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Association Between Sublingual Buprenorphine-Naloxone Exposure and Dental Disease

Oral buprenorphine is a key therapy for the treatment of opioid use disorder. In January 2022, the US Food and Drug Administration[1] alerted health professionals of the potential risk of dental adverse events (dental caries or tooth loss) with long-term use of sublingual or buccal formulations of buprenorphine (usually combined with naloxone). The alert was based on data from case reports, which might be prone to selection bias. We undertook a pharmacoepidemiologic study of sublingual buprenorphine/naloxone and dental adverse events.

Methods | We used the PharMetrics database (IQVIA),[2] which captures patient-level data including prescriptions dispensed in the US as well as inpatient and outpatient physician diagnoses (through the *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision*). We used a random sample of

Table 1. Baseline Characteristics of Users of Sublingual Buprenorphine (BPN)/Naloxone, Transdermal BNP, and Oral Naltrexone

Characteristics	No. (%)		
	Sublingual BPN/naloxone (n = 21 404)	Transdermal BPN (n = 5385)	Naltrexone (n = 6616)
Age, mean (SD), y	35.6 (12.6)	53.0 (15.6)	43.2 (14.4)
Sex			
Men	13 144 (61.4)	1913 (35.5)	3365 (50.9)
Women	8260 (38.6)	3472 (64.5)	3251 (49.1)
Follow-up, mean (SD), y	2.2 (2.4)	2.3 (2.1)	2.6 (2.7)
Comorbidities			
Sjögren syndrome	44.9 (0.21)	93.2 (1.73)	23.2 (0.35)
Inflammatory bowel disease	278.3 (1.3)	150.8 (2.8)	115.1 (1.74)
Diabetes	1586 (7.41)	1361.9 (25.29)	705.9 (10.67)
HIV	51.4 (0.24)	7 (0.13)	11.2 (0.17)
Xerostomia	30 (0.14)	52.2 (0.97)	15.2 (0.23)
Smoking	1406.2 (6.57)	626.8 (11.64)	449.9 (6.8)
Alcohol use	10 098.4 (47.18)	1580 (29.34)	4133 (62.47)
Tricyclic antidepressant use	355.3 (1.66)	315 (5.85)	84 (1.27)
Previous opioid use	11 714.4 (54.73)	710.8 (13.2)	1411.2 (21.33)
Chronic pain	1628.8 (7.61)	1407.1 (26.13)	136.3 (2.06)
Illicit drug use[a]	969.6 (4.53)	18.8 (0.35)	265.3 (4.01)
Dentist visits, mean (SD)	0.38 (2.10)	0.20 (1.51)	0.19 (1.38)

[a] Previous use of heroin or cocaine.

Table 2. Hazard Ratios for Dental Adverse Events and Dental Caries or Tooth Loss Among Different Risk Categories

Outcome	Incidence per 1000 person-years	Cases, No.	Hazard ratio	
			Crude	Adjusted (95% CI)[a]
Dental adverse events[b]				
Transdermal BPN	12.2	150	1	1 [Reference]
Sublingual BPN/N	21.6	1033	1.8	1.42 (1.17-1.73)
Naltrexone	10.9	187	1	1 [Reference]
Sublingual BPN/N		1033	1.91	1.67 (1.41-1.98)
Dental caries or tooth loss				
Transdermal BPN	3.5	44	1	1 [Reference]
Sublingual BPN/N	8.2	393	2.31	1.57 (1.11-2.23)
Naltrexone	3.8	66	1	1 [Reference]
Sublingual BPN/N		393	1.99	1.71 (1.29-2.27)
Sensitivity analyses[c]				
Including those receiving 3 prescriptions				
Transdermal BPN		60	1	1 [Reference]
Sublingual BPN/N		763	1.84	1.76 (1.30-2.38)
Naltrexone		51	1	1 [Reference]
Sublingual BPN/N		763	2.08	1.97 (1.46-2.66)
Excluding those with opioid use, alcohol use, diabetes, smoking, and illicit drug use				
Transdermal BPN		50	1	1 [Reference]
Sublingual BPN/N		221	1.68	1.54 (0.89-2.66)
Naltrexone		50	1	1 [Reference]
Sublingual BPN/N		221	1.64	1.74 (1.25-2.43)
Including those with history of opioid use				
Transdermal BPN		31	1	1 [Reference]
Sublingual BPN/N		644	1.5	1.41 (1.15-1.72)
Naltrexone		54	1	1 [Reference]
Sublingual BPN/N		644	1.65	1.70 (1.43-2.02)
Including those with history of chronic pain				
Transdermal BPN		46	1	1 [Reference]
Sublingual BPN/N		96	1.91	1.42 (1.17-1.73)
Naltrexone		5	1	1 [Reference]
Sublingual BPN/N		96	1.88	1.67 (1.41-1.98)

Abbreviations: BPN/N, buprenorphine/naloxone; HR, hazard ratio.

[a] Adjusted for variables in Table 1 and stratified by exact age.

[b] Include tooth, gum, and pulp-related conditions and defined with 1 prescription.

