles for that potential confounder. Standardized differences of less than .25 are an indication of appropriate balance.[33]

Outcome Model

The relative risk of opioid abuse between tapentadol and oxycodone was estimated using a logistic regression model, with the binary indicator of incident opioid abuse diagnosis as the outcome variable and the exposure status and propensity score quintiles as covariates. The estimates from the 2 databases were then pooled using a random effects model. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. For outcomes of low frequency, as is the case with abuse, odds closely approximate risks, so we refer to the more familiar term, risk. Oxycodone was used as the referent group such that ORs <1 indicate a lower risk of an abuse diagnosis with tapentadol.

Dose Assessment

Daily dose of opioid at baseline was calculated and to allow comparison converted into tapentadol equivalent doses using a 5:1 conversion ratio.[2]

Sample Size

Approximately 1,000 subjects initially exposed to tapentadol were needed to detect a 2-fold decrease in the risk of abuse, assuming a 3% risk of abuse among those who were initially exposed to oxycodone,[15] with 80% power, an alpha error of 5%, and a ratio of oxycodone to tapentadol subjects of 10:1.

Sensitivity Analyses

We evaluated the robustness of the propensity score model by performing the analysis with and without

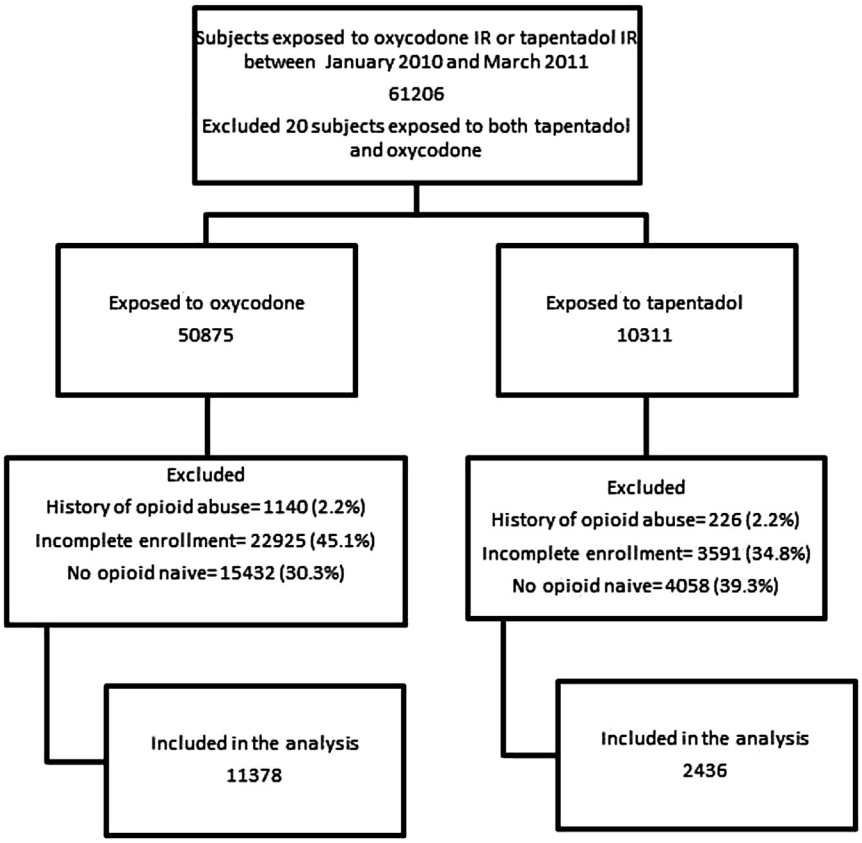

Figure 1. Flow diagram in Optum database. Numbers represent subjects who failed to meet each one of the inclusion criteria. The percentages use the number of exposed patients as denominators.

trimming of patients with nonoverlapping propensity scores.[34] We also performed matching as an alternative propensity score adjustment strategy to stratification. We implemented a nearest available matching algorithm with a 1:1 tapentadol to oxycodone ratio in the Optum database and, because of the larger sample size, a 1:2 match in the MarketScan database, and a propensity score difference smaller than .1. We then built a conditional logistic regression to obtain the relative risk of opioid abuse diagnosis between tapentadol and oxycodone while respecting the matches.

The analyses were conducted using SAS, version 9.3 (SAS Institute Inc, Cary, NC). The New England Institutional Review Board determined that this study was not human subjects research and was exempt from review.

Results

There were 13,814 subjects from the Optum database who met the inclusion criteria (11,378 initially exposed to oxycodone, 2,436 to tapentadol) and 25,553 subjects from the MarketScan database who met the inclusion criteria (21,728 initially exposed to oxycodone, 3,825 to tapentadol). Figs 1 and 2 show the number of subjects who failed to meet each one of the inclusion criteria in each of the databases.

