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Evidence on Buprenorphine Dose Limits: A Review

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Objectives: As overdose deaths from fentanyl continue to increase, optimizing use of medications for opioid use disorder has become increasingly important. Buprenorphine is a highly effective medication for reducing the risk of overdose death, but only if a patient remains in treatment. Shared decision making between prescribers and patients is important to establish a dose that meets each patient's treatment needs. However, patients frequently face a dose limit of 16 or 24 mg/d based on dosing guidelines on the Food and Drug Administration's package label.

Methods: This review discusses patient-centered goals and clinical criteria for determining dose adequacy, reviews the history of buprenorphine dose regulation in the United States, examines pharmacological and clinical research results with buprenorphine doses up to 32 mg/d, and evaluates whether diversion concerns justify maintaining a low buprenorphine dose limit.

Results: Pharmacological and clinical research results consistently demonstrate buprenorphine's dose-dependent benefits up to at least 32 mg/d, including reductions in withdrawal symptoms, craving, opioid reward, and illicit use while improving retention in care. Diverted buprenorphine is most often used to treat withdrawal symptoms and reduce illicit opioid use when legal access to it is limited.

Conclusions: In light of established research and profound harms from fentanyl, the Food and Drug Administration's current recommendations on target dose and dose limit are outdated and causing harm. An update to the buprenorphine package label with recommended dosing up to

32 mg/d and elimination of the 16 mg/d target dose would improve treatment effectiveness and save lives.

Key Words: buprenorphine, dose limit, opioid use disorder

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More than 80,000 Americans died of opioid overdoses in 2021, an increase of 61% in only 2 years.¹ The mortality surge is largely due to exposure to unregulated, illicitly manufactured fentanyl and its analogues (hereafter referred to as “fentanyl”). Fentanyl's lethality is conferred by its exceedingly high potency and lipophilicity.² Buprenorphine and methadone, the 2 most effective medications for opioid use disorder (MOUDs),³ remain valuable tools to treat opioid use disorder (OUD) and reduce fentanyl overdose death and other harms. It is more important than ever to optimize their use at scale.

Dr. Nora Volkow, Director of the US National Institute on Drug Abuse, observes that “higher rates of tolerance and physical dependence associated with repeated fentanyl use might necessitate higher doses of methadone or buprenorphine than for other OUDs.”⁴ Evolving research findings suggest a dangerous trend toward lower rates of MOUD initiation and retention since fentanyl use became prevalent, as well as a trend toward higher required doses of methadone.^{5,6}

The increased lethality of the drug supply highlights the importance of patient-centered care, which respects and responds to individuals' specific health needs and desired health outcomes, and ensures that patient values drive healthcare decisions.⁷ Examples of effective patient-centered strategies in treating substance use disorders include use of harm reduction principles, trauma-informed care, and peer recovery support.^{8–10} A key component of patient-centered care in buprenorphine treatment for OUD is shared decision making in titrating the dose to achieve mutually agreed-upon treatment goals.^{11,12} Instead of collaboration, however, patients frequently face absolute dose limits of 16 or 24 mg/d. These limits often lead to inadequate protection against fentanyl use because of persistent withdrawal symptoms and craving—ultimately inducing patients to leave treatment.^{13,14}

In medicine, we are generally concerned about too high a dose being potential “poison.”¹⁵ However, underdosing (eg, with oxygen, vasopressors, and antibiotics) can also lead to patient harm. Widespread underdosing of buprenorphine, if responsible for treatment failure, could directly harm many patients whose primary goals are simply to survive and avoid withdrawal.¹⁶ Because ongoing use of illicit fentanyl is frequently lethal, the rationale for buprenorphine dose limits must be evaluated carefully and justified using the highest standards of evidence.

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Our examination of buprenorphine dosing begins with a discussion of patient-centered goals and clinical criteria for determining dose adequacy. We then present relevant pharmacological principles and research results regarding buprenorphine dose dependence. The history of buprenorphine dose regulation in the United States is reviewed in this context. We then describe nearly 3 decades of clinical evidence for a dose-response relationship with benefits extending to at least 32 mg/d, including the specific implications of pregnancy on dosing. We conclude by briefly examining the buprenorphine diversion concerns that are closely tied to existing dose-limit policy (Box 1).

