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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.*

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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]

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