In each database, subjects in the tapentadol group were older, more likely to be women, and more likely to have back pain than subjects in the oxycodone group (Table 2).

The daily dose of opioid at baseline was slightly higher in the tapentadol group than in the oxycodone group in both databases. The median tapentadol equivalent daily dose in the tapentadol group was 300.0 mg versus 250.0 mg in the oxycodone group in the Optum database and 300.0 mg versus 214.3 mg in the MarketScan database. There was no observed difference in other opioid use between the tapentadol and oxycodone groups, and the majority of persons in each cohort had no other opioid use (25th–75th percentile, 0–2).

The models to calculate the propensity score included 365 variables in the Optum database and 370 variables in the MarketScan database. After stratification on the propensity score, most standardized differences in baseline characteristics got smaller (Table 2), indicating that a better balance was achieved. Similarly, the standardized differences for each one of the confounders in each one of the quintiles of the propensity score were very small, especially in the first 4 propensity score categories in each database, confirming the good balance achieved with the propensity score (Appendixes 3 and 4).

In each database, a higher percentage of subjects in the oxycodone group than in the tapentadol group received opioid abuse diagnoses. After adjustment, the risk of developing an opioid abuse diagnosis remained

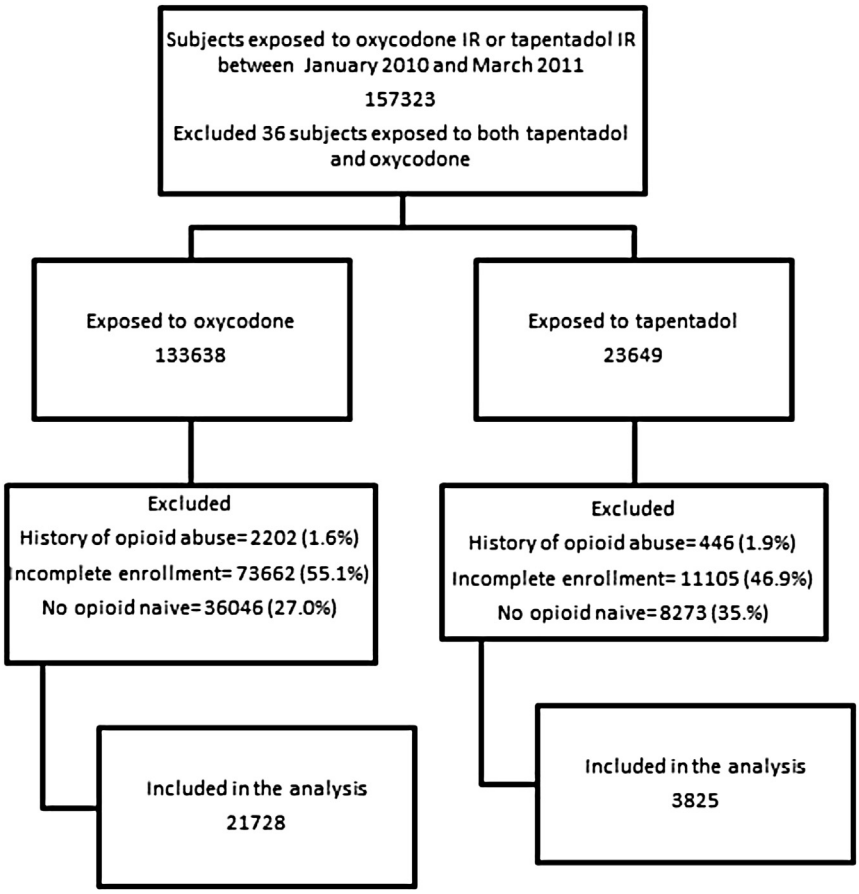

Figure 2. Flow diagram in MarketScan database. Numbers represent subjects who failed to meet each one of the inclusion criteria. The percentages use the number of exposed patients as denominators.

Table 2. Baseline Characteristics of Subjects Exposed to Tapentadol and Oxycodone With Standardized Differences Before and After Propensity Score Adjustment

