

**FDA Drug Topics:**  
*An Update on Transmucosal  
Buprenorphine and Dental Caries*

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# Learning Objectives

1. Discuss the national opioid crisis, opioid use disorder, and available treatments
2. Describe cases of dental caries with the use of transmucosal buprenorphine-containing products
3. Review FDA's framework for updating product labeling and explain FDA's findings and the resulting regulatory action
4. Summarize how healthcare providers can help mitigate these adverse events

# Presentation Outline

- Background
  - Opioid Crisis and Opioid Use Disorder
- Overview and review of safety signal
- Description of FDA regulatory framework
- Action, communication, and reaction
- Takeaways/Summary
- Challenge Questions
- *Panel discussion and Q & A*



# **OPIOID CRISIS AND OPIOID USE DISORDER (OUD)**

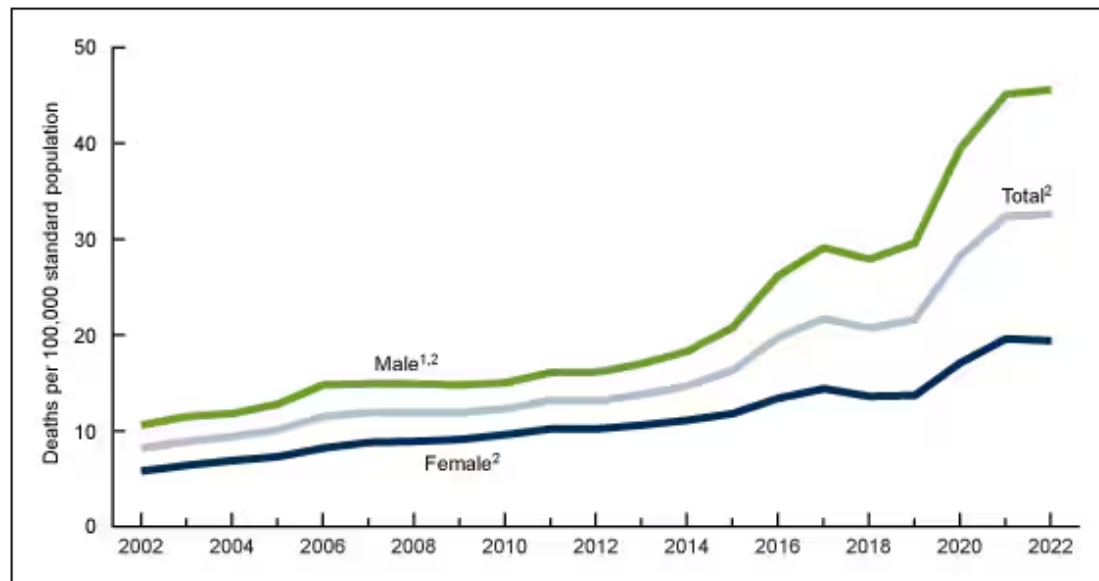
# Opioid Crisis

- Opioid crisis declared a Public Health Emergency on October 26, 2017
- “Crisis” is a broad term covering many aspects of the public health issue:
  - Misuse and Abuse
  - Addiction (Opioid Use Disorder (OUD))
  - Overdose
  - Death

# Overdose Deaths

- 107,941 drug overdose deaths occurred in 2022
  - 32.6 deaths per 100,000 people
  - Age-adjusted rate quadrupled from 2002-2022

Figure 1. Age-adjusted rate of drug overdose deaths, by sex: United States, 2002–2022



from National Center on Health Statistics: <https://www.cdc.gov/nchs/products/databriefs/db491.htm>

