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A Claims Analysis of the Utilization of Tramadol for Acute Pain in Patients Prescribed Buprenorphine/Naloxone for Opioid Use Disorder

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A Claims Analysis of the Utilization of Tramadol for Acute Pain in Patients Prescribed Buprenorphine/Naloxone for Opioid Use Disorder

Abstract

Objective: To determine the prevalence of tramadol prescribing among commercially insured adults receiving medication assisted therapy (MAT) with buprenorphine/naloxone.

Design: We conducted a cross-sectional descriptive study to evaluate the use of tramadol among patients prescribed buprenorphine/suboxone for MAT.

Setting: This study utilized data from 2010 to 2013 Optum Clinformatics Data Mart (OptumInsight, Eden Prairie, MN). This cohort is an administrative health claims database from a large national insurer. This data included pharmacy and medical care utilization and information describing patient enrollment.

Patients, Participants: Patients were 12 to 64 years of age and had complete and available medical, pharmacy and administrative records in the Optum Clinformatics Data Mart during study period.

Main Outcome Measures: Patients who received at least one paid claim for buprenorphine/naloxone from 2010 to 2013 and also received at least one overlapping pharmacy dispensing for tramadol were identified for analysis. We determined if the concurrent buprenorphine/naloxone and tramadol dispensings were from the same or a different prescriber.

Results: In this analysis of 18,734 U.S. commercially insured patients receiving MAT with buprenorphine/naloxone, we identified 1,198 (6.4%) patients who received at least one overlapping dispensing for tramadol during a four-year period spanning 2010 through 2013. Among these patients, 266 (1.42%) were co-prescribed buprenorphine/naloxone and tramadol from the same provider.

Conclusions: These results suggest that the use of tramadol among patients receiving buprenorphine/naloxone is not uncommon. Further study is warranted to further determine the

benefits and risks associated with the use of tramadol for pain management among patients prescribed buprenorphine/naloxone.

Introduction

Practitioners in primary care and emergency medicine frequently encounter patients with acute pain resulting from injuries or medical procedures. Chronic pain is also frequently encountered by practitioners as one of the most common reasons for an office visit, as reported by an estimated 20 to 50 percent of patients seen in a primary care setting.[1–3] For many patients with opioid use disorder (OUD), medication assisted treatment (MAT) with buprenorphine-containing medications can be central to an effective recovery program. Consequently, there are a substantial and growing number of patients receiving buprenorphine/naloxone on a chronic basis. The clinical management of pain syndromes is a challenge among all patients, and particularly in the care of patients prescribed buprenorphine/naloxone for MAT.

Opioid medications exert their analgesic effects through various receptors: mu, delta and kappa and other non-opioid receptors; with the most important analgesic effects mediated by mu1.[4] Buprenorphine is an opioid medication having high affinity for the mu-opioid receptors, with low intrinsic activity. At dosages typically prescribed for MAT, it provides limited analgesic effect while blocking other opioids from binding to the mu-receptor, thereby reducing opioid craving and the potential for illicit opioid use.[5,6] While these pharmacologic features are advantageous in the context of OUD, buprenorphine is not commonly utilized in the management of acute pain. Furthermore, many patients with OUD suffer from chronic pain disorders.[7]

Evidence-based strategies for pain management among patients receiving MAT with buprenorphine/naloxone are limited, presenting practitioners with a challenging clinical scenario.[8–11] Practice guidelines issued by the American Society of Addiction Medicine (ASAM) for the Use of Medications in the Treatment of Addiction Involving Opioid Use consider patients with pain as a special population.[12] These recommendations state that when medications are prescribed acetaminophen and NSAIDs should be considered initially, or for mild acute pain, the buprenorphine dosage may be increased on a temporary basis and administered in a divided

schedule rather than as a single daily dose. When acute pain is severe, the injectable form of buprenorphine may be used, or the drug may be discontinued in favor of a high potency opioid medication, as the strong binding of buprenorphine to mu-receptors can limit the analgesic effectiveness of co-administered opioid analgesic medications.[13] Adding an opioid agonist while continuing buprenorphine/naloxone may yield a favorable response, yet there is limited evidence to support the safety of this approach. Discontinuing buprenorphine/naloxone and initiating an opioid for pain management can be problematic for patients diagnosed with OUD and less severe pain presentations because it simultaneously destabilizes the patient's MAT while re-exposing the patient to the risks of opioid medication use. Mixed agonist and antagonist analgesics, such as pentazocine, nalbuphine and butorphanol, are also best avoided due to the likelihood of precipitating withdrawal symptoms.[14]