	Optum Database				*MarketScan Database*			
Characteristic	*Oxycodone*	*Tapentadol*	*Standardized Difference Before Propensity Score*	*Standardized Difference After Propensity Score*	*Oxycodone*	*Tapentadol*	*Standardized Difference Before Propensity Score*	*Standardized Difference After Propensity Score*
Number of subjects	11378	2436			21728	3825		
Age, mean ± SD	43.79 ± 17.65	47.52 ± 12.90	.24	.04	42.12 ± 15.51	46.17 ± 11.59	.30	.07
Women, n (%)	5858 (51.49)	1574 (64.61)	.27	.01	11905 (54.79)	2492 (65.15)	–.21	.01
Variable, n (%)								
Arthritis	2935 (25.80)	665 (27.30)	.03	.10	5229 (24.07)	942 (26.63)	.01	.08
Back pain	1708 (15.01)	552 (22.66)	.20	.09	2834 (13.08)	867 (22.67)	.25	.09
Benzodiazepine use	1434 (12.60)	413 (16.95)	.12	.08	2934 (13.50)	716 (18.72)	.14	.11
Drug abuse excluding opioids	569 (5.00)	72 (2.96)	–.09	.26	622 (2.86)	54 (1.41)	–.07	.06
Mood/anxiety disorders and depression	1173 (10.31)	266 (10.92)	.02	.15	2165 (9.96)	374 (9.78)	–.01	.09
Fractures	849 (7.46)	74 (3.04)	–.18	.01	1447 (6.66)	92 (2.41)	–.18	–.13
Headaches	639 (5.62)	133 (5.46)	–.01	.06	970 (4.46)	175 (4.58)	.01	–.07
Malignancy	2650 (23.29)	490 (20.11)	–.08	–.14	4354 (20.04)	586 (15.32)	–.12	.00
Musculoskeletal pain	2946 (25.89)	723 (29.68)	.08	.13	4927 (22.68)	971 (25.39)	.06	.16
Other	229 (2.01)	54 (2.22)	.01	.01	278 (1.28)	40 (1.05)	–.01	.00
Reproductive system pain	249 (2.19)	64 (2.63)	.02	–.04	458 (2.11)	80 (2.09)	.00	–.02
Visceral pain	1764 (15.50)	207 (8.50)	–.22	.08	2843 (13.08)	294 (7.69)	–.18	–.09
Wound injury	458 (4.03)	37 (1.52)	–.12	.22	827 (3.81)	42 (1.10)	–.12	–.07
Neuropathy	302 (2.65)	139 (5.71)	.14	.05	520 (2.39)	139 (3.63)	.06	.01

Abbreviation: SD, standard deviation.

Table 3. Subjects Who Developed Opioid Abuse Diagnosis in the Tapentadol and Oxycodone Groups: Unadjusted and Adjusted OR

Database	Oxycodone IR n (%)	Tapentadol IR n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR After Excluding Subjects Without Complete Propensity Score Overlap (95% CI)	Adjusted OR After Matching on Propensity Score (95% CI)
Optum						
Abuse	75 (.66)	7 (.29)	.43 (.1–.94)	.26 (.12–.59)	.28 (.12–.62)	.20 (.08–.54)
No abuse	11303 (99.34)	2429 (99.71)				
MarketScan						
Abuse	105 (.48)	12 (.31)	.65 (.32–1.2)	.42 (.22–.79)	.45 (.23–.85)	.33 (.14–.79)
No abuse	21623 (99.52)	3813 (99.69)				

higher in the oxycodone group than in the tapentadol group in each database (Table 3). Overall, the risk of developing abuse diagnoses was much smaller with tapentadol than with oxycodone (pooled estimate for abuse, OR = .35, 95% CI = .21–.58; Fig 3).

The sensitivity analyses provided similar results to the main analyses. After excluding subjects without complete propensity score overlap, 10,111 subjects initially exposed to oxycodone and 2,434 subjects initially exposed to tapentadol in the Optum database and 19,013 subjects initially exposed to oxycodone and 3,806 subjects initially exposed to tapentadol in the MarketScan database were included in the analyses. The standardized differences in each of the quintiles of the propensity score were similarly small compared with the ones in the main analysis. As in the main analyses, the risk of developing an abuse diagnosis was much smaller in subjects exposed to tapentadol than in subjects exposed to oxycodone in each database (Table 3).

The results after matching were similar to the main analyses as well. In the Optum database, a total of 4,018 subjects were matched, half initially exposed to tapentadol and half to oxycodone. In the MarketScan database, 5,817 subjects were matched, 1,939 initially exposed to tapentadol and 3,878 to oxycodone. The risk of developing an abuse diagnosis was much smaller with tapentadol than with oxycodone in each of the databases: OR = .20, 95% CI = .08–.54, in the Optum database and OR = .33, 95% CI = .14–.79, in the MarketScan database.

Discussion

The odds of receiving an abuse diagnosis among those who initiated opioid use with tapentadol IR was 65% lower than the risk of receiving an abuse diagnosis among those who initiated opioid use with oxycodone IR. The fact that the risk of receiving an abuse diagnosis with tapentadol was similarly low in the 2 claims databases and that the results remained similar in the sensitivity analyses provide confidence in the findings of the study. The relatively low affinity of tapentadol for the mu-opioid receptor may explain its lower abuse risk.

