January 24, 2022

Janet Woodcock, MD
Acting Commissioner
U.S. Food & Drug Administration
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Re: A Call for the FDA to Retract its Safety Communication Regarding Buprenorphine

Dear Acting Commissioner Woodcock

The United States has experienced a record number of tragic opioid overdose deaths since the beginning of the Covid-19 pandemic.[1] During the course of a year, over 100,000 people—family members, friends, community members—died from substance-related overdoses, the majority involving an illicitly-manufactured version of the opioid fentanyl. Over one million Americans have died from opioid overdoses between 1999 and the present.[2]

But there is hope. The medications buprenorphine and methadone reduce mortality from opioid use disorder (OUD) by over 50%.[3] They are the gold standard for care and allow people to begin a sustained recovery and get their lives back.[4–6]

On January 12, the Food and Drug Administration (FDA) issued a Drug Safety Communication concerning one of these medications, buprenorphine, and a risk of dental problems.[7,8] Buprenorphine, as a tablet or film, must be dissolved in the mouth to be effective.

The FDA based its Communication on 305 cases of dental problems since 2002 when buprenorphine was first approved. In 2019 alone, 2.4 million Americans were taking buprenorphine, 1.7 million with a prescription and 700,000 without a prescription.[9] The overall number of people who have taken the medication during the past twenty years is much higher.

Among the FDA's reviewed cases:

- 279 (91%) patients had prior dental problems
- The median time to diagnosis was 2 years
- 192 (63%) patients had 1 tooth affected.

More than 40% of Americans have experienced dental pain in the past year.[10] With 2.4 million Americans taking buprenorphine, at least 960,000 (40%) would be expected to experience dental pain. 305 people is 0.032% of 960,000. In this epidemiologic circumstance, it is not possible to conclude a

causal relationship between exposure to a medication and dental pain when there is such a small proportion compared to the base rate. The duration from initial exposure to dental symptoms was two years which, given the range of confounds, also makes it impossible to establish causality.

In addition, the mechanism of causation is implausible. A medication that affects all dentition is unlikely to harm only a single tooth—as occurred in nearly two-thirds (63%) of cases—or affect so few people. Though the Communication does not explicitly state a mechanism for medication-induced harm, it recommends clinicians "Counsel patients that after the medicine has completely dissolved in the oral mucosa, to gently rinse their teeth and gums with water and then swallow."[8] Patients are advised to let buprenorphine completely dissolve, then "take a large sip of water, swish it gently around your teeth and gums, and swallow."[8] These recommendations seem to either indicate a need for extra fluid in the mouth or a toxic dental effect from contact with the medication; neither of these reasons has scientific support.

Methadone, another gold standard treatment for opioid use disorder, has been falsely said to "eat the bone"—including teeth—and people have not used it for this reason. Like other medications, methadone may cause somewhat less saliva production, and saliva is protective of teeth. This reduction in saliva (the medical term is "xerostomia") is caused by hundreds of medications (see Appendix A), both prescribed and over the counter, from asthma inhalers to over-the-counter pain medication.[11] The FDA has not issued a Communication about any of these other drug classes or medications though they may affect dentition.

In its Communication, the FDA also recommends health care professionals:

> Counsel patients that severe and extensive tooth decay, tooth loss, and tooth fracture have been reported with the use of this medicine and it is important to visit their dentist to closely monitor their teeth.[8]

Simultaneously, the FDA also advises that the "benefits of buprenorphine medicines clearly outweigh the risks."[8] It would be difficult for many people to proceed with a medication after being warned that their teeth may be so detrimentally affected. Indeed, people are already ambivalent about taking a medication that saves lives and supports sustained recovery.[12,13] Much of this ambivalence is due to stigma.[14,15] Patients' family and friends may even want them to stop the medication.[16] When people do seek care, access to buprenorphine is low or absent in many areas, and many pharmacies do not stock the medication.[17–19]

The actions the FDA recommends for patients in the Communication are currently impossible in the United States:

> Schedule a dentist visit soon after starting this medicine and inform your dentist that you are taking buprenorphine, and schedule regular dental checkups while taking this medicine. Your dentist can customize a tooth decay prevention plan for you. Notify both your health care professional and your dentist immediately if you experience any problems with your teeth or gums.[7]

Many Americans, especially those who take buprenorphine, do not have access to quality dental care they can afford.[20] Even in states that have robust Medicaid dental coverage for adults, only about 10% of people treated with buprenorphine obtain care.[21] Tooth decay in our nation is worsened by limited affordable preventive and therapeutic dental care, inadequately scaled water fluoridation, and consumption of cariogenic foods.[22]

In summary, this FDA Communication, which has not been based on solid research evidence, can have predictable harmful effects:

- Further stigma for taking a medication that saves and improves lives;[15]
- Conflation with existing, disproven dental fears about methadone, another life-saving medication;
- A false choice for patients: risk severe dental problems or risk grave harm from opioids;
- Clinicians will have yet one more reason not to prescribe buprenorphine as they are now advised to conduct a lengthy discussion about oral health.[7]

To avoid these consequences as much as possible, and because of the flawed analysis regarding causation, we call for the FDA to immediately and fully retract its Drug Safety Communication of January 12, 2022.

This is not a time to lose momentum in expanding life-saving care for Americans with opioid use disorder. It is actually recovery *with* buprenorphine that better enables a person to obtain the dental care they have long needed.

Respectfully,

American Academy of Addiction Psychiatry (AAAP)
American College of Academic Addiction Medicine (ACAAM)
American College of Medical Toxicology (ACMT)
American Osteopathic Academy of Addiction Medicine (AOAAM)
American Society of Addiction Medicine (ASAM)
Association for Multidisciplinary Education and Research in Substance use and Addiction (AMERSA)
California Society of Addiction Medicine (CSAM)
College of Psychiatric and Neurologic Pharmacists (CPNP)
Massachusetts Medical Society (MMS)
Massachusetts Society of Addiction Medicine (MASAM)
Oregon Society of Addiction Medicine (ORSAM)

cc: Miriam Delphin-Rittmon, Ph.D., Assistant Secretary for Mental Health and Substance Use and the leader of the Substance Abuse and Mental Health Services Administration (SAMHSA)

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Appendix A

Categories of Drugs Associated with Xerostomia[11]

None of these classes, or their included medications, has had an FDA Drug Safety Communication regarding xerostomia.

1. Analgesics (centrally acting)
2. Angiotensin-converting enzyme inhibitors
3. Anorexiants
4. Antacids
5. Antiacne agents
6. Antiallergy agents
7. Antianxiety agents
8. Anticholinergic/antispasmodic agents
9. Anticonvulsants
10. Antidepressants
11. Antidiarrheal agents
12. Antidysrhythmics
13. Antihistamines
14. Antihypertensives
15. Antinausea agents
16. Antiparkinsonism agents
17. Antipsychotics
18. Bronchodilators
19. Calcium channel blockers
20. Decongestants
21. Diuretics
22. Muscle relaxants
23. Opioid analgesics
24. Nonsteroidal anti-inflammatory drugs
25. Sedatives
26. Smoking-cessation agents