Prescribing buprenorphine: What is the role and risk of monoproduct?

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Developed with Support of the Maine Substance Use Disorder Learning Collaborative

March 2024

Key

Buprenorphine (both combo and mono) = buprenorphine

Buprenorphine monoproduct = BUP, mono

Buprenorphine/naloxone = BUP-N, combo

Background

Buprenorphine is one of the most effective medications prescribed in outpatient healthcare. It treats and reduces many of the consequences of opioid use disorder (OUD) including mortality by 50-60% (Sordo et al., 2017). Even though buprenorphine is a partial mu opioid agonist, it retains opioid activity and can still be diverted and/or used in a high-risk fashion – namely through intravenous injection (IV), but also nasal insufflation (IN). Transmucosal buprenorphine combined with naloxone (BUP-N) was developed in an effort to counter this problem. (Moratti et al., 2010; Lowfall and Walsh, 2014) Theoretically, because naloxone has low transmucosal but high IV bioavailability, naloxone would only interfere with the effect of buprenorphine when BUP-N is used IV, blocking the injected buprenorphine agonist effect and/or precipitating withdrawal in people with opioid dependence who have recently used opioids. This concept, and evidence supporting it, has influenced clinical practice, with guidelines and policies favoring prescription of the combination (BUP-N) over the monoproduct (BUP) in the United States and internationally (Lowfall and Walsh, 2014; Substance Abuse and Mental Health Services Administration (SAMHSA), 2021; American Society of Addiction Medicine (ASAM), 2021). Over time, however, it has become clear that the blunting effect of injected naloxone is only partial, and the risk of precipitated withdrawal is due to both buprenorphine (as a partial agonist which displaces a full agonist) and naloxone. Further, this risk is dependent on several factors (ie, timing, dose), and can often be avoided (Lowfall and Walsh, 2014; Blazes and Morrow, 2020). With the dissonance between theory and experience, the question of how effective naloxone is as a deterrent to misuse has been raised (Dhagudu et al., 2020, Blazes and Morrow, 2020; Grande, 2022).

In addition, transmucosal bioavailability of naloxone is typically 3-10% but can be as high as 30%, and in some individuals may produce side effects, the most common of which are headaches, nausea and diaphoresis. (Strickland and Burson, 2018) These symptoms typically resolve over time but their occurrence has led some to question the preference for BUP-N, or at least, the policy restrictions that are often placed on monotherapy. (Grande, 2022; Newcomb, 2023; Blazes and Morrow; 2022) For example, in Virginia, no more than 3% of a provider's buprenorphine prescriptions may be for take-home transmucosal BUP.[1] Figure 1 shows the state level variation in ratio of BUP-N to BUP prescribed to patients on Medicaid in 2020. Maine ranked number eight in the country for prescribing relatively more BUP-N than BUP, with about 35 BUP-N prescriptions per enrollee for every one BUP prescription. (Dana et al, 2024) In Maine there is no stated cap on prescribing however outside of pregnancy a prior authorization is required to obtain BUP for patients with Medicaid.

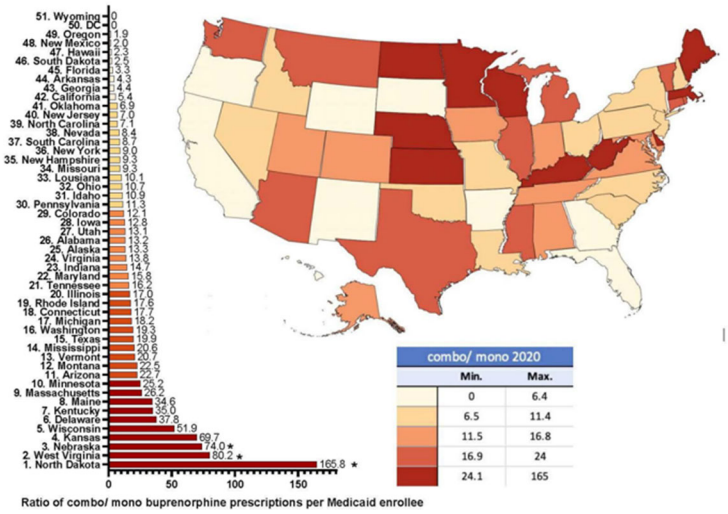
We have examined the literature and present here a short synthesis of available data with which to consider this question: **What evidence supports the preference for combination product (BUP-N) vs monotherapy (BUP)?**

Figure 1. State by State Map of Ratio of BUP-N: BUP Prescription Per Medicaid Enrollee, 2020 (Dana et al., 2024)

Impact of Naloxone Added to Buprenorphine

Multiple lines of evidence indicate that the presence of naloxone can impact the experience of people using buprenorphine through IV and IN routes.