Tramadol was FDA-approved for marketing in the United States in March 1995 for the relief of moderate to severe (acute and chronic) pain in adults.[15] Tramadol's mechanism of action is different from traditional opioid medications. It possesses additional (non-opioid) analgesic activity that is considered to be at least as strong as the opioid receptor analgesic effect of the drug.[16] Tramadol has a relatively weak affinity for opioid receptors (mainly the mu type) and for neuronal reuptake of norepinephrine and 5-hydroxytryptamine (5-HT[Serotonin]) in addition to enhanced release of 5-HT.[17,18] Tramadol exists as two enantiomers with analgesic properties and different analgesic mechanisms: The opioid analgesic mechanism resides primarily in the (+) enantiomer of the O-desmethyl (M1) metabolite of tramadol which acts as a selective *mu*-receptor agonist. The *mu*-receptor affinity of tramadol is 10-fold less than that of codeine, but the M1 metabolite has 300 times greater affinity compared to the parent compound.[19] The (+)-tramadol enantiomer also inhibits serotonin reuptake, while the (-) tramadol enantiomer inhibits norepinephrine reuptake; the reuptake inhibition of both of these neurotransmitters enhance inhibitory descending pain-modulation pathways.[20] These two mechanisms act synergistically

to produce pain control. Tramadol was second to hydrocodone as the most prescribed narcotic analgesic in the U.S. in 2016[21] and there is evidence that utilization has increased with the recent federal reclassification of hydrocodone as a schedule II drug.[22]

Tramadol's unique mechanism of action might provide utility in the management of moderate to severe acute pain in patients receiving MAT with buprenorphine/naloxone. The disadvantages of tramadol in this setting include the risk of the patient's misuse of an albeit weaker opioid, potential increased risks of adverse effects due to additive central nervous system effects in combination with buprenorphine, and an increased the risk of seizure. These risks are weighed against the risk of a potentially fatal relapse of OUD associated with the disruption of MAT with buprenorphine/naloxone.

We determined the prevalence of concurrent prescribing of tramadol and buprenorphine/naloxone using healthcare claims data from a large national commercial insurer, comparing across US regions and by patient demographics. Our findings present a basis to discuss the possible utility of tramadol as a therapeutic option for managing acute pain among patients prescribed buprenorphine/naloxone for MAT.

Methods

We conducted cross-sectional descriptive study evaluating tramadol prescription dispensings use among patients prescribed buprenorphine/naloxone for MAT during a four-year period spanning 2010 to 2013, using the Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN). Optum Clinformatics Data Mart is an administrative health claims database from a large national insurer. This data included pharmacy and medical care utilization and information describing patient enrollment.

We identified all patients having at least one paid claim for buprenorphine/naloxone during between January 1, 2010 and December 31, 2013 using NDC codes listed within the FDA directory. Patients were included in the analysis if they were 12 to 64 years of age at the time of paid claim during our study period. Patients age 65 years and older were excluded because they were substantially underrepresented in the dataset, while patients under age 12 were excluded as data regarding the safety and effectiveness of buprenorphine/naloxone are lacking in children. We identified patients who also received at least one dispensing for concurrent use of tramadol, defined as having at least one day of overlap between paid prescription claims for each medication, as referenced by the prescriptions' fill date and days' supply. We also determined if the concurrent buprenorphine/naloxone and tramadol dispensings were from the same prescriber and reported these findings separately; however, information regarding provider specialty was unavailable.

We determined the number and percentage of concurrent pharmacy dispensings for buprenorphine/naloxone and tramadol overall, and according to age, gender, and US geographic region, as of the first date of dispensing of buprenorphine/naloxone. For patients who received pharmacy dispensings for tramadol, we determined the type of pain documented as neuropathic, nocioceptive, inflammatory or other pain syndrome as documented within 60 days (30 days preceding or following) of the tramadol dispensing. The statistical significance of differences in the frequency of current prescribing within these subgroups was determined using the t-test for patient age, and the chi square test for the binary and categorical variables. All statistical tests were two-sided and conducted at a 0.05 significance level and analyses were performed using SAS Enterprise Guide Version 7.1 (Cary, North Carolina, USA).

Results

We identified 18,734 patients who received at least one dispensing for buprenorphine/naloxone during 2010-2013. The mean age of the study population was 35.47 years (SD ±11.45) and

approximately two-thirds of patients were male. The data source included greater patient representation from the US South and Midwest regions, and this was reflected in our study population's demographics, as approximately 70% of patients were from these areas.