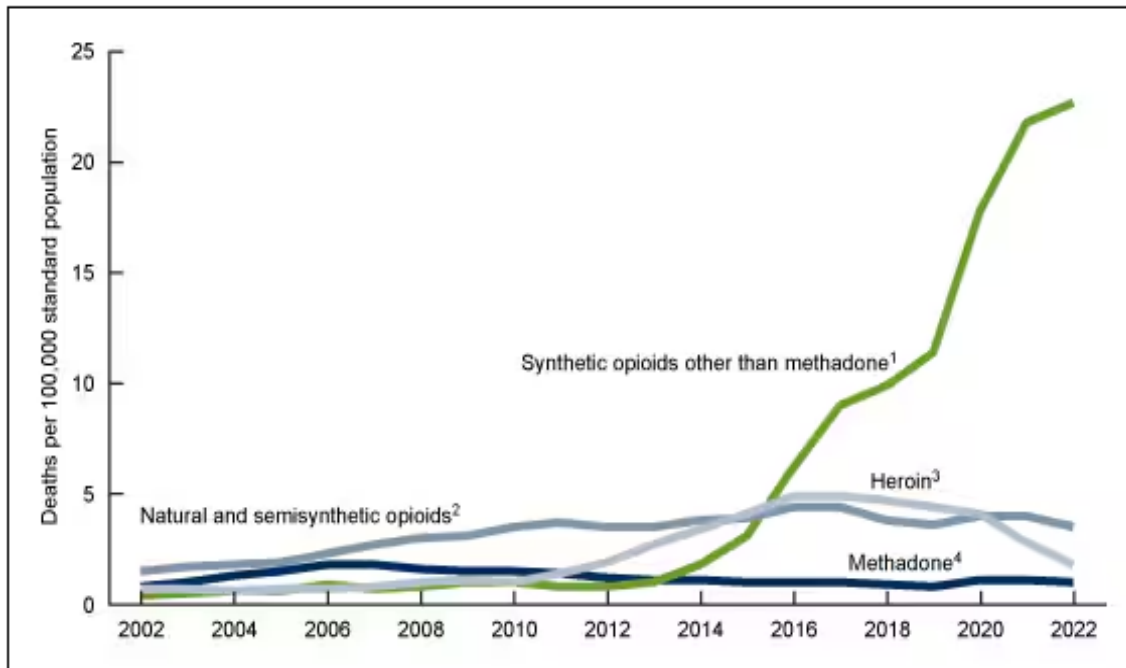
(SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file)

# Current Landscape of Opioid-involved Deaths



- Heroin
  - 2021 = 2.8/100k
  - 2022 = 1.8/100k
- Natural & semi-synthetic
  - 2021 = 4.0/100k
  - 2022 = 3.5/100k
- Methadone
  - 2021 = 1.1/100k
  - 2022 = 1.0/100k
- Synthetic opioids other than methadone, which includes fentanyl, fentanyl analogs, and tramadol
  - 2002 = 0.4/100,000
  - 2013 = 1.0/100,000
  - 2022 = 22.7/100,000

Figure 4. Age-adjusted rate of drug overdose deaths involving opioids, by type of opioid: United States, 2002–2022



from National Center on Health Statistics: <https://www.cdc.gov/nchs/products/databriefs/db491.htm>

(SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data file)

# Opioid Use Disorder (DSM-5)



At least 2 of the following within a 12-month period:

1	Opioids are often taken in larger amounts or over a longer period of time than intended.
2	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4	Craving, or a strong desire to use opioids.
5	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
6	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
7	Important social, occupational or recreational activities are given up or reduced because of opioid use.
8	Recurrent opioid use in situations in which it is physically hazardous
9	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
10	*Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
11	*Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

**Mild = 2-3**

**Moderate = 4-5**

**Severe 6 or more**

\* These criteria not considered for those individuals taking opioids under appropriate medical supervision.



# Need for Treatment

## Need

- In 2022, estimated six million people in the US had an opioid use disorder
- Estimated 3.7% of US adults need OUD treatment

## Utility

- Medications for the treatment of opioid use disorder (MOUD) decrease opioid-related mortality and overdose
- Evidence-based treatment is a pillar of the Department of Health and Human Services Overdose Prevention Framework

## Availability

- Three FDA-approved treatments for OUD
  - Naltrexone
  - Methadone
  - Buprenorphine

# Buprenorphine

- Brief regulatory history
  - 1982: Original approval for pain
  - 2002: Approval for OUD
    - Often found in combination with naloxone
    - Available sublingual tablets and films
      - **TMB = transmucosal buprenorphine**
    - Also as subcutaneous implant, extended-release injection
  - 2015: new formulations and dosing regimens approved for pain
- Mechanism of Action
  - Partial agonist a mu-opioid receptor
  - Antagonist at kappa receptor