[1] https://www.dhp.virginia.gov/medicine/do



cs/FAQPrescribingBuprenorphine.pdf

Inpatient studies *(Middleton* et al.*, 2011; Jones* et al.*, 2015 & 2017; Comer and Collins, 2002; Comer* et al.*, 2010; Dhaghadu* et al.*, 2020; all with conflicts except the latter)*

BUP-N vs BUP onset and peak effects

Inpatient studies, while mostly funded or conflicted by pharmaceutical company support, show with relative consistency that IV or IN use of both BUP and BUP-N are reinforcing but that those effects are faster in onset and occur to a greater degree (peak effect) for BUP than for BUP-N. A delay to peak effect with BUP-N compared with BUP was demonstrated both in non-opioid dependent volunteers (Middleton, 2011) as well as in studies with opioid dependent volunteers on maintenance therapy (Jones 2017- hydrocodone maintenance, Dhaghadu et al., 2020 – buprenorphine maintenance). This is consistent with the pharmacokinetics of naloxone (see Table 1) which has an earlier peak (i.e. lower Tmax), shorter half-life and shorter duration of clinical effect than IV buprenorphine (Umbricht et al., 2004, Middleton et al., 2011, Heustis et al., 2013, Jones et al., 2017). So, while not initially advertised as such, part of the impact of naloxone in BUP-N on drug likability may be through delaying and blunting the peak effect of the buprenorphine component when it is injected.

Table 1. Naloxone and Buprenorphine pharmacokinetic parameters of interest

	Half Life (hours)	Time to peak effect Tmax (min)	Peak clinical effect duration (hours)	Bioavailability (%)
Naloxone (IV)	0.5 – 1	<3	0.25	100 (IV) 24-30 (IN) 3-10 (transmucosal)
Buprenorphine (IV) doses 2mg-16mg	21 – 28	<10	0.25 – 3	100 (IV) 38-44 (IN) 35-55 (transmucosal)

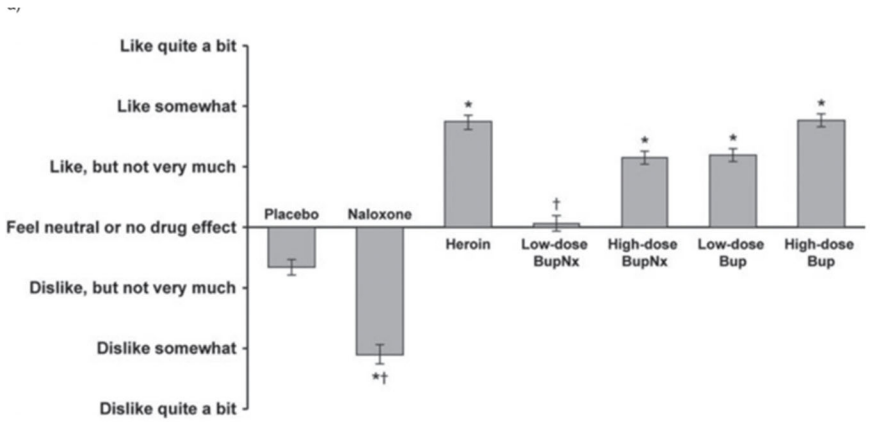
Subjective responses to IV/IN BUP and BUP-N tend to favor BUP, especially at lower maintenance doses

- As one example of differences in response to IV administration with those maintained on a full opioid agonist, Jones et al., (2017) showed similar likability

for IV heroin, BUP 6mg, and BUP 8mg, while lower doses of BUP and any dose of BUP-N were more similar to placebo.

- As an example of difference in response to IV administration <u>for those on buprenorphine maintenance,</u> Comer et al. (2010) reported upon people stabilized on varying doses of buprenorphine (2, 8 and 24mg). When challenged with IV heroin (25mg), low dose (4 or 8mg) and high dose (8 or 16mg) BUP and BUP-N, participants chose to self-administer high-dose BUP-N less than high-dose BUP ($P < 0.05$) and low-dose BUP-N less than low-dose BUP ($P = 0.0002$).
- Figure 1 shows, a subjective measure of "likability" from the same study. Using this measure, all challenge drugs were more likeable than placebo except IV low dose BUP-N.