TREATMENT GOALS AND DOSE ADEQUACY

From a pharmacological standpoint, an adequate maintenance dose of buprenorphine will^{17,18}

1. Eliminate negative reinforcement by suppressing opioid withdrawal symptoms and craving that can lead to illicit opioid use,
2. Eliminate positive reinforcement by blocking the euphoric and motivational (drug-seeking) effects of illicit opioid use, and
3. Eliminate the toxicity of illicit opioid use by blocking its respiratory depression and associated overdose harm.

The American Society of Addiction Medicine recommends 4 similar goals: (1) suppress opioid withdrawal, (2) block the effects of illicit opioids, (3) reduce opioid craving and stop or reduce the use of illicit opioids, and (4) promote and facilitate patient engagement in recovery-oriented activities including psychosocial intervention.¹⁹

National agencies and treatment guidelines for OUD emphasize the importance of patient-centered care, but only 1 of 31 existing quality metrics concerns patient preferences.⁷ When asked, a key goal for patients is to find a “comfortable and effective” dose, which in turn requires “open, trusting and collaborative healthcare provider relationships.”²⁰ One patient’s words epitomize the disempowering effect of clinician-driven care: “I went through withdrawals for 2.5 months every morning ... because I didn’t have my dose high enough ... and when I would go to see [my doctor] I would ask can you please up my dose and my doctor would say ‘no.’”²⁰

After arriving at a shared decision regarding dosing, patients and clinicians still often encounter multiple barriers. Policies of their clinic, health system, or pharmacy may limit dosing to 16 mg/d—the target dosage identified by the Food and Drug Administration’s (FDA’s) product label—or the FDA maximum of 24 mg/d. Clinicians may encounter a health in-

surance limit or the delay and inconvenience of required prior authorization. Continuity of an effective dose may be additionally jeopardized when the patient transfers to a more restrictive clinician or setting (eg, between residential and outpatient treatment or from the community to a jail or prison).

BUPRENORPHINE PHARMACOLOGY: DOSE DEPENDENCE

Correlation of Buprenorphine Dose with Receptor Occupancy and Full Agonist Opioid Effects

Optimal buprenorphine dosing has long been a focus of research. A 2003 study, for example, maintained heroin-dependent volunteers on different doses of buprenorphine, measuring mu-opioid receptor (MOR) occupancy together with buprenorphine’s degree of protection from both negative reinforcement (withdrawal and craving) and positive reinforcement (rewarding effect of high-dose hydromorphone).²¹ Compared with placebo, daily buprenorphine dosing of 2, 16, and 32 mg produced prefrontal cortex MOR occupancy of 47%, 90%, and 96%. Other brain regions relevant to addiction, for example, the amygdala and nucleus accumbens, also showed near-maximal MOR occupancy (94%–98%) at 32 mg/d when measured near peak daily levels.¹⁷

As buprenorphine dose and MOR occupancy increase, different clinically beneficial effects occur at different thresholds.²¹ Blockade of the rewarding effects of illicit opioids occurs at a higher dose than eliminating withdrawal symptoms and craving (Fig. 1). In clinical studies, the dose threshold for craving (which includes drug-related dreams and post-dream distress) varies between and within individuals based on circumstances; overall, there is greater relief from craving at higher doses.²²

Early pharmacology studies of buprenorphine require careful interpretation for several reasons. (1) Most use a single dose or once-daily dosing to measure peak and minimum plasma concentrations and time course of decay (Fig. 2); more frequent dosing may be preferred by some patients because of improved stability of plasma concentration.²³ (2) Protective effects of buprenorphine when heroin was the prevalent illicit opioid must be reevaluated in the context of the current drug supply; fentanyl’s potency is ≥ 20 times that of hydromorphone, so many fentanyl-dependent individuals will require a higher buprenorphine dose and MOR occupancy than found in the 2003 study to block withdrawal, craving, and opioid reward.^{21,24} (3) Individual variability is substantial; sublingual buprenorphine’s bioavailability varies between individuals²⁵ by a factor of 3, and individuals vary widely in the doses they require for specific protections against withdrawal, craving, and opioid reward blockade.²¹ Dose limits disregard this known variability, jeopardizing an individual patient’s care.