## A New Era of OUD Treatment

The Drug Addiction Treatment Act of 2000 is no longer in effect

As of June 2023, all DEA-registered prescribers of controlled substances must complete 8 hours of training on MOUD

This greatly increases the number of possible prescribers and hopefully increases access

# SAFETY SIGNAL

# How it Began...

- Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance II (DPV II) monitors FDA's Adverse Event Reporting System (FAERS)
- July 2018: A report was found of patient who experienced dental caries following the use of sublingual product containing buprenorphine/naloxone
- A disproportionality analysis published using WHO database hypothesized that products containing buprenorphine have a high disproportionality for dental caries
- OSE opened a tracked safety issue (known today as a Newly Identified Safety Signal (NISS)) and an investigation ensued

# Sublingual Buprenorphine

- Can be used sublingually *or* buccal (but not per-oral)

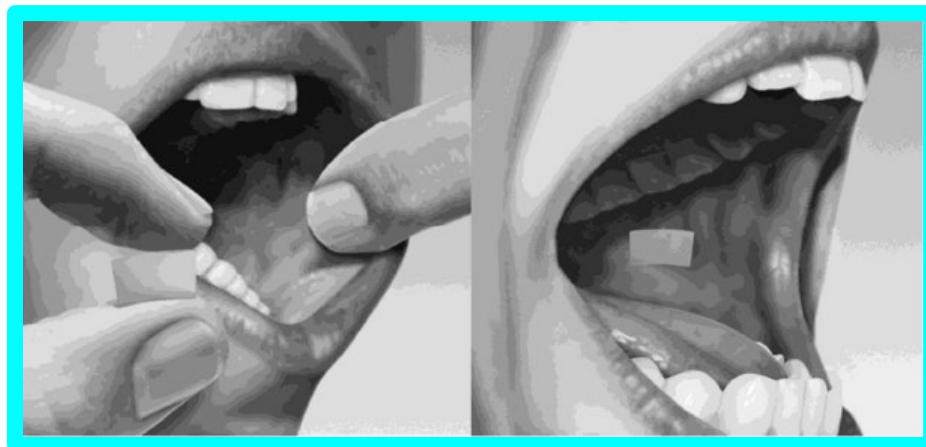


## Sublingual Administration

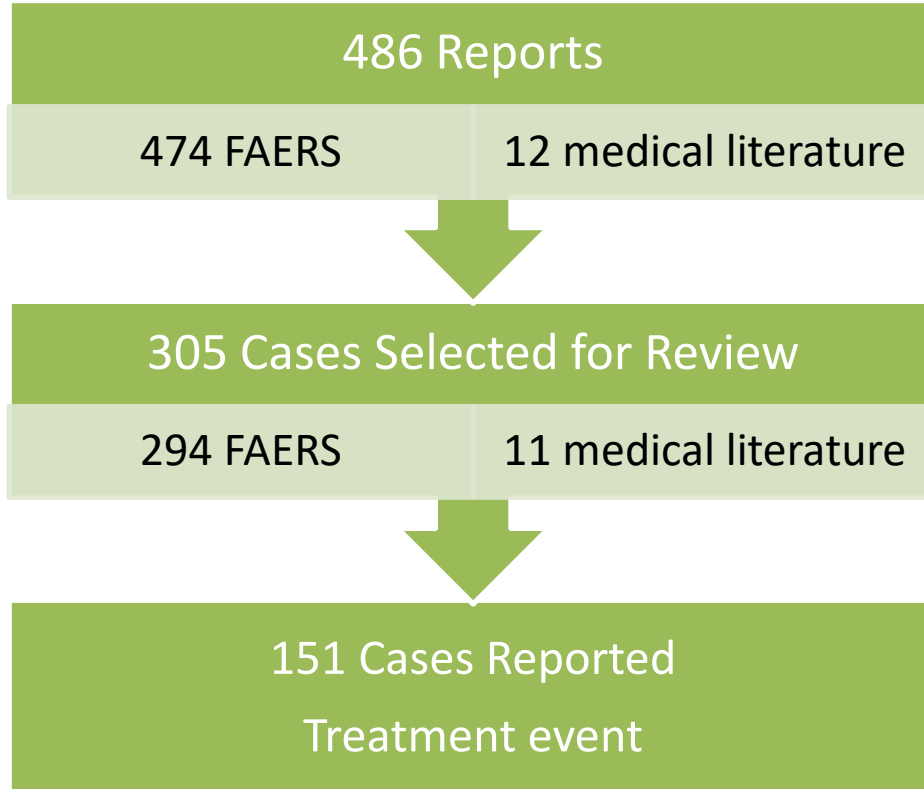
Place one film under the tongue, **close to the base on the left or right side**. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. **The film must be kept under the tongue until the film is completely dissolved**. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first two films have dissolved.