Figure 1: Impact of IV administration of various drug challenges on "liking" in people with OUD maintained on buprenorphine, Comer et al., 2010



*P < 0.001 compared with placebo; †P < 0.005 compared with heroin

In this same study, "Willingness to take again" was greater than placebo for all IV BUP and IV BUP-N high dose while low dose BUP-N was no different than placebo. And when compared with heroin, a sort of inverse was true – where high dose BUP had similar willingness to take again as heroin, willingness was significantly lower for all BUP-N and low dose BUP. (Comer et al., 2010).

- Use of IN BUP was also shown to have greater impact on "good effects, liking, high and would pay" while effects of IN BUP-N were not different than placebo. (Jones et al., 2015)
- In general, while typical maintenance doses show small differences between effects of IV BUP and BUP-N challenges (Dhaghadu et al., 2020), differences between IN/IV BUP and BUP-N challenges are more obvious at buprenorphine maintenance doses of 2mg, than at higher maintenance

doses (Jones et al., 2015, Comer et al., 2010). 2mg maintenance does not reflect therapeutic dosing but may reflect situations where people are not consistently adherent to maintenance therapy.

Induction of Withdrawal

For those dependent on opioids, IV or IN use of BUP-N *may* induce withdrawal more readily than BUP when the mu receptors are occupied by full agonists. However, when the maintenance drug is buprenorphine, the effect of IN/IV BUP-N seems to be more variable and probably sensitive to factors like mu receptor saturation, and amount of insufflated/injected drug absorbed. The following details support this:

- IV BUP-N - but not BUP- precipitated opioid withdrawal in study volunteers receiving maintenance hydrocodone (Jones et al., 2017). This is consistent with early BUP-N trials with OUD patients on full agonists (Mendelson et al., 1997 and Jones et al., 2015 – summarizing earlier data).
- Withdrawal arising from injection of BUP-N vs BUP is less consistent when the maintenance medication is buprenorphine. In Jones et al. (2015), study volunteers on maintenance buprenorphine were challenged with 8mg doses of IN BUP-N of various ratios, (ie, typical 8/2mg, as well as lower ratios, ie, 8/8 and 8/16). “Bad” drug effect was found at all maintenance doses, for all ratios of IN BUP-N, but not for IN BUP 8mg. However, BUP 16mg IN did produce a bad effect when maintenance doses were higher (8mg, 16mg). It may be that the naloxone was responsible for the bad effect of the BUP-N at lower doses but that buprenorphine induced opioid toxicity created the “bad” effect at higher total buprenorphine doses. Withdrawal symptoms were not seen in two other studies with volunteers maintained on buprenorphine (Comer et al., 2010, Dhaghadu et al., 2020). This variability may be due to differences in opioid receptor saturation states (ie adequacy of maintenance doses, the dose of the challenge- low in Dhaghadu et al., 2020), or route of administration (ie IN vs IV)).
- In Dhaghadu et al., 2020, volunteers were maintained on an average 15mg buprenorphine, and challenged with injection of 2mg BUP-N with greater relative amounts of naloxone than the typical 4:1 (ie, BUP-N 2/0.5mg, 2/1mg, 2/2mg). More naloxone was associated with less drug liking and sedation but no withdrawal. The lack of withdrawal observed in this experiment may be due to the relatively high maintenance dose combined with the relatively low dose of the IV challenge and suggests that the naloxone in combination products will not precipitate withdrawal in those on a therapeutic maintenance dose of buprenorphine.