There were 1,198 (6.39%) patients who received at least one overlapping dispensing for tramadol during the study period, and among these patients, 266 (1.42% of the overall study population) were co-prescribed buprenorphine/naloxone and tramadol from the same provider. These results are presented in Tables 1 and 2. Of the patients receiving overlapping dispensings for tramadol with buprenorphine/naloxone from differing providers, 45% (535/1198) were female. A greater percentage of female patients received a concurrent tramadol dispensing compared male patients (8.21% versus 5.43% respectively, $p < 0.0001$). This trend was also observed for the sub-group where the prescribing was by the same provider (females: 1.83%, male: 1.20%, $P = 0.003$). The mean age of patients who received tramadol dispensings was slightly higher than patients who did not receive tramadol dispensings (age 38.86 years versus 35.20 years, $p < 0.001$). A higher percentage of patients received tramadol dispensings in the south as compared with the northeast (6.92% versus 4.75% respectively, $p < 0.001$). When including the criterion that the buprenorphine/naloxone and tramadol be prescribed by the same provider, co-prescribing rates were lowest in the northeast (1.03%) and highest in the Midwest (2.01%, $p = 0.003$). In the majority of concurrent prescriptions (63%), tramadol dispensings did not have an outpatient visit within the 60-day window where a particular pain diagnosis was documented. Pain diagnoses documented during the medical care visit within the 60-day window of the tramadol prescription were nocioceptive (30% of cases), neuropathic (2%), or inflammatory (1%); while other pain diagnoses represented 5% of total pain documentations.

Discussion

Our findings indicate that the concurrent use of buprenorphine/naloxone and tramadol is occurring in clinical practice, as 6.4% of all patients utilizing buprenorphine/naloxone had at least 1 overlapping prescription for tramadol during the study timeframe. This finding is consistent with other research indicating that patients prescribed buprenorphine/naloxone often continue to receive prescriptions for other opioid medications. For example, an analysis of patients initiating buprenorphine across 11 states (n = 38,096) found that 43.2% of patients received at least one dispensing for another opioid medication during the treatment episode.[23] Another study examining pharmacy records within Pennsylvania Medicaid during 2007 to 2012 found that 34.7% of patients prescribed buprenorphine also received dispensings for other opioids.[24] While these studies included tramadol in the categorization of other opioids, they did not specifically report rates of co-prescribing with tramadol.

In our study, it is possible that a substantial number of the tramadol prescriptions were issued by prescribers who were unaware that the patient was also utilizing buprenorphine/naloxone. Our study timeframe precedes the widespread implementation of state prescription drug monitoring programs, which provide prescribers with details of patients' controlled substance utilization. We consider it to be likely that many tramadol prescribers in our study were unaware that the patient was also utilizing buprenorphine/naloxone, yet also that others prescribed the combination intentionally. As a sub-analysis, we examined overlapping use of buprenorphine/naloxone and tramadol when prescribed from the same provider. We identified 266 such instances, representing 1.42% of all patients utilizing buprenorphine/naloxone during our study period. This suggests that for these cases some providers considered tramadol to be an acceptable option for treating pain when patients were also utilizing buprenorphine/naloxone, although perhaps they were unaware of the nature of the risks of co-prescribing these medications.

The use of tramadol is discouraged among patients prescribed buprenorphine/naloxone. The product labeling includes a black box warning that tramadol should not be prescribed concomitantly with other central nervous system (CNS) depressants, as the combination increases risk of respiratory depression and death.[25] Yet the labeling also notes that for such patients, tramadol should be reserved for patients lacking adequate treatment alternatives, and when prescribed, patients should be monitored for sedation and respiratory depression; however, such monitoring is likely not practical in the outpatient setting. Additionally, the labeling notes that mixed agonist/antagonist and partial agonist opioids (e.g. buprenorphine) may diminish the effectiveness of tramadol, and states that the concomitant use of these medications should be avoided.

Prescribers should also be aware of genetic polymorphisms causing variation in tramadol metabolism via cytochrome P450 isoenzymes 2D6, 2B6 and 3A4, with CYP2D6 being integral in converting tramadol to its more potent M1 metabolite.[26] Ultra-rapid metabolizers may produce greater levels of this active metabolite and be at a greater risk of experiencing CNS depression with tramadol use, particularly when taken concurrently with buprenorphine.[27,28] Ethiopians and Saudi Arabians are more likely to be rapid metabolizers (10-26%), followed by Caucasians (5-10%), and less commonly African Americans (2-3%), Indians (3.5%), Hispanics and Asians (approximately 1% within each group). In contrast, poor metabolizers (up to 10% of European Caucasians) may fail to experience pain relief. Genetic testing or pharmacogenomic analysis is becoming available that would allow for the identification of polymorphisms in individual patient CYP 2D6 enzymes that could alter tramadol metabolism.[31,32] Patients receiving MAT therapy for their OUD who are also receiving treatment with tramadol for acute pain would be ideal candidates for these pharmacogenomic tests. Strong CYP2D6 inhibitors such as amitriptyline, bupropion, duloxetine, fluoxetine and paroxetine will likely diminish tramadol's effectiveness as an analgesic.[32] Other important risks of tramadol that prescribers

must consider include an enhanced seizure risk,[25] its potential teratogenicity, and at least theoretically, the risk of serotonin syndrome among patients prescribed multiple serotonergic medications. [33,34]