The observed lower risk of receiving an abuse diagnosis associated with tapentadol in this study aligns with its lower risk of opioid doctor shopping behavior.[9] A retrospective cohort study in a longitudinal prescription database compared the risk of opioid doctor shopping behavior between opioid-naïve patients who

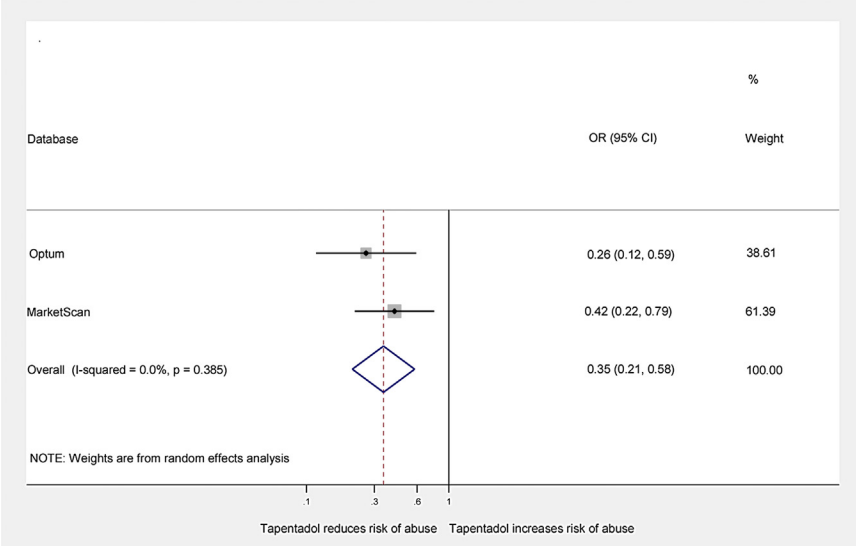

Figure 3. Meta-analysis of the risk of opioid abuse diagnosis of tapentadol IR and oxycodone IR. Each line presents the relative estimate for abuse obtained in a database with its 95% CI. The size of the box represents the weight given to that estimate. The diamond represents the overall effect estimate. The risk of abuse with tapentadol is lower than the risk of abuse with oxycodone.

initiated opioid use with tapentadol IR and those who initiated with oxycodone IR and found that the risk of opioid doctor shopping (subjects with overlapping opioid prescriptions written by different prescribers and filled at ≥3 pharmacies) was 72% lower in subjects exposed to tapentadol than in subjects exposed to oxycodone (OR = .28, 95% CI = .22–.35).[9] The relative reductions in the risks of opioid doctor shopping behavior and receiving an opioid abuse diagnosis are of similar magnitude. The results of the present study also align with data from pharmacovigilance studies, which suggest a lower risk of abuse.[11] One of these studies included an assessment of the street price of tapentadol, which was found to be one-tenth the street price of oxycodone on a per-milligram basis,[37] or half the street price of oxycodone after adjustment for potency. These overall findings provide reassurance that the lower risk of receiving an abuse diagnosis of tapentadol is neither the result of a peculiarity of a particular database nor the endpoint assessed.

The findings of lower risks of shopping behavior and receiving an abuse diagnosis associated with tapentadol are in contrast with results of a likeability study that showed that in opioid-experienced individuals, the subjective effects of tapentadol were comparable to the subjective effects of oral hydromorphone, and with animal data studies that showed that tapentadol exhibited rewarding and reinforcing effects that were similar to the ones produced by other opioids.[22] The different contexts in which these studies were performed, and the different types of subjects included in these studies, may contribute to the disparity of their findings.

Tapentadol IR was launched in 2009 and has been on the U.S. market for much less time than oxycodone IR. It could be argued that there might have not been enough time for abusers to experiment with tapentadol. Data from the Researched Abuse, Diversion and Addiction-Related Surveillance, a surveillance system that monitors the abuse, misuse, and diversion of prescription opioids, suggest that abuse can be seen very soon after a new opioid is marketed.[13] Nonetheless, definitive proof for the lower risk of abuse of tapentadol will need to await longer experience with tapentadol because the desirability of an opioid can change over time.[13]

Limitations

The ICD-9 codes we used to define abuse diagnosis included codes for opioid dependence as well as abuse. Opioid dependence does not necessarily imply abuse. Opioid abuse has been defined as the use of an opioid for psychic effects or any harmful use of the opioid.[42] In contrast, opioid dependence is a state of adaptation that is manifested by withdrawal syndrome, diminution of the analgesic effect over time (tolerance), or dose escalation.[1,4,29,42] However, many physicians use the terms "opioid abuse," "opioid addiction," and "opioid dependence" interchangeably, and other studies that have assessed opioid abuse combined the codes as well.[15,16]

Despite the fact that the codes for abuse and dependence are combined, opioid abuse is likely to be underascertained in claims databases. Potential reasons for underrecording of abuse include lack of recognition of the condition; reluctance to put a potentially damaging diagnosis in the patient's record, especially in the absence of certainty; and, because claims databases were developed to facilitate commercial transactions, the fact that reimbursement considerations could affect which diagnosis codes to use.[25]

The incidence of opioid abuse diagnosis in our study was .6%. Though similar to the incidence reported in other claims database studies,[41] this abuse rate is more than 10 times lower than what has been reported in past prospective studies (range, 5–31%).[23,38] In our current study, we observed an absolute risk reduction of ≤.5%. If the true incidence of abuse is in fact 10 times higher, then the impact on the absolute risk reduction could be 10 times greater. In contrast, as long as the underreporting is similar in the 2 groups, the extent of underestimation does not bias the odds ratios reported in our study.