## Buccal Administration

Place one film **on the inside of the right or left cheek**. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. **The film must be kept on the inside of the cheek until the film is completely dissolved**. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.



# Key Findings from OSE/DPV-II Search



- Most common course of treatment of the tooth/teeth was “extractions/pulled/removed” which occurred in 71 instances
- Many cases were reported by providers, provided extensive documentation, and demonstrated temporal association

*While it has been reported that substance use disorders increase major oral health functional and esthetic problems associated with periodontal disease, caries, infections, and tooth loss, many cases found described severe dental issues in patients with no prior history of dental problems*

# FAERS Case #1

- 30-year-old male
- Buprenorphine/naloxone SL film 8mg BID for OUD
- PMH included addiction to oral pain meds, “impeccable teeth,” no concomitant medications
- After 1 year of therapy, experienced severe tooth decay with 15 dental caries
- Treatment with unspecified dental work
- Treatment with buprenorphine/naloxone continued

# FAERS Case #2

- 25-year-old female
- Buprenorphine/naloxone SL film for OUD
- PMH: mother reported daughter's teeth were in “perfect condition” with no dental caries or dental problems
- After 1.5 years of therapy, experienced rapid deterioration of teeth (some began falling out)
- After 3 years, all teeth removed





# REVIEW OF SAFETY SIGNAL

# Summary of Case Characteristics

- 50% female
- Age:
  - Mean: 41.8 years
  - Median: 36.2 years
  - Range: 18-71 years
- HCP reporting: 65/305 (~21%)
- Serious outcomes = 131
- Number of teeth: 182
  - Two or more (e.g., “teeth”): 113
  - “Majority”: 6
  - “All”: 11
- Formulation reported: 238
  - Film only: 143
  - Tablet only: 48
  - Tablet and Film: 47
- Indication for use: 194
  - Opioid Dependence: 173
  - Pain: 28
- Time to Diagnosis: 136
  - Mean: 31.5 months
  - Median: 24.25 months
  - Range: 0.5-182 months

# FAERS Case #3

- 53-year-old-male
- Buprenorphine/naloxone SL film for OUD
- PMH: chronic pain, open heart surgery
- Denied history of dental caries
- After initiating SL product, patient experienced 15 dental caries over a time period of ~2 years
- Patient had *regular* dental cleanings every 3 months
- Diagnosed with dental caries at each 6-month visit while on the product

# FAERS Case #4

- 34-year-old-female
- Buprenorphine (single ingredient) SL tablet
- Experienced “deterioration of tooth enamel and significant damage to teeth in the region of [product] dissolution”
- PMH: previous enrollment in methadone program, denial of continued use of “street” drugs
- Dental exams every 6 months while on methadone
- Teeth in “good condition” at time of switch to buprenorphine SL
- After toothache developed between visits, dentist noticed patient’s “front teeth” all needing filling in the region where SL product was used

# Literature



**Suzuki, J., L. Mittal, and S. B. Woo. 2013. 'Sublingual buprenorphine and dental problems: a case series', *Prim Care Companion CNS Disord*, 15.**

- Mean age 34.4 years, predominantly white (91%), taking buprenorphine for a mean of 45.7 months (range 5-77) at a mean dose of 11.6mg/day (range, 2-20mg), took the medication a mean of 3.2 times per day.
- Average of 8.9 minutes (range 1-30 min) to dissolve completely
- Mean number of caries: 5.2 (range, 0-24)
- Majority of subjects (54.5%) reported tooth pain

