



Colorado Society of Addiction Medicine

A Chapter of American Society of Addiction Medicine

U.S. Food and Drug Administration (FDA)
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Re: Buprenorphine Labeling Recommendations

Drafted By:

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Endorsed By:

California Society of Addiction Medicine
Hawaii Society of Addiction Medicine
Illinois Society of Addiction Medicine
Massachusetts Society of Addiction Medicine
New York Society of Addiction Medicine
Oregon Society of Addiction Medicine
Pennsylvania Society of Addiction Medicine
Utah Society of Addiction Medicine.

In each of their respective states, these are the largest medical specialty societies representing physicians and clinicians specializing in the prevention and treatment of addiction. Together, these organizations represent a large proportion of the nation's addiction specialist workforce, practicing in a diverse range of states.

Action Requested:

This Citizen Petition (CP) asks the U.S. Food & Drug Administration (FDA) to take the following actions:

- 1) Update language in the labeling of sublingual buprenorphine products approved to treat opioid use disorder (OUD). This CP requests that labeling include the following statement:
Following initiation, buprenorphine dose should be titrated based on the prescriber's clinical judgment to alleviate symptoms enough to enable patients to maintain discontinuation of illicit opioid use. Evidence suggests that 16mg per day or more may reduce risk of overdose death more effectively than lower doses. Some patients may require a higher than average dose due to significant inter-patient variability in opioid tolerance, drug absorption, and drug metabolism such as during pregnancy.
- 2) Issue a drug safety communication (DSC) to providers highlighting the potential clinical benefit of sublingual buprenorphine doses $\geq 16\text{mg/day}$ in patients with OUD.

Current labeling for sublingual and/or buccal buprenorphine products is inadequate to meet the needs of the American population during a synthetic opioid overdose epidemic. For example, Section 2.5 of the labeling for Suboxone reads: “The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.”¹ This language does not account for data from the peer-reviewed literature showing improved outcomes among patients taking doses >24mg/day.

Statement of Grounds:

The opioid epidemic is a serious national crisis. Recent estimates from the Centers for Disease Control and Prevention (CDC) suggest that opioid overdose deaths in the United States reached a record high of 75,674 in the 12-month period from April 2020 to April 2021, increased from 56,064 the year before.² An important contributor to the dramatic surge in opioid-related deaths is the proliferation of fentanyl and other synthetic analogues, which offer potency 50 to 100 times greater than morphine.³ Although the opioids driving the current epidemic are orders of magnitude greater in potency than previous generations of narcotics, buprenorphine dosing recommendations have not adjusted to meet this reality.

Opioid receptor agonists like methadone and buprenorphine play key roles in medications for addiction treatment (MAT) for the management of opioid use disorder (OUD). MAT reduces the risk of serious adverse outcomes in patients with OUD, including recidivism, overdose, and death.^{4,5} Although the complete mu opioid receptor agonism of methadone provides effective suppression of fentanyl-related craving and withdrawal symptoms, significant barriers exist in access to methadone treatment for OUD.⁶ In the U.S., methadone can only be dispensed at federally certified opioid treatment programs (OTPs) when treating OUD. While recent estimates suggest that 83% of individuals in the US live within 10 miles of a facility offering medication for OUD, only 10.8% of these facilities offer methadone.⁷ Additionally, although the current opioid epidemic affects both rural and urban communities, most OTPs are in urban centers.⁸

¹ Drugs@FDA. Accessed on 5/2/2022 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022410s042lbl.pdf

² Accessed on 4/28/2022 from https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

³ Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths - United States, 2013-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(5152):1419-1427. Published 2018 Jan 4. doi:10.15585/mmwr.mm675152e1

⁴ Ma J, Bao YP, Wang RJ, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Mol Psychiatry*. 2019;24(12):1868-1883. doi:10.1038/s41380-018-0094-5

⁵ Baser O, Chalk M, Fiellin DA, Gastfriend DR. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care*. 2011;17 Suppl 8:S235-S248.

⁶ “Regulation of the Treatment of Opioid Use Disorder with Methadone” American Society of Addiction Medicine. Published 2021 Oct 23. Accessed 8/7/2022.

⁷ Cantor J, Powell D, Kofner A, Stein BD. Population-based estimates of geographic accessibility of medication for opioid use disorder by substance use disorder treatment facilities from 2014 to 2020. *Drug Alcohol Depend*. 2021;229(Pt A):109107. doi:10.1016/j.drugalcdep.2021.109107

⁸ Lister JJ, Weaver A, Ellis JD, Himle JA, Ledgerwood DM. A systematic review of rural-specific barriers to medication treatment for opioid use disorder in the United States. *Am J Drug Alcohol Abuse*. 2020;46(3):273-288. doi:10.1080/00952990.2019.1694536

Alternatively, buprenorphine may be more accessible for patients seeking MAT. Unlike methadone, buprenorphine can be prescribed and filled at outpatient pharmacies. Federal regulatory changes during the COVID-19 pandemic further improved access to buprenorphine by eliminating the requirement for initial in-person evaluation prior to prescription. Based on research trials conducted prior to 2002, the current FDA buprenorphine/naloxone package insert reads that the maintenance dose of buprenorphine/naloxone is “generally in the range of 4mg/1mg buprenorphine/naloxone to 24mg/6mg buprenorphine/naloxone per day depending on the individual patient and clinical response.” It further specifies that, “dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.”⁹ This language does not reflect the current literature – described below – which supports the potential for improved outcomes for patients with OUD with daily buprenorphine doses greater than 24mg.