Improved Safety at Higher Doses

Buprenorphine is extremely safe in comparison to full agonist opioids owing to its ceiling effect on inducing respiratory depression.²⁶ Buprenorphine also provides protection against overdose toxicity of full agonist opioids such as fentanyl because of its high lipophilicity and high affinity for MOR and consequent functional antagonism.² In a 2022 study, opioid-tolerant

Box 1. Key Points

1. Current FDA guidance for buprenorphine dosing recommends a target dosage of 16 mg/d and a dose range of 4 to 24 mg/d.
2. Decades of independent research establish evidence that individualization of doses at least up to 32 mg/d increases patient safety and retention in care.
3. Strict dose limits less than 32 mg/d harm patients in the context of widespread lethal fentanyl.

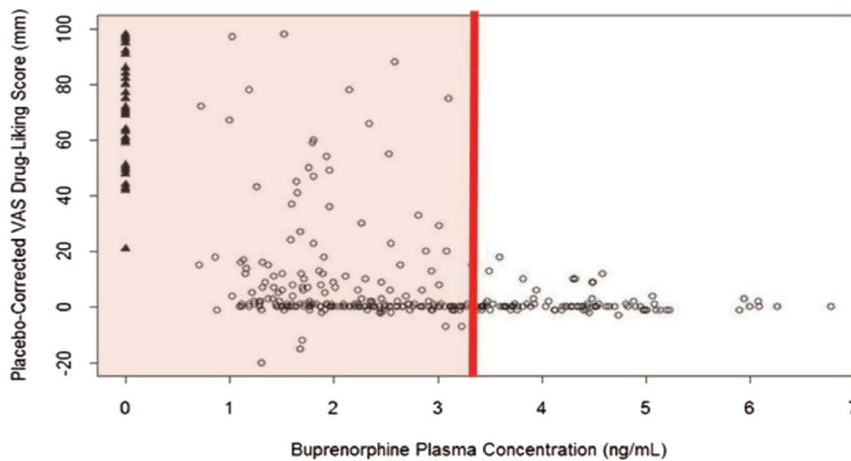


FIGURE 1. Drug liking versus plasma buprenorphine concentration. VAS represents the strength of patient drug “liking” of a high-dose challenge (18 mg) of intravenous hydromorphone, as a function of buprenorphine plasma concentration achieved with XR-BUP. A steady-state buprenorphine exposure of greater than 3.3 ng/mL (equivalent to plasma concentration with 32 mg/d after 12 hours with once-daily dosing; see Fig. 2) was required to suppress the rewarding opioid effect (red bar), the red shaded area indicates susceptibility to reward at lower concentrations. Each participant was measured at multiple exposure levels. Individual subject scores are shown as filled triangles without buprenorphine (a concentration of 0 ng/mL) and as open circles with different buprenorphine plasma concentrations. There is wide variability among subjects. VAS, visual analog scale; XR-BUP, extended-release buprenorphine. Source: *Highlights of prescribing information. Sublocade (buprenorphine extended-release) injection, for subcutaneous use, CIII.* FDA; 2022 (p. 30). <https://www.sublocade.com/Content/pdf/prescribing-information.pdf>.

participants were infused with increasing stepwise buprenorphine doses targeted to steady-state plasma concentrations of 1, 2, and 5 ng/mL.²⁷ At each step, participants then received infusions of

fentanyl at cumulative doses that would produce apnea in the absence of buprenorphine. Apnea was completely suppressed at 5 ng/mL of buprenorphine, but at its lower concentrations