Counterbalancing these important risks is the need for effective options for managing acute pain among patients with OUD without disrupting a successful MAT modality and placing the patient at risk for relapse and overdose death. There are an increasing number of patients utilizing MAT who require buprenorphine for treatment of their OUD and these patients can be expected to suffer acute and chronic pain, perhaps more often than the general population. There is a dearth of evidence to guide and inform practice. Tramadol's unique pharmacology involving both opioid-receptor and serotonergic action provides a theoretical mechanism for effective analgesic effect when used concomitantly with buprenorphine. The data we analyzed suggest that tramadol and buprenorphine/naloxone are being used concurrently in community practice, albeit by a relatively small number of patients. Tramadol may have a role in the treatment of acute and chronic pain in selected patients receiving buprenorphine/naloxone, necessitating further study of its associated risks and health outcomes.

Our study had several limitations. First, our study utilized administrative claims data describing medications dispensed from retail pharmacies. We were unable to determine if patients actually consumed the medications, or to what extent patients were adherent to buprenorphine or tramadol. Patients may have also been instructed to temporarily discontinue buprenorphine/naloxone while using tramadol. Also, our results were derived from a US commercially insured population, and should not be generalized to other populations including Medicaid or Medicare. Additionally, in recent years most states have implemented Prescription Drug Monitoring Programs, which alert prescribers to the patient's use of controlled substances prescribed by other practitioners. Our results precede the widespread implementation of these programs. Our use of a cross-sectional study design also includes limitations, as our analyses

are associations which are subject to selection bias, confounding, and measurement error, therefore, the findings in this study are hypothesis generating to inform the development and implementation of future studies. Additionally, we did not examine the use of tapentadol, butorphanol or injectable buprenorphine as alternatives for acute pain, deciding instead to focus on tramadol, which is available in a low cost generic form and is generally accessible without barriers under typical pharmacy insurance plan designs. Finally, we were unable to fully describe the pain syndromes experienced by the patients because characteristics such as the history and degree of pain are difficult to ascertain using secondary data sources.

Conclusions

In this analysis of 18,734 US commercially insured patients receiving buprenorphine/naloxone, we identified 1,198 (6.4%) patients who received at least one overlapping dispensing for tramadol, and 266 patients (1.42%) who were co-prescribed buprenorphine/naloxone and tramadol from the same provider. These results suggest that the use of tramadol in this population is not uncommon. Further study is warranted to determine the potential utility of tramadol for pain management among patients prescribed buprenorphine/naloxone.

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Table 1. Use of Tramadol among 18,734 Commercially-Insured Patients Receiving Dispensings for Buprenorphine/Naloxone in 2010-2013

Characteristic	Patients receiving buprenorphine/naloxone and no concurrent use of tramadol		Patients with at least 1 instance of concurrent use of buprenorphine/naloxone and tramadol		p-value
Overall, N (%)	17,536	(94%)	1,198	(6.39)	n/a
Patient Age, Years, Mean (SD)	35.20	(11.4)	38.86	(11.3)	< 0.001
Gender, N (%)					
Female	5,983	(91.79)	535	(8.21)	<0.001
Male	11553	(94.57)	663	(5.43)	
U.S. Region, N (%)					
Northeast	2,507	(95.25)	125	(4.75)	<0.001
Midwest	3,427	(93.12)	253	(6.88)	
South	8,974	(93.08)	667	(6.92)	
West	2,622	(94.49)	153	(5.51)	

Table 2. Use of Tramadol among 18,734 Commercially-Insured Patients Receiving Dispensings for Buprenorphine/Naloxone in 2010-2013 where both Medications were Issued by the Same Prescriber

Characteristic	Patients receiving buprenorphine/naloxone and no concurrent use of tramadol from the same prescriber		Patients with at least 1 instance of concurrent use of buprenorphine/naloxone and tramadol from the same prescriber		p-value
Overall, N (%)	18,468	(99%)	266	(1.42)	n/a
Patient Age, Years, Mean (SD)	35.41	(11.4)	40.51	(11.2)	< 0.001
Gender, N (%)					
Female	6399	(98.17)	119	(1.83)	0.003
Male	12069	(98.80)	147	(1.20)	
U.S. Region, N (%)					
Northeast	2605	(98.97)	27	(1.03)	0.003
Midwest	3606	(97.99)	74	(2.01)	
South	9518	(98.72)	123	(1.28)	
West	2733	(98.49)	42	(1.51)	