# Product-Specific Information\*



DRUG X adheres to the moist buccal mucosa and will completely dissolve after application, usually within 30 minutes

Median dissolve time of DRUG Y was 5 minutes while the median dissolve time of DRUG Z was 12.5 minutes

Mean in vivo dissolution time is 17.6 minutes for 8 mg tablet, 8.13 minutes for 2 mg tablet

Dissolution testing described combination product needing 7 minutes to dissolve

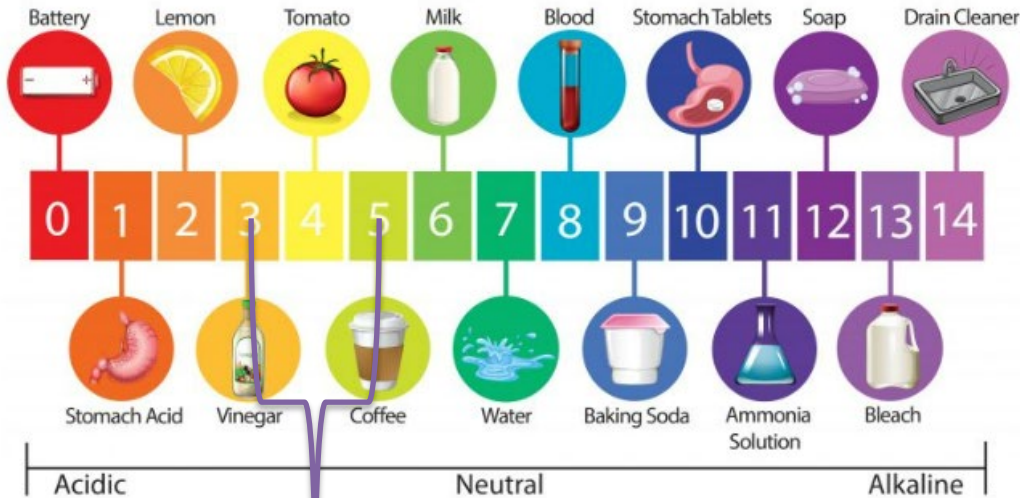
The mean dissolution time (seconds) was 241 (cold beverage), 261 (hot beverage), 222 (room temperature water)

*\* Information listed is from different products*

# Biological Plausibility

<https://www.microkit.us/the-role-of-ph-value-in-titration/>

## The pH Scale



Buprenorphine is stable in solution at a pH of 3.5-5.5

- Dental caries can result from activity of acids on tooth structure
  - Normal pH of saliva is between 6.7 and 7.4
  - When pH drops below 5.5, acid begins to erode enamel
- Prolonged exposure to acidic environment would be expected to contribute to dental adverse events

# REGULATORY FRAMEWORK



# Food and Drug Administration Amendments Act of 2007 (FDAAA)



- Signed into law September 27, 2007
- Section 901 of the Act adds section 505(o)(4) to the Federal Food, Drug, and Cosmetic Act
- **Authorizes FDA to require safety labeling changes for the following products:**
  - Prescription drugs with an approved NDA
  - Biological products with an approved BLA
  - Prescription drugs with an approved ANDA (if the reference listed drug is not currently marketed)

# Regulatory Authority

- 505(o)(4): FDA can require, and if necessary, *order* labeling changes **if FDA becomes aware of New Safety Information** that FDA believes should be included in the labeling of a drug.
- *What is “New Safety Information?”*
  - 505-1(b) defines it as “information derived from a clinical trial, an adverse event report, a postapproval study, peer reviewed biomedical literature, data derived from postmarket risk identification and analysis system, or other scientific data deemed appropriate by FDA”

# What Can be Changed?

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

**WARNING: TITLE OF WARNING**  
*See full prescribing information for complete boxed warning.*

- Text (4)
- Text (5.x)

## -----RECENT MAJOR CHANGES-----

Section Title, Subsection Title (x.x) M/YYYY  
Section Title, Subsection Title (x.x) M/YYYY