Treatment retention is an important outcome in OUD management, and is associated with reduced all-cause mortality in patients with OUD.¹⁰ A 2014 study by Hser et al. showed a linear relationship between medication dose and retention for patients receiving buprenorphine, with no reported serious adverse medication-related outcomes among patients receiving doses >24 mg/day.¹¹ Similarly, Pizzicato et al. showed that doses >24 mg/day were associated with significantly greater 180-day buprenorphine adherence when compared to doses <16 mg/day.¹² In a meta-analysis of 21 international randomized controlled trials with a total of over 2,700 participants, patients receiving buprenorphine dosages from 16-32 mg/day showed better retention in treatment than groups receiving <16mg/day, with fewer urine tests positive for opiates and cocaine.¹³ In a 2003 in-vivo study of five volunteers with heroin-dependent OUD, Greenwald et al. showed that sublingual buprenorphine dose-dependently increased mu opioid receptor occupancy, with near-maximal receptor occupancy levels occurring at doses of 32mg/day (89%-99% occupancy relative to placebo).¹⁴ The study further demonstrated that high buprenorphine occupancy of mu receptors correlated with decreased withdrawal and reward symptoms, with near-maximal effects observed at doses of 32mg/day. A 2014 review of the literature by the same author concluded that buprenorphine doses of 16mg/day may be adequate to achieve clinically meaningful opioid blockade in some patients; however, achieving blockade of the subjective effects of high opioid doses in *most* patients may require buprenorphine doses greater than 24

⁹ <https://www.suboxone.com/pdfs/prescribing-information.pdf>

¹⁰ Laroche M, et al. [Medication for opioid use disorder after nonfatal opioid overdose and association with mortality. A cohort study](#) (link is external). *Annals of Internal Medicine*. June 19, 2018.

¹¹ Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*. 2014 Jan;109(1):79-87. doi: 10.1111/add.12333. Epub 2013 Oct 9. PMID: 23961726; PMCID: PMC3947022.

¹² Pizzicato LN, Hom JK, Sun M, Johnson CC, Viner KM. Adherence to buprenorphine: An analysis of prescription drug monitoring program data. *Drug Alcohol Depend*. 2020 Nov 1;216:108317. doi: 10.1016/j.drugalcdep.2020.108317. Epub 2020 Sep 28. PMID: 33035714.

¹³ Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. *J Addict Dis*. 2012;31(1):8-18. doi: 10.1080/10550887.2011.642758. PMID: 22356665.

¹⁴ Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*. 2003;28(11):2000-2009. doi:10.1038/sj.npp.1300251

to 32mg/day.¹⁵ One study of hospitalized adult men with OUD showed a single high dose (32mg, 64mg, 96mg) of sublingual buprenorphine reduced cravings in a dose-response manner over the next 5 days, with no serious adverse cardiovascular or respiratory events observed.¹⁶ Multiple trials of sublingual buprenorphine doses >24mg show similar efficacy and safety profiles.¹⁷

Furthermore, pregnant women may need higher doses of medications for opioid use disorder due to increased volume of distribution and increase hepatic clearance, leading to subtherapeutic plasma concentrations.¹⁸ The current labeling language is thus restrictive by not accounting for the need for increased doses among this population; amending the language would provide the flexibility needed to treat all patients with OUD, including pregnant patients. Importantly, studies have shown no relationship between dose and risk of neonatal abstinence syndrome – so no increased incidence of NAS would be expected with higher doses among pregnant women.¹⁹

We recognize these data are predominantly observational, and that no high-quality clinical trials evaluating outcomes between dosing groups exist to support or refute our recommendation. However, FDA has taken labeling and/or regulatory action on spontaneous case reports – so there is a precedent for changing labeling in the setting of imperfect data. Adjusting the recommended dosing limits around one of the core treatment modalities for OUD is one action the FDA can take that can help improve outcomes for patients and providers fighting in the opioid epidemic. A change in labeling can have a significant impact on insurance coverage for MOUD, driving patient access to medication and engagement in treatment. Reducing barriers to accessing care is a key step that can create lasting change. As fentanyl and other synthetic opioids drive increasing mortality across the country, increasing access to evidence-based dosages for one of the few FDA-approved medications for OUD is a change within the FDA's regulatory scope that could have significant impact on connecting patients to effective treatment. Methadone's relative inaccessibility and the difficulty of initiating naltrexone therapy for many patients leaves buprenorphine a prime target for regulatory reform to improve the public's health.