The findings of this study represent a privately insured population and therefore may not generalize to other populations of interest, such as the elderly or the uninsured.

Physicians prescribed tapentadol or oxycodone to the patients for clinical indications, and therefore patients were not randomized. We controlled for the effect of potential confounders through propensity score adjustment, which permits the inclusion of a large number of confounders. The balancing properties of the propensity score are well known, but limited to the confounders included in the models. Therefore, unobserved baseline differences cannot be ruled out and those differences could explain the results.

In summary, subjects who initiated opioid treatment with tapentadol IR had a lower risk of receiving an opioid abuse/dependence diagnosis than subjects who initiated opioid treatment with oxycodone IR. However, the risk with tapentadol IR is not absent. Opioid prescribers and patients must be aware of the risk of abuse associated with all opioids and of changes in opioid desirability over time.

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Appendix 1. List of Codes to Identify Tapentadol IR and Oxycodone IR

Oxycodone	*Tapentadol*
Oxycodone 5 MG Oral Tablet [M-Oxy]	Tapentadol 50 MG Oral Tablet
Oxycodone 20 MG/ML Oral Solution [Oxydose]	Tapentadol 75 MG Oral Tablet
Oxycodone 5 MG Oral Capsule [Oxynorm]	Tapentadol 100 MG Oral Tablet
Oxycodone 5 MG Oral Capsule [Oxyrapid]	Tapentadol 100 MG Oral Tablet [Nucynta]
Oxycodone Hydrochloride 1 MG/ML Oral Solution	Tapentadol 50 MG Oral Tablet [Nucynta]
Oxycodone Hydrochloride 1 MG/ML Oral Solution [Roxicodone]	Tapentadol 75 MG Oral Tablet [Nucynta]
Oxycodone Hydrochloride 10 MG Oral Capsule	
Oxycodone Hydrochloride 10 MG Oral Tablet	
Oxycodone Hydrochloride 10 MG Oral Tablet [Dazidox]	
Oxycodone Hydrochloride 10 MG/ML Oral Solution	
Oxycodone Hydrochloride 15 MG Oral Tablet	
Oxycodone Hydrochloride 15 MG Oral Tablet [Roxicodone]	
Oxycodone Hydrochloride 20 MG Oral Capsule	
Oxycodone Hydrochloride 20 MG Oral Tablet	
Oxycodone Hydrochloride 20 MG Oral Tablet [Dazidox]	
Oxycodone Hydrochloride 20 MG/ML Oral Solution	
Oxycodone Hydrochloride 20 MG/ML Oral Solution [ETH-Oxydose]	
Oxycodone Hydrochloride 20 MG/ML Oral Solution [Oxyfast]	
Oxycodone Hydrochloride 20 MG/ML Oral Solution [Roxicodone]	
Oxycodone Hydrochloride 30 MG Oral Tablet	
Oxycodone Hydrochloride 30 MG Oral Tablet [Roxicodone]	
Oxycodone Hydrochloride 5 MG Oral Capsule	
Oxycodone Hydrochloride 5 MG Oral Capsule [Oxy IR]	
Oxycodone Hydrochloride 5 MG Oral Tablet	
Oxycodone Hydrochloride 5 MG Oral Tablet [Endocodone]	
Oxycodone Hydrochloride 5 MG Oral Tablet [Percolone]	
Oxycodone Hydrochloride 5 MG Oral Tablet [Roxicodone]	
Oxycodone Hydrochloride 5 MG Oral Tablet [Oxecta]	
Oxycodone Hydrochloride 7.5 MG Oral Tablet	
Oxycodone Hydrochloride 7.5 MG Oral Tablet [Oxecta]	

Appendix 2. List of Codes to Known Confounders: Drug Abuse Excluding Opioids and Mood and Anxiety Disorders and Depression