## -----INDICATIONS AND USAGE-----

PROPRIETARY NAME is a *[[insert FDA established pharmacologic class text phrase]]* indicated for ... (1)

Limitations of Use  
Text (1)

## -----DOSAGE AND ADMINISTRATION-----

- Text (2.x)
- Text (2.x)

## -----DOSAGE FORMS AND STRENGTHS-----

Dosage form(s): strength(s) (3)

## -----CONTRAINDICATIONS-----

- Text (4)
- Text (4)

## -----WARNINGS AND PRECAUTIONS-----

- Text (5.x)
- Text (5.x)

## -----ADVERSE REACTIONS-----

Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## -----DRUG INTERACTIONS-----

- Text (7.x)
- Text (7.x)

## -----USE IN SPECIFIC POPULATIONS-----

- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/YYYY

# Warnings and Precautions

- Intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are ***serious*** or are ***otherwise clinically significant***.
- To include the adverse event in this section there should be **reasonable evidence of a causal association**, *but a causal relationship need not have been definitively established.*

# Serious or Otherwise Clinically Significant

## Serious

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect

*Based on appropriate medical judgement, may jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes in the above list*

## Otherwise Clinically Significant

- Indication
  - Seriousness relative to the disease or condition treated
- Incidence
  - High absolute risk or rate of occurrence
- Other
  - Potential serious outcome unless regimen is adjusted
  - Reaction that can be managed with appropriate patient selection, monitoring, and prevention or management is needed to avoid potentially serious outcome
  - An adverse reaction that can significantly affect patient compliance, **particularly when noncompliance has potentially serious consequences**

# FAERS Case #5

- 36-year-old-female
- SL buprenorphine/naloxone
- Experienced rapid tooth loss over 14 months while on the product
- Teeth became soft and brittle, chipped just by brushing or chewing soft foods
- Had X-rays 14 months before starting SL buprenorphine, “showed none of the insane damages (that) had happened to teeth”
- Dentist stated never seen tooth decay like this
- Did not have the means to have teeth fixed, would hide teeth when talking, most severely affected teeth were pulled
- **On unknown date, patient stopped taking SL buprenorphine/naloxone**

# Causal Association?



Factors	Findings
1. Frequency of Reporting	Hundreds of cases
2. Adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials?	(n/a, no clinical trial data found explored this adverse event)
3. Evidence of a dose-response relationship	Possibly, though cases <i>may</i> have been more closely tied to dosing frequency than dose
4. Extent to which the adverse event is consistent with the pharmacology of the drug	Strong biological plausibility for the <i>sublingual</i> dosage form
5. Temporal association between drug administration and event	Case descriptions often had reliable information on dental health prior to starting treatment
6. Existence of dechallenge and rechallenge experience	(n/a, very little information on dechallenge/rechallenge experiences)
7. Whether adverse event is known to be caused by related drugs	<i>Yes and no...</i>

# Caused by Related Drugs???

- Few cases involving other SL/transmucosal forms of opioids
  - Already labeled (note: different composition)
- 305 cases of dental caries involving TMB
  - 28 of 305 implicated a brand name SL product indicated for *pain*
  - Notable as well that the dosing for this product is around 10x less than that of TMB for OUD
- Zero cases involving buprenorphine depot (OUD)
- Zero cases involving buprenorphine transdermal (Pain)



# Regulatory Decision

- These cases of dental caries were determined to be serious *and* otherwise clinically significant
- The totality of evidence provided reasonable evidence of a causal association between the drug *in this dosage form* and the adverse event
- This type of adverse event has implications for prescribing decisions and for patient management
- **A new Warnings and Precautions statement was warranted**



# REGULATORY ACTION

# New Safety Information (NSI)

- Section 505(o)(4) requires FDA provide NSI to require changes
  - 305 cases
  - Evidence of rampant caries
  - 71/305 cases resulted in tooth extraction
  - *Acknowledged that the presence of substance use disorder may increase major oral health problems*
  - 26/305 cases occurred in patients with no prior history of dental problems (well documented)
  - 28/305 cases occurred in patients taking the product for the pain indication

# Labeling – 5 Warnings and Precautions (first paragraph)



- **5.x Dental Adverse Events**

Cases of dental caries, some severe (i.e., tooth fracture, tooth loss), have been reported following the use of transmucosal buprenorphine-containing products. Reported events include cavities, tooth decay, dental abscesses/infection, rampant caries, tooth erosion, fillings falling out, and, in some cases, total tooth loss. Treatment for these events included tooth extraction, root canal, dental surgery, as well as other restorative procedures (i.e., fillings, crowns, implants, dentures). Multiple cases were reported in individuals without any prior history of dental problems.