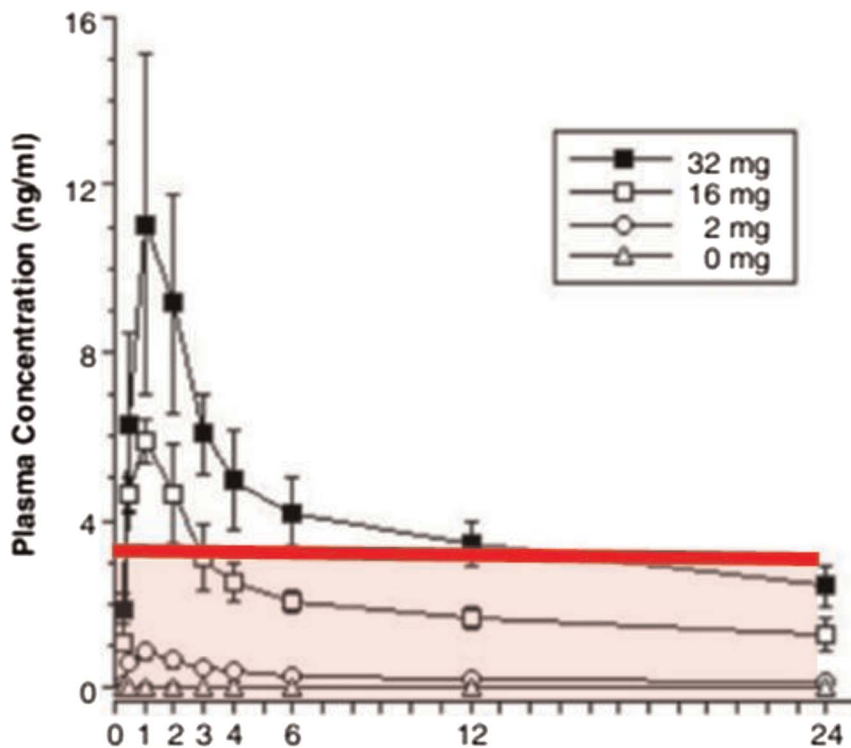


FIGURE 2. Buprenorphine plasma concentration versus time at different doses. Plasma concentration of buprenorphine over a 24-hour blood sampling period after once-daily dosing in 5 heroin-dependent volunteers maintained on 0, 2, 16, and 32 mg/d buprenorphine. The thick line at 3 ng/mL is at the level required to suppress drug “liking” of a high-dose hydromorphone challenge and the red shaded area indicates concentrations where such drug “liking” occurs (Fig. 1). Adapted with permission from Greenwald et al.²¹

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TABLE 1. United States Buprenorphine Regulatory Dose Limits and Guidance, and Original Research, Reviews, and Other Guidance Supporting Buprenorphine Dosing up to 32 mg/d