Drug Abuse Excluding Opioids	*ICD-9*	*Mood and Anxiety Disorders and Depression*	*ICD-9*
Alcohol dependence syndrome	303	Mood disorder in conditions classified elsewhere	293.83
Acute alcoholic intoxication	303.0	Anxiety disorder in conditions classified elsewhere	293.84
Acute alcoholic intoxication in alcoholism, unspecified drinking behavior	303.00	Bipolar I disorder single manic episode	296.0
Acute alcoholic intoxication in alcoholism, continuous drinking behavior	303.01	Manic disorder, single episode, unspecified degree	296.00
Acute alcoholic intoxication in alcoholism, episodic drinking behavior	303.02	Bipolar I disorder, single manic episode, mild	296.01
Acute alcoholic intoxication in alcoholism, in remission	303.03	Bipolar I disorder, single manic episode, moderate	296.02
Other and unspecified alcohol dependence	303.9	Bipolar I disorder, single manic episode, severe, without mention of psychotic behavior	296.03
Other and unspecified alcohol dependence, unspecified drinking behavior	303.90	Bipolar I disorder, single manic episode, severe, specified as with psychotic behavior	296.04
Other and unspecified alcohol dependence, continuous drinking behavior	303.91	Bipolar I disorder, single manic episode, in partial or unspecified remission	296.05
Other and unspecified alcohol dependence, episodic drinking behavior	303.92	Manic disorder, single episode, in full remission	296.06
Other and unspecified alcohol dependence, in remission	303.93	Manic disorder recurrent episode	296.1
Drug dependence	304	Manic disorder, recurrent episode, unspecified degree	296.10
Sedative hypnotic or anxiolytic dependence	304.1	Manic disorder, recurrent episode, mild degree	296.11
Sedative, hypnotic or anxiolytic dependence, unspecified	304.10	Manic disorder, recurrent episode, moderate degree	296.12
Sedative, hypnotic or anxiolytic dependence, continuous	304.11	Manic disorder, recurrent episode, severe degree, without mention of psychotic behavior	296.13
Sedative, hypnotic or anxiolytic dependence, episodic	304.12	Manic disorder, recurrent episode, severe degree, specified as with psychotic behavior	296.14
Sedative, hypnotic or anxiolytic dependence, in remission	304.13	Manic disorder, recurrent episode, in partial or unspecified remission	296.15
Cocaine dependence	304.2	Manic disorder, recurrent episode, in full remission	296.16
Cocaine dependence, unspecified use	304.20	Major depressive disorder single episode	296.2
Cocaine dependence, continuous use	304.21	Major depressive disorder, single episode, unspecified degree	296.20
Cocaine dependence, episodic use	304.22	Major depressive disorder, single episode, mild degree	296.21
Cocaine dependence, in remission	304.23	Major depressive disorder, single episode, moderate degree	296.22
Cannabis dependence	304.3	Major depressive disorder, single episode, severe degree, without mention of psychotic behavior	296.23
Cannabis dependence, unspecified use	304.30	Major depressive disorder, single episode, severe degree, specified as with psychotic behavior	296.24
Cannabis dependence, continuous use	304.31	Major depressive disorder, single episode, in partial or unspecified remission	296.25
Cannabis dependence, episodic use	304.32	Major depressive disorder, single episode in full remission	296.26
Cannabis dependence, in remission	304.33	Major depressive disorder recurrent episode	296.3
Amphetamine and other psychostimulant dependence	304.4	Major depressive disorder, recurrent episode, unspecified degree	296.30
Amphetamine and other psychostimulant dependence, unspecified use	304.40	Major depressive disorder, recurrent episode, mild degree	296.31
Amphetamine and other psychostimulant dependence, continuous use	304.41	Major depressive disorder, recurrent episode, moderate degree	296.32
Amphetamine and other psychostimulant dependence, episodic use	304.42	Major depressive disorder, recurrent episode, severe degree, without mention of psychotic behavior	296.33
Amphetamine and other psychostimulant dependence, in remission	304.43	Major depressive disorder, recurrent episode, severe degree, specified as with psychotic behavior	296.34
Hallucinogen dependence	304.5	Major depressive disorder, recurrent episode, in partial or unspecified remission	296.35
Hallucinogen dependence, unspecified use	304.50	Major depressive disorder, recurrent episode, in full remission	296.36
Hallucinogen dependence, continuous use	304.51	Bipolar affective disorder, manic, unspecified degree	296.40
Hallucinogen dependence, episodic use	304.52	Bipolar I disorder, most recent episode (or current) manic, mild	296.41
Hallucinogen dependence, in remission	304.53	Bipolar I disorder, most recent episode (or current) manic, moderate	296.42
Other specified drug dependence	304.6	Bipolar I disorder, most recent episode (or current) manic, severe, without mention of psychotic behavior	296.43
Other specified drug dependence, unspecified use	304.60	Bipolar I disorder, most recent episode (or current) manic, severe, specified as with psychotic behavior	296.44
Other specified drug dependence, continuous use	304.61	Bipolar I disorder, most recent episode (or current) manic, in partial or unspecified remission	296.45
Other specified drug dependence, episodic use	304.62	Bipolar I disorder, most recent episode (or current) manic, in full remission	296.46