# Labeling – 5 Warnings and Precautions (second paragraph)



Refer patients to dental care services and encourage them to have regular dental checkups while taking TRADENAME. Educate patients to seek dental care and strategies to maintain or improve oral health while being treated with transmucosal buprenorphine-containing products. Strategies include, but are not limited to, gently rinsing teeth and gums with water then swallowing after TRADENAME has been completely dissolved in the oral mucosa. Advise patients to wait at least one hour after taking TRADENAME before brushing teeth [*see Dosing and Administration (2.x), Information for patients (17), Medication Guide*].

# Labeling – 2. Dosage and Administration

- 2.1 Important Dosage and Administration Information
- 2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose
- 2.3 Induction
- 2.4 Maintenance
- **2.5 Method of administration**

Advise patients to do the following after the product has completely dissolved in the oral mucosa: take a sip of water, swish gently around the teeth and gums, and swallow. Advise patients to wait for at least one hour after taking TRADENAME before brushing teeth *[see Warnings and Precautions (5), Postmarketing experience (6.2), Information for Patients (17), and the Medication Guide]*



# Labeling – 17 Information for Patients

- Advise patients that, after TRADENAME has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking TRADENAME before brushing teeth.
- Refer patients to dental care services and encourage them to have regular dental checkups while taking TRADENAME. Instruct patients to inform their dentist that they have started therapy on TRADENAME

# Labeling – Medication Guide



- **Under “How should I take TRADENAME?”**
  - After TRADENAME is completely dissolved, rinse your mouth with water and swallow. Wait for at least one hour before brushing teeth.
  - Report any problems with your teeth immediately to your provider and schedule an appointment with a dentist. Tell your dentist that you have started taking TRADENAME.





# **COMMUNICATIONS PLAN AND PUBLIC RECEPTION**

# FDA warns about dental problems with buprenorphine medicines dissolved in the mouth to treat opioid use disorder and pain



*Benefits for use outweigh these risks and oral care can help*

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[Español](#) [Drug Safety Podcast](#)

1-12-2022 FDA Drug Safety Communication

[Drug Safety Communication](#) (PDF - 94 KB)

What safety concern is FDA announcing?	▼
What is FDA doing?	▼
What is buprenorphine and how can it help me?	▼
What should patients and caregivers do?	▼
What should health care professionals do?	▼
What did FDA find?	▼
What is my risk?	▼
How do I report side effects from buprenorphine?	▼
How can I get new safety information on medicines I'm prescribing or taking?	▼
Facts about buprenorphine	▼
Additional Information for Patients and Caregivers	▼
Additional Information for Health Care Professionals	▼
Data Summary	▼
References	▼



# Communications Plan

# Professional Uptake / Reception



Orally dissolving buprenorphine for opioid use disorder linked to caries

[Stuart L. Segelnick, DDS, MS](#) · [Mea A. Weinberg, DMD, MSD, RPh](#)



## NEW DENTAL WARNING FOR BUPRENORPHINE

- The labeling for transmucosal buprenorphine products will now include a warning that the drug may cause serious dental problems such as tooth decay, cavities, oral infections, and tooth loss.
- Nurses and NPs should complete an oral history and assessment prior to patients beginning treatment. Patients should be informed of these potential adverse effects and encouraged to receive regular dental care.