Year	US Agency/Entity	Agency/ Entity Max Dose	Independent Publication Type	Independent Publication Max Dose	Comments
1994			Pharmacology ²⁹	32 mg	Buprenorphine plasma concentration increased linearly with sublingual dose up to 32 mg, with a plateau in typical opioid agonist effects (positive mood, sedation, respiratory depression, and miosis) at 16 mg/d or lower.
1999			Pharmacology ³⁰	44 mg/70 kg	Doses ranging from 16 mg/70 kg to 44 mg/70 kg resulted in dose-related increase in plasma levels.
1999			Observational ³¹	32 mg/d	In this unblinded extension of a double-blind study, 80% of patients who chose to increase their dose to 32 mg/d remained at that dose (P. Bevan, R. Benckiser, written communication, August 4, 1999)
2002			Pharmacology ³²	32 mg/d	Higher doses of BUP/NX produced higher buprenorphine plasma levels and greater blockade of rewarding hydromorphone effects.
2002	FDA Package Insert (NDA-720 Approval) ³³	24 mg/d			Target dose is “a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4 mg to 24 mg per day depending on the individual.”
2003			Pharmacology ²¹	32 mg/d	Daily maintenance on 2, 16, and 32 mg/d produced prefrontal cortex MOR occupancy rates of 47%, 90%, and 96%, respectively, correlated with increased protection from withdrawal symptoms and hydromorphone reward.
2004	CSAT TIP 40 ³⁴	32 mg/d			“Continue dose increases up to a maximum of 32/8 mg per day. Nearly all patients will stabilize on daily doses of 16/4–24/6 mg; some, however, may require up to 32/8 mg daily.”
2005			Pharmacology ³⁵	32 mg/d	Buprenorphine reduces the reinforcing and subjective effects of heroin in a dose-dependent manner.
2007			UK Guidance ³⁶	32 mg/d	“In general, daily doses of between 12 and 16 mg (and up to 32 mg in some cases) would seem appropriate for long-term prescribing.”
2007			Clinical trial ¹¹	32 mg/d	Participants were allowed buprenorphine dose increases to 32 mg/d. The final mean (SD) buprenorphine dose was 29.6 (4.7) mg/d.
2008			Observational ³⁷	32 mg/d	“Higher maintenance doses of buprenorphine (12–32 mg/day) ... were associated with ... improved chance of a successful outcome.”
2009			FDA submission ³⁸	≥32 mg/d	34% of participants used at least 24 mg/d including 8% at least 32 mg/d.
2009	FDA NDA for Suboxone Film ³⁸	24 mg/d			
2010	FDA REMS ³⁹	24 mg/d			
2010	FDA Package Insert ⁴⁰	24 mg/d			Same as 2002 with added statement: “Doses higher than 24 mg/6 mg have not been demonstrated to provide any clinical advantage.”
2012			Observational ⁴¹	32 mg/d	Flexible dosing up to 32 mg/d increased treatment retention.
2014			Clinical trial ⁴²	32 mg/d	Pain scores decreased among patients transitioned from high-dose opioids to buprenorphine. Mean (SD) final dose was 28.1 (5.9) mg.
2017			UK Guidance ⁴³	32 mg/d	“Effective maintenance treatment with buprenorphine involves doses in the range of 12–16 mg for most patients dependent on heroin, with some needing up to 32 mg.”
2017	FDA Package Insert ⁴⁴	24 mg/d			Same as 2010 with added statement: “The recommended target dosage of Suboxone sublingual tablet is 16/4 mg.”
2018			Queensland Guidance ⁴⁵	32 mg/d	“Most clients require buprenorphine doses in the range 12–24 mg to achieve stabilization, although some clients require higher (e.g., up to 32 mg/day) or lower (4–8 mg/day) doses to achieve their treatment goal.”
2018	Congressional Research Service ⁴⁶				“Put simply, research implies that as the dose of buprenorphine increases, retention in treatment improves.”
2019			Observational ⁴⁷	32 mg/d	Incidence of hepatitis C infection was reduced in the higher-dose group. Cites FDA
2020	ASAM Focused Update ¹⁹	24 mg/d			
2021	VA/DoD Guideline ⁴⁸	32 mg/d			“Usual dose 12–16 mg/d (up to 32 mg/d).”
2021			Review ⁴⁹	32 mg/d	“At a time when fentanyl and high potency opioids are available, many patients may need doses of buprenorphine above 16 mg and should be offered doses up to 32 mg daily.”
2021	SAMHSA TIP 63 ³	24 mg/d			Cites FDA
2022			Observational ⁵⁰	32 mg/d	Optimal dosing strategy (minimum dose 16 mg with increases up to 32 mg/d in response to opioid use) reduced the risk of relapse by 13% for 12 wk.
2022	FDA Package Insert ⁵¹	24 mg/d			Same as 2017

at 2 and 1 ng/mL, fentanyl had an appreciable effect on decreasing ventilation. A concentration of 5 ng/mL is slightly higher than the average plasma concentration achieved with 32 mg/d of sublingual buprenorphine (Fig. 2).²¹