[c] For the primary outcome of dental adverse events only.

patients from 2006 to 2020, with patients required to have 1 year of health care contact (physician contact or prescription drug use) before cohort entry. Ethics approval was obtained by the University of British Columbia's clinical research ethics board with a waiver of informed consent.

We created a cohort of new users of sublingual buprenorphine/naloxone and 2 active comparator groups (used for opioid use disorder)—new users of either transdermal buprenorphine or oral naltrexone. We created a 1-year look back from cohort entry, excluding patients with previous use of the 3 study drugs in the prior year. Cohort members were followed up from the first prescription to the first occurrence of a dental adverse event, defined as any disease of the teeth, gums, or pulp. A secondary outcome of dental caries or tooth loss was also examined. Cohort members were followed up to the occurrence of an event, termination of health coverage, switch to a competing study drug, or end of follow-up (October 2020).

Cox regression models were constructed to compute hazard ratios (HRs) comparing dental adverse events with sublingual buprenorphine/naloxone vs transdermal buprenorphine and vs oral naltrexone, stratifying for exact age and adjusting for covariates (**Table 1**). We also examined confounding by indication[3] by performing sensitivity analyses restricting the analysis to patients without opioid or alcohol use, illicit drug use, diabetes, or smoking. Because some patients can also use sublingual buprenorphine/naloxone for chronic pain (as an off-label use), we repeated the analysis in patients with previous opioid use or chronic pain. To control for exposure misclassification, we examined the risk in sublingual buprenorphine/naloxone users with at least 3 prescriptions. HRs were considered statistically significant if the 95% CI for that estimate did not cross 1.0. All analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results | A total of 21 404 new users of sublingual buprenorphine/naloxone, 5385 users of transdermal buprenorphine, and 6616 users of oral naltrexone were identified. The groups differed on age, sex, and a number of comorbidities (Table 1).

The incidence of any dental adverse event was 21.6 per 1000 person-years with sublingual buprenorphine/naloxone, 12.2 per 1000 person-years with transdermal buprenorphine, and 10.9 per 1000 person-years with oral naltrexone. The adjusted HRs were 1.42 (95% CI, 1.17-1.73) for sublingual buprenorphine/naloxone vs transdermal buprenorphine and 1.67 (95% CI, 1.41-1.98) for sublingual buprenorphine/naloxone vs oral naltrexone. The incidence of dental caries or tooth loss was 8.2 per 1000 person-years with sublingual buprenorphine/naloxone, 3.5 per 1000 person-years with transdermal buprenorphine, and 3.8 per 1000 person-years with oral naltrexone. For dental caries or tooth loss, the HRs were 1.57 (95% CI, 1.11-2.23) for sublingual buprenorphine/naloxone vs transdermal buprenorphine and 1.71 (95% CI, 1.29-2.27) for sublingual buprenorphine/naloxone vs oral naltrexone. Results were generally similar for the different sensitivity analyses (**Table 2**).

Discussion | This study found an increase in the risk of adverse dental outcomes associated with sublingual buprenorphine/naloxone compared with transdermal buprenorphine and oral naltrexone. Sublingual buprenorphine/naloxone is acidic in nature.[4] Patients are instructed to hold the tablet under the tongue for 5 to 10 minutes to maximize absorption.[5] Thus, prolonged acidic exposure of the drug in the mouth might lead to tooth damage. Study limitations include lack of information on patient oral hygiene, possible unmeasured confounding, capture of only dental events serious enough to be reported to a physician, and inability to fully ascertain the indication for the medications. Clinicians might consider drugs other than sublingual buprenorphine/naloxone in patients with previous dental problems. These patients might also benefit from regular oral health examinations by their dentist.

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COMMENT & RESPONSE

Trends in Adverse Event Rates Among Hospitalized Patients From 2010 to 2019

To the Editor A recent article[1] reported a significant decline in 21 measures of hospital adverse events across 4 adverse event domains from 2010 to 2019 based on abstracted data from the Medicare Patient Safety Monitoring System (MPSMS) for patients with 4 principal diagnoses.[1] In May 2022, the US Department of Health and Human Services, Office of Inspector General (OIG) released the results of a nationally representative medical record review with a less positive message.[2] The OIG's study found that 25% of Medicare patients experienced a harm event in October 2018, which was not statistically different from the rate of 27% that the OIG reported a decade ago.[3]

The OIG looked for all causes of patient harm, regardless of whether the harm event was on a prescribed list. The resulting OIG report describes a wide range of events and contributing factors, such as delays in needed surgery, aspiration, intravenous fluid overload, and oversedation due to opioids.

Hospitals have devoted substantial attention to patient safety in recent years and the reductions found in this study[1] are encouraging. The Centers for Medicare & Medicaid Services (CMS) also has reported declines for certain events.[4] Yet a key message of the OIG report is that the range of patient harm is much wider than that captured by federal payment policies and tracked by efforts such as the MPSMS. Of the events identified in the OIG report, only 5% were on lists for hospital-acquired conditions that can affect payment by the CMS, on lists for the Hospital-Acquired Condition Reduction Program, or on lists for the Deficit Reduction Act Hospital-Acquired Condition Measures.

The OIG report makes a strong case that prescribed lists miss the majority of patient harm events and that high rates