Appendix 2. Continued

Drug Abuse Excluding Opioids	*ICD-9*	*Mood and Anxiety Disorders and Depression*	*ICD-9*
Other specified drug dependence, in remission	304.63	Bipolar affective disorder, depressed, unspecified degree	296.50
Combinations of drug dependence excluding opioid type drug, unspecified use	304.80	Bipolar I disorder, most recent episode (or current) depressed, mild	296.51
Combinations of drug dependence excluding opioid type drug, continuous use	304.81	Bipolar I disorder, most recent episode (or current) depressed, moderate	296.52
Combinations of drug dependence excluding opioid type drug, episodic use	304.82	Bipolar I disorder, most recent episode (or current) depressed, severe, without mention of psychotic behavior	296.53
Combinations of drug dependence excluding opioid type drug, in remission	304.83	Bipolar I disorder, most recent episode (or current) depressed, severe, specified as with psychotic behavior	296.54
Unspecified drug dependence	304.9	Bipolar I disorder, most recent episode (or current) depressed, in partial or unspecified remission	296.55
Unspecified drug dependence, unspecified use	304.90	Bipolar I disorder, most recent episode (or current) depressed, in full remission	296.56
Unspecified drug dependence, continuous use	304.91	Bipolar I disorder, most recent episode (or current) mixed, unspecified	296.60
Unspecified drug dependence, episodic use	304.92	Bipolar I disorder, most recent episode (or current) mixed, mild	296.61
Unspecified drug dependence, in remission	304.93	Bipolar I disorder, most recent episode (or current) mixed, moderate	296.62
Nondependent abuse of drugs	305	Bipolar I disorder, most recent episode (or current) mixed, severe, without mention of psychotic behavior	296.63
Alcohol abuse	305.0	Bipolar I disorder, most recent episode (or current) mixed, severe, specified as with psychotic behavior	296.64
Alcohol abuse, unspecified drinking behavior	305.00	Bipolar I disorder, most recent episode (or current) mixed, in partial or unspecified remission	296.65
Alcohol abuse, continuous drinking behavior	305.01	Bipolar affective disorder, mixed, in full remission	296.66
Alcohol abuse, episodic drinking behavior	305.02	Bipolar I disorder, most recent episode (or current) unspecified	296.7
Alcohol abuse, in remission	305.03	Bipolar disorder, unspecified	296.80
Tobacco use disorder	305.1	Atypical manic disorder	296.81
Cannabis abuse	305.2	Atypical depressive disorder	296.82
Cannabis abuse, unspecified use	305.20	Other and unspecified bipolar disorders	296.89
Cannabis abuse, continuous use	305.21	Unspecified episodic mood disorder	296.90
Cannabis abuse, episodic use	305.22	Other specified episodic mood disorder	296.99
Cannabis abuse, in remission	305.23	Depressive type psychosis	298.0
Hallucinogen abuse	305.3	Anxiety states	300.0
Hallucinogen abuse, unspecified use	305.30	Anxiety state, unspecified	300.00
Hallucinogen abuse, continuous use	305.31	Panic disorder without agoraphobia	300.01
Hallucinogen abuse, episodic use	305.32	Generalized anxiety disorder	300.02
Hallucinogen abuse, in remission	305.33	Other anxiety states	300.09
Sedative hypnotic or anxiolytic abuse	305.4	Agoraphobia with panic disorder	300.21
Sedative, hypnotic or anxiolytic abuse, unspecified	305.40	Agoraphobia without mention of panic attacks	300.22
Sedative, hypnotic or anxiolytic abuse, continuous	305.41	Social phobia	300.23
Sedative, hypnotic or anxiolytic abuse, episodic	305.42	Dysthymic disorder	300.4
Sedative, hypnotic or anxiolytic abuse, in remission	305.43	Affective personality disorder	301.1
Cocaine abuse	305.6	Affective personality disorder, unspecified	301.10
Cocaine abuse, unspecified use	305.60	Chronic hypomanic personality disorder	301.11
Cocaine abuse, continuous use	305.61	Chronic depressive personality disorder	301.12
Cocaine abuse, episodic use	305.62	Cyclothymic disorder	301.13
Cocaine abuse, in remission	305.63	Obsessive-compulsive personality disorder	301.4
Amphetamine or related acting sympathomimetic abuse, unspecified use	305.70	Acute reaction to stress	308
Amphetamine or related acting sympathomimetic abuse, continuous use	305.71	Predominant disturbance of emotions	308.0