HISTORY OF US BUPRENORPHINE DOSE LIMITS

Buprenorphine was first synthesized in 1966, and its therapeutic potential for OUD was first described in 1978.²⁸ At the time of FDA approval in 2002, available evidence (Table 1)

demonstrated linear increases in plasma concentration up to 32 mg/d with a dose-dependent blockade of hydromorphone rewarding effects, a plateau at 16 mg/d or lower in opioid agonist effects such as positive mood and respiratory depression, and preference by some patients for 32 mg/d (Table 1). Based on that evidence, dosing up to 32 mg/d was endorsed in the Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment (CSAT) 2004 recommendations (TIP 40).³⁴

The FDA's 2002 package insert, however, stated that their dosing recommendations were based on 3 studies in which dose effectiveness was evaluated over a range from 6 to 24 mg/d. Without further explanation or comment on minimum or maximum dose, the insert stated that the daily dose was "likely to be in the range of 4 mg to 24 mg."³³ Two decades later, despite robust peer-reviewed evidence demonstrating benefit at higher doses (Table 1), the package label dose range remains unchanged.

In 2009, the new drug application (NDA) for Suboxone film referenced a study protocol (RB-US-07-001) allowing doses up to 32 mg/d or more.³⁸ In response to the FDA's questioning about the off-label dosing, Reckitt-Benckiser, the manufacturer of Suboxone, noted the "clinical reality" that dosing up to 32 mg/d was both recommended and common, despite their own efforts and the FDA package label wording.

Indeed, in the RB-US-07-001 study, 34% of participants used a maintenance dose of at least 24 mg/d, including 16% with at least 28 mg/d and 8% with at least 32 mg/d.^{38(p37)} Despite these study findings, existing SAMHSA recommendations, increasing peer-reviewed clinical evidence of protective advantages of a higher dose range (Table 1), and "clinical reality," the FDA's 2010 revised package label actually *tightened* maximum dosing guidance, stating: "Dosages higher than [24 mg/day] have not been demonstrated to provide any clinical advantage." That statement remains on the current (2022) package label.⁵¹

In 2010—just as heroin superseded prescription pain medications as the predominant cause of opioid overdose deaths—the FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) required for approval of Suboxone film stated the following:

The reported lack of significant increase in brain mu-receptor occupancy between doses of 16 mg and 32 mg would imply that there should be little difference in clinical effectiveness at doses between 16 mg and 24 mg in most patients.

*When a patient expresses a need for a higher dose, consider the possible causes (e.g., environmental stressors or psychosocial issues that increase cravings or possible drug interactions). Before increasing the patient's dose, explore other alternatives. Also consider the possibility that the patient may be exaggerating symptoms to obtain additional medication for diversion.*³⁹

Dosing recommendations for buprenorphine are therefore different from those for other FDA-regulated medications: (1) unlike other medications where dosing is determined based on clinical findings, buprenorphine's dosing is derived from the surrogate marker of MOR occupancy (and even then, at peak rather than the more clinically relevant average or minimum levels), and (2) patients' requests for higher doses are not to be taken at face value but instead are to be regarded with suspicion because, per

the REMS language, patients may exaggerate symptoms for secondary gain. Despite current widespread calls for de-stigmatizing substance use disorders and promoting patient-centered treatment—including from government agencies—stigma and judgment are firmly embedded in the FDA's dosing guideline.

DOSING EVIDENCE FROM CLINICAL RESEARCH

Clinical studies of OUD treatment generally use a combination of the following outcomes: (1) retention in care; (2) substance use measured by drug testing; and (3) OUD consequences such as overdose, drug-related medical conditions, hospitalization and emergency department use, incarceration, housing instability, or unemployment. Hereinafter are descriptions of chronologically ordered studies where doses of buprenorphine up to 32 mg/d and patient perception of dose adequacy were consequential for improved outcomes. Additional studies are listed in Table 1.