While recognizing the FDA does not regulate the practice of medicine, we also encourage the FDA to oppose the imposition of arbitrary buprenorphine dose limits imposed by state Medicaid programs, state medical boards, and/or insurance carriers.

¹⁵ Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend.* 2014;144:1-11. doi:10.1016/j.drugalcdep.2014.07.035

¹⁶ Ahmadi, J., Jahromi, M.S., Ghahremani, D. *et al.* Single high-dose buprenorphine for opioid craving during withdrawal. *Trials* 2018; 19, 675. <https://doi.org/10.1186/s13063-018-3055-z>

¹⁷ Shulman M, Wai JM, Nunes EV. Buprenorphine Treatment for Opioid Use Disorder: An Overview. *CNS Drugs.* 2019;33(6):567-580.

¹⁸ Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, Crocetti M, Dudas R, Harrow C, Huestis MA, Jansson LM, Lantz M, Lester BM, Milio L. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend.* 2005 Jul;79(1):1-10. doi: 10.1016/j.drugalcdep.2004.11.013. PMID: 15943939.

¹⁹ Wong J, Saver B, Scanlan JM, Gianutsos LP, Bhakta Y, Walsh J, Plawman A, Sapienza D, Rudolf V. Does Maternal Buprenorphine Dose Affect Severity or Incidence of Neonatal Abstinence Syndrome? *J Addict Med.* 2018 Nov/Dec;12(6):435-441. doi: 10.1097/ADM.0000000000000427. PMID: 29905586.

Tennessee Department of Health guidelines, for example, impose excessive documentation standards on prescribers to treat patients with >16mg/day buprenorphine for greater than a month – and then to either hand over care to an addiction specialist, or document in the chart why the patient has not been referred to an addiction specialist.²⁰ We support deploying addiction medicine specialists far and wide; however, such guidelines are the addiction medicine equivalent of requiring primary care providers to transfer statin-receiving patients to a cardiologist – an unnecessary and resource-draining policy which strains patient, provider, and system in the name of stigma. In contrast, Washington state’s Medicaid program has removed prior authorization requirements for transmucosal buprenorphine formulations approved for OUD up to 32 mg/day.²¹ Data is currently being collected on patient outcomes in Washington following this policy revision; however, based on unpublished data presented by Lucinda Grande MD at the American Society of Addiction Medicine conference in March 2022, the change has been welcomed by patients and providers alike with evidence of enhanced engagement among patients receiving higher doses of buprenorphine.²²

Changing labeling dosing language is not without risk. A concern among patients, prescribers, and regulators alike is the potential for medication diversion. Changing the labeling for buprenorphine products could result in more medication being prescribed, leading to the potential for patients to divert their prescriptions for a variety of reasons. A substantial amount of diverted buprenorphine is used to treat withdrawal symptoms rather than for euphoric effect.²³ The relative benefits and risks must be weighed, though, to generate a balanced and reasonable response to a worsening public health crisis. Fentanyl – not diverted buprenorphine – is killing thousands of Americans each year. As Doernberg et al. state in their 2018 commentary in *Substance Abuse*, “Although diversion and illicit use of buprenorphine are not desired outcomes, weighing the relative risks and benefits of buprenorphine when generating policies and practices related to its accessibility is critical. Risks attendant to diversion exist but are relatively small compared with the risk created when treatment access is restricted.”²⁴ The FDA has an opportunity to refocus the dialogue not on criminal justice, but instead on the importance of providing appropriate, evidence-based treatment to people who need it.

The factual and legal grounds for the petition, including all supporting material, as well as information known to the petitioner that may be unfavorable to the petitioner’s position, have been reviewed.

²⁰ Tennessee Nonresidential Buprenorphine Treatment Guidelines, 2021 Update. Accessed on 5/2/2022 from https://www.tn.gov/content/dam/tn/mentalhealth/documents/2018_Buprenorphine_Treatment_Guidelines.PDF

²¹ Accessed on 4/28/2022 from https://www.hca.wa.gov/assets/billers-and-providers/MAT_buprenorphine_products.pdf

²² Grande L et al. “Buprenorphine dose limits: What’s the evidence?” ASAM 2022.

²³ Chilcoat HD, Amick HR, Sherwood MR, Dunn KE. Buprenorphine in the United States: Motives for abuse, misuse, and diversion. *J Subst Abuse Treat.* 2019 Sep;104:148-157. doi: 10.1016/j.jsat.2019.07.005. Epub 2019 Jul 12. PMID: 31370979.

²⁴ Doernberg M, Krawczyk N, Agus D, Fingerhood M. Demystifying buprenorphine misuse: Has fear of diversion gotten in the way of addressing the opioid crisis?, *Substance Abuse* 2019; 40:2, 148-153, DOI: [10.1080/08897077.2019.1572052](https://doi.org/10.1080/08897077.2019.1572052)

Environmental Impact Statement:

As this petition is strictly about dosing recommendations for already-approved medical products, no environmental impact statement is indicated.

Attestation:

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

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