News > Medscape Medical News

## Orally Dissolving Buprenorphine Tied to Severe Tooth Decay, FDA Warns

January 13, 2022



World ▾ US Election Business ▾ Markets ▾ Sustainability ▾ Legal ▾ Breakingviews ▾ Technology ▾

Healthcare & Pharmaceuticals

## FDA flags risk of dental issues from use of opioid addiction drug buprenorphine



# Social Media Reaction



Omg I f\*\*\*ing knew it! I'm glad they acknowledge it finally!

So that's why some of my teeth are rotting... my teeth were f\*\*\*ing fine at the beginning of the year, and they just nose dived over the last 6 months, with me starting subs in April...

I f\*\*\*in knew my teeth issues were from this s\*\*\*. Never had any problems before n now teeth r breaking, cavities in all my teeth n have no insurance so what do I have to do? Pull the teeth as they get too bad. It makes me just cry inside as I was so proud of my teeth n constantly brush n floss them. It's so depressing...I rarely smile anymore.

I had strong beautiful teeth when I started [redacted] in 2008. Had to have every single tooth yanked in 2017 for dentures. I couldn't even get implants if they were affordable due to my gums couldn't support them.

The above being said, I am still thankful for [redacted] for all of the reasons we take it. I just hate that many of us weren't aware of the dental ramifications. Oh well, at least I DID get healthier once all of those terrible teeth came out of my head!

My teeth my have not been great but when i started using bupe my teeth literally started to break apart after like 6-8 months

This is honestly the biggest thing I did not plan out when I became a junkie. It got exponentially worse in 6 months on subs vs 10 years on heroin.

Yes, I brush and floss regularly. I've had cavities in the past but this is RAPID, like 10 years worth of decay in one year.

It good to know they are finally taking notice to long-term side effects of buprenorphine

# New Science

## Research Letter

December 13, 2022

### Association Between Sublingual Buprenorphine-Naloxone Exposure and Dental Disease

Mahyar Etminan, PharmD, MSc<sup>1</sup>; Ramin Rezaeianzadeh, BSc<sup>1</sup>; Abbas Kezouh, PhD<sup>2</sup>; et al





> Author Affiliations | Article Information

JAMA. 2022;328(22):2269-2271. doi:10.1001/jama.2022.17485

Etminan, Mahyar, Ramin Rezaeianzadeh, Abbas Kezouh, and Kevin Aminzadeh. 2022. 'Association Between Sublingual Buprenorphine-Naloxone Exposure and Dental Disease', JAMA, 328: 2269-71.

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.<sup>4</sup> Patients are instructed to hold the tablet under the tongue for 5 to 10 minutes to maximize absorption.<sup>5</sup> Thus, prolonged acidic exposure of the drug in the mouth might lead to tooth damage.

## Sublingual/Buccal buprenorphine and dental problems: a pharmacovigilance study

Romain Barus , François Montastruc , Claire de Canecaude, Haleh Bagheri, Agnès Sommet  & Maryse Lapeyre-Mestre 

Pages 1283-1287 | Received 25 May 2023, Accepted 09 Aug 2023, Published online: 21 Aug 2023

🗣️ Cite this article  <https://doi.org/10.1080/14740338.2023.2247962>



Barus, R., F. Montastruc, C. de Canecaude, H. Bagheri, A. Sommet, and M. Lapeyre-Mestre. 2023. 'Sublingual/Buccal buprenorphine and dental problems: a pharmacovigilance study', Expert Opin Drug Saf, 22: 1283-87.

**Conclusions:** Sublingual/buccal buprenorphine might increase the risk of reporting dental problems. However, these results do not modify the benefits of sublingual/buccal buprenorphine in the treatment of opioid use disorders.

# Summary

1. The U.S. is still in an opioid overdose crisis, but treatments, like transmucosal buprenorphine for opioid use disorder are available
2. FDA detected a signal involving transmucosal buprenorphine and dental caries, reviewed the scientific information
3. FDA's review of the safety signal determined that the dental caries were serious, otherwise clinically significant, and there was reasonable causal association between the drug and the event; thus a new Warnings and Precautions statement was added to TMB products, per FDA's authority
4. Healthcare providers can help by being aware of this adverse event, discussing with their patients, monitoring for such events, and encouraging regular dental checkups while on TMB.



# Q & A PANEL

# Q&A Panelists



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Office of New Drugs



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