In a 2007 randomized controlled trial in outpatients, dosing was determined by patient-perceived adequacy.¹¹ A stepped-care strategy was evaluated in which initial buprenorphine/naloxone (BUP/NX) doses were increased up to a maximum of 32/8 mg/d; participants were switched to methadone if an adequate BUP/NX dose could not be achieved. Among participants who remained on BUP/NX (17 of 48 participants), the mean (SD) final dose was 29.6 (4.7) mg/d. Twenty participants switched to methadone with a mean (SD) final dose of 111.0 (11.7) mg/d, and 11 dropped out. There was no difference in retention or toxicology results between those who remained on BUP/NX and those who switched to methadone.

A 2012 meta-analysis of 21 randomized controlled trials (N = 2703) compared outcomes between higher- and lower-dose groups (16–32 vs <16 mg/d).⁴¹ The higher-dose group had better retention and fewer positive test results for opioids and cocaine.

In a 2012 observational analysis, gradual dose titration was performed up to 32 mg/d and toxicology testing was performed regularly.⁵² Initial testing more frequently showed illicit opioids in the higher-dose group (>16–32 mg/d, average of 27.5 ± 4.8 mg/d) compared with the lower-dose group (up to 16 mg/d, average of 11.5 ± 4.8 mg/d). However, frequency of illicit opioid use in the higher-dose group ultimately dropped to the level of the lower-dose group. The authors concluded that buprenorphine dosing up to 32 mg/d can work well in patients for whom a lower dose is inadequate.

In a 2014 secondary analysis of a large data set, treatment retention at 24 weeks increased linearly with buprenorphine dose, reaching 60% in the 30- to 32-mg/d dose range.⁵³ The linear relationship suggests that doses greater than 32 mg/d might further improve retention. Illicit opioid use decreased as buprenorphine dose increased.

Patients at higher buprenorphine doses had more consistent adherence to treatment in a 2020 study of prescription monitoring program data for 10,000 patients.⁵⁴ Treatment adherence, defined as >80% of the first 180 days of treatment covered by prescriptions, was 5 times more likely among those whose last dose was ≥24 mg/d relative to those at <16 mg/d.

People who inject opioids may especially benefit from higher buprenorphine doses, according to findings from a 2022 trial of monthly extended-release buprenorphine (XR-BUP) subcutaneous injections.¹⁸ Participants with a history of

injection use were more likely to remain opioid-abstinent at the higher dose (300 mg monthly for 6 months) compared with the lower dose (300 mg monthly for 2 months, then 100 mg monthly for 4 months), whereas participants with no injection history experienced abstinence at the same rate on both regimens. The higher-dose XR-BUP resulted in an average plasma concentration higher than the average achieved with sublingual buprenorphine at 32 mg/d. XR-BUP may be more convenient than multiple daily doses of sublingual buprenorphine for some patients who prefer a higher dose range, although it can be difficult to access or obtain insurance coverage.

Buprenorphine Dosing in Pregnancy

During pregnancy, multiple physiological changes affect buprenorphine plasma concentrations. By the third trimester, cardiac output and plasma volume each increase by 50%, and activity of the cytochrome P450 CYP3A4 enzyme (which metabolizes buprenorphine) increases by 38%.⁵⁵ Demonstrated pharmacokinetic changes include increased volume of distribution, increased drug clearance, and decreased time to trough concentrations.⁵⁶ As a result, buprenorphine plasma concentration is ~50% lower during late pregnancy compared with baseline.⁵⁶

A patient who is initially stable on buprenorphine may thus experience increasing withdrawal symptoms during pregnancy. Opioid withdrawal in the pregnant person, should it occur, causes a harmful catecholamine surge leading to uterine contractions and a decrease in uterine blood flow and fetal oxygen level, which in turn lead to an increased risk of miscarriage, intrauterine growth restriction, and preterm birth. Keeping the patient safely out of withdrawal during pregnancy by using higher dosing is critical for the overall well-being of the patient and expected newborn. Buprenorphine requirements in some individuals may exceed 32 mg/d.⁵⁷

Multiple studies have found a lack of relationship between the parent's buprenorphine dose and the risk of neonatal opioid withdrawal syndrome (also known as neonatal abstinence syndrome).⁵⁸ These results may reassure clinicians caring for pregnant patients with OUD that it is safe to titrate buprenorphine dose to meet the needs of the patient without increasing the risk of withdrawal symptoms in the newborn.