Appendix 2. Continued

Drug Abuse Excluding Opioids	*ICD-9*	*Mood and Anxiety Disorders and Depression*	*ICD-9*
Amphetamine or related acting sympathomimetic abuse, episodic use	305.72	Predominant disturbance of consciousness	308.1
Amphetamine or related acting sympathomimetic abuse, in remission	305.73	Predominant psychomotor disturbance	308.2
Antidepressant type abuse, unspecified use	305.80	Other acute reactions to stress	308.3
Antidepressant type abuse, continuous use	305.81	Mixed disorders as reaction to stress	308.4
Antidepressant type abuse, episodic use	305.82	Unspecified acute reaction to stress	308.9
Antidepressant type abuse, in remission	305.83	Adjustment reaction	309
Other mixed or unspecified drug abuse	305.9	Adjustment disorder with depressed mood	309.0
Other, mixed, or unspecified drug abuse, unspecified use	305.90	Adjustment reaction with prolonged depressive reaction	309.1
Other, mixed, or unspecified drug abuse, continuous use	305.91	Adjustment reaction with predominant disturbance of other emotions	309.2
Other, mixed, or unspecified drug abuse, episodic use	305.92	Separation anxiety disorder	309.21
Other, mixed, or unspecified drug abuse, in remission	305.93	Emancipation disorder of adolescence and early adult life	309.22
		Specific academic or work inhibition	309.23
		Adjustment disorder with anxiety	309.24
		Adjustment disorder with mixed anxiety and depressed mood	309.28
		Other adjustment reactions with predominant disturbance of other emotions	309.29
		Adjustment disorder with disturbance of conduct	309.3
		Adjustment disorder with mixed disturbance of emotions and conduct	309.4
		Posttraumatic stress disorder	309.81
		Adjustment reaction with physical symptoms	309.82
		Adjustment reaction with withdrawal	309.83
		Other specified adjustment reactions	309.89
		Unspecified adjustment reaction	309.9
		Depressive disorder, not elsewhere classified	311
		Overanxious disorder specific to childhood and adolescence	313.0
		Misery and unhappiness disorder specific to childhood and adolescence	313.1

Appendix 3. Standardized Differences Before and After PS Adjustment in the MarketScan Database

Variable	Standardized Difference in First PS Quintile	Standardized Difference in Second PS Quintile	Standardized Difference in Third PS Quintile	Standardized Difference in Fourth PS Quintile	Standardized Difference in Fifth PS Quintile	Standardized Difference Before PS	Overall Standardized Difference After PS
Age	.02	.10	.12	.13	–.02	.30	.07
Arthritis	.02	.07	.01	.14	.16	.01	.08
Back pain	.13	.12	.12	.12	–.05	.25	.09
Benzodiazepine use	.06	.05	–.06	.06	.41	.14	.11
Drug abuse excluding opioids	–.01	–.02	.02	.06	.20	–.07	.06
Mood/anxiety disorders and depression	.00	.01	–.03	.18	.22	–.01	.09
Index year (2010)	.03	.00	–.01	.08	.06	–.08	.03
Women	–.13	–.02	.12	.21	–.17	–.21	.01
Fractures	–.04	–.15	–.03	–.09	–.33	–.18	–.13
Headaches	.02	–.02	–.07	–.07	–.22	.01	–.07
Malignancy	.02	–.09	–.21	.18	.10	–.12	.00
Musculoskeletal pain	.11	.11	.07	.18	.32	.06	.16
Neuropathy	.03	.07	.04	.00	–.10	.06	.01
Other	–.01	–.01	.04	.04	–.06	–.01	.00
Reproductive system pain	.01	.02	–.01	–.02	–.09	.00	–.02
Visceral pain	–.04	–.10	–.03	–.02	–.23	–.18	–.09
Wound injury	–.04	–.05	–.03	.05	–.25	–.12	–.07

Abbreviation: PS, propensity score.

Appendix 4. Standardized Differences Before and After PS Adjustment in the Optum Database

Variable	Standardized Difference in First PS Quintile	Standardized Difference in Second PS Quintile	Standardized Difference in Third PS Quintile	Standardized Difference in Fourth PS Quintile	Standardized Difference in Fifth PS Quintile	Standardized Difference Before PS	Overall Standardized Difference After PS
Age	.00	.09	.09	.02	–.01	.24	.04
Arthritis	.03	.04	.02	.15	.23	.03	.10
Back pain	.04	.08	.11	.12	.14	.20	.09
Benzodiazepine use	.03	.00	.00	.19	.19	.12	.08
Drug abuse excluding opioids	.03	–.01	–.11	.15	.70	–.09	.26
Mood/anxiety disorders and depression	.06	–.02	–.06	.02	.59	.02	.15
Index year (2010)	–.05	–.01	.03	–.06	.53	–.16	.06
Women	.23	.00	–.27	–.21	.32	.27	.01
Fractures	–.03	–.10	–.15	.02	.24	–.18	.01
Headaches	.03	–.09	–.08	–.04	.36	–.01	.06
Malignancy	.06	–.15	–.17	–.29	–.21	–.08	–.14
Musculoskeletal pain	.12	.03	.21	.12	.17	.08	.13
Neuropathy	.12	.12	.11	–.02	–.10	.14	.05
Other	.02	.07	–.02	.11	–.11	.01	.01
Reproductive system pain	.05	–.04	–.05	–.08	–.09	.02	–.04
Visceral pain	–.06	–.08	–.05	.12	.30	–.22	.08
Wound injury	–.03	–.06	.00	–.11	.77	–.12	.22

Abbreviation: PS, propensity score.