DIVERSION

Diversion is the unauthorized rerouting of prescription medication to someone for whom it was not intended. Clinicians cite risks of diversion and related Drug Enforcement Agency investigation as primary reasons they do not prescribe this lifesaving treatment.⁵⁹ Federal regulatory agency concern for buprenorphine diversion dates to the 1990s when the BUP/NX combined product was developed to “minimize the likelihood of diversion.”⁶⁰ More recently, the same concern for diversion drove development of XR-BUP formulations.⁶⁰

An actionable item at the 2014 Buprenorphine Summit convened by SAMHSA and the National Institutes of Health demonstrates the assumed linkage between higher doses and diversion: “Provide guidance to the field about the range of possible effective doses, and the lack of evidence for added benefit of more than 24 mg daily, to reduce habitual overprescribing that may be fueling diversion.”⁶¹ That specified dose limit references the FDA's

inaccurate claim of no clinical advantage greater than 24 mg/d. Federal leadership has predictably led to codification of inadequate dose limits in insurance coverage, which, in turn, has driven clinical practice and raised unwarranted pharmacy concerns.⁶²

Actual harms ascribed to buprenorphine diversion—overdose, injection, and/or the development of OUD—are rare in the United States. Instead, the most common use of nonprescribed buprenorphine is self-treatment of OUD when legal access is unavailable.^{63–65} Risk of overdose death is actually reduced among people who use nonprescribed buprenorphine,⁶⁶ and those who have taken nonprescribed buprenorphine are more likely to enter into formal treatment should it become available.⁶⁷

Prescribing expertise and experience influences prescriber attitudes and behavior regarding diversion. Those with greater prescribing experience are more likely to believe that treatment access barriers are the major cause of diversion.⁶⁸ Concerns about harms of diversion are strongly associated with the inaccurate belief that diversion increases accidental overdoses.⁶⁸ Prescribers from specialties with addiction treatment expertise, who are as aware of diversion risk as other prescribers, are less likely to terminate treatment for suspected diversion.⁶⁹ One interpretation of these findings is that experienced prescribers are performing a cost-benefit analysis, considering diversion as a potential cost to be weighed against known benefits—including prevention of death and harm—for the patient and community.

CONCLUSIONS

There is robust evidence that buprenorphine's dose-dependent benefits for treating OUD extend at least up to 32 mg/d. Evidence for diversion harm is minimal, yet the consequences of inadequate dosing are predictable and catastrophic. Clinicians and regulators assume that the FDA's buprenorphine package label is evidence based. Unfortunately, the current label language contradicts established evidence and is antiquated regarding harms from fentanyl. However, to avoid off-label prescribing, clinicians must adhere to the specified target dose of 16 mg/d and limit of 24 mg/d—even if that leads to violation of principles of patient-centered care and inadvertently risks their patients' lives. For patients experiencing dose inadequacy within current FDA dosing guidelines, despite effective self-administration technique, transition to methadone or XR-BUP may be an option, but significant barriers frequently impede access to both.

To correct the label language, the FDA should (1) remove mention of a target dosage, (2) return to the 2004 CSAT dosing recommendation of up to 32 mg/d, and (3) recommend that the dose be titrated with consideration of patient-perceived dose adequacy up to the maintenance level that works best for the patient's recovery, which in some cases may exceed 32 mg/d. This review does not address the optimal initial dose or titration strategy, both of which may vary widely among individuals.

The federal government recently demonstrated recognition of the urgency of improving treatment of OUD by eliminating the buprenorphine waiver and requiring addiction treatment education for all DEA-licensed prescribers. The FDA should seize this moment to update the buprenorphine label, honoring the needs of—and providing evidence-based guidance to—many new prescribers and their patients.

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