Self-report Studies

- Self-report data collected in large surveys from Australia soon after the introduction of combination product showed that people injected BUP-N less than BUP or methadone, and also had less removal of supervised doses (supervised administration being standard of care in Australia at the time). (Larance et al., 2011, Larance et al., 2014, Larance et al., 2016)
    - When adjusting for total doses dispensed, more BUP than BUP-N was injected, removed, or diverted (10% vs 5, 12% vs 9, and 5 vs <1% respectively). (Larance et al., 2011).
    - Two years after release of BUP-N film, a survey conducted with n=444 people who inject drugs (PWID) not on MOUD and n=492 people on MOUD. (Larance et al., 2016)
        - Among PWID, injection was higher for BUP than BUP-N, but there was no difference in street price.
        - Among patients on MOUD, BUP was more likely removed (31% BUP, 15% BUP-N film, 11% BUP-N tab) and more likely injected (28% BUP vs 7-10% BUP-N).
        - Adjusted for markers of severity, OR for injection of BUP was 9x that of BUP-N.
    - Important: These studies were undertaken during a period where BUP-N was new and common messaging about potential to induce withdrawal may have affected use behaviors.
- Data reported from surveillance systems in the US, with ties to pharmaceutical funding of the film product, suggested that *among people entering treatment for MOUD*, 30-day past month use of BUP "to get high" was 6.5x that of BUP-N films and 2.2x compared with BUP-N tablets. Injection of BUP was 20x that of BUP-N films and 2.5x that of BUP-N tabs. (Lavonas et al., 2014).
- In Finland, in the late 90s when treatment was limited, and supply of heroin from Afghanistan was lost, buprenorphine became the main opioid of illicit use. In this context, 80% of survey respondents among people attending a needle exchange program cited IV BUP-N as "bad", vs 20% who said it was similar to IV BUP. Additionally, BUP-N had a lower street value (12 euros for 8mg BUP-N vs 28 euros for 8mg BUP vs 80-120 euros for a daily dose of heroin). (Lowfall and Walsh, 2014, Alho et al., 2007).
- In Malaysia, where BUP was replaced by BUP-N due to widespread injection use, a survey of people who inject buprenorphine (PWIB) reported that higher doses of IV BUP-N were required than doses of IV BUP (2.5mg vs 1.9mg). (Bruce et al., 2009) In focus groups, PWIB usually tried BUP-N, reported not liking it, and cited using it only for purposes of withdrawal treatment as it produced less euphoria than BUP. (Vicknassingham et al., 2010).

Summarizing and Adding Context

In addition to the pharmacology and pharmacokinetics of various buprenorphine formulations, the circumstances in which injection or insufflation of buprenorphine occurs determines naloxone's impact as a deterrent to misuse. As such, the degree of risk with prescribing BUP vs BUP-N will vary by individual and over time. Below is an attempt to summarize the information gleaned from studies and put it into context for clinical application.

Individual Context

- *Dose of misused buprenorphine:* Higher doses of IN/IV buprenorphine would generally be more reinforcing. However, there is probably a ceiling to this effect (Jones et al., 2017). And, in the presence of high maintenance doses, higher IV BUP doses can be aversive due to opioid toxicity.
- *Presence of naloxone* seems to reduce some of buprenorphine's reinforcing effect, blunting the immediacy and height of a peak clinical opioid effect.
- *Mu receptor status – low occupancy:* People in opioid withdrawal, with low mu opioid receptor occupancy may experience resolution of withdrawal or even euphoria from buprenorphine injection. The experience would depend on the degree of withdrawal, the dose of injected buprenorphine and the presence of naloxone
- *Mu receptor status- high occupancy:* For those on relatively high buprenorphine maintenance doses, the difference between IN/IV BUP and BUP-N is probably low. For those recently using full opioid agonists, IV use carries the possibility of inducing withdrawal. This seems to be due to the injected buprenorphine as well as naloxone. The risk is greater with higher IN/IV doses, something that may be avoided or minimized with serial IN/IV use of lower doses. (Yokell et al., 2011).

  Not described in the literature is what difference there is between IV BUP vs BUP-N after recent use of long acting fentanyls (either long acting analogues or with accumulation in adipose with repeat dosing). Experience with methadone suggests that the risk of precipitated withdrawal will be higher with IV BUP-N than IV BUP. (Mendelson et al., 1997). It is also unclear how xylazine injection, often cut into fentanyl, will impact potential for precipitated withdrawal after IV use of BUP or BUP-N.

Policy and treatment context: In general, when access to treatment for OUD is limited, diversion and misuse of buprenorphine of any form is increased. Other factors contribute, including what opioids are available in the illicit drug market and at what cost. For example, in situations where the only available opioid for non-

medical use was buprenorphine (ie, Finland in early 2000s), IV or IN use was high whether as BUP-N or BUP. The impact of treatment structure became evident in Malaysia, where indiscriminate buprenorphine prescribing to those at high risk for IV use was incentivized among providers without training or treatment guidelines, and was associated with significant amounts of IV use. And in situations where treatment is available but doses are inadequate, IN or IV routes of use may be used as a way to increase absorbed dose. These circumstances may preferentially increase the illicit value of monoproduct given its pharmacology and pharmacokinetics. (Lowfall and Walsh, 2014; Yokell et al., 2011)

While a full discussion about the reasons for, and risk of, buprenorphine diversion and misuse is beyond the scope of this document, it is worth acknowledging that the risks vary depending on the activity. One of the most commonly cited reasons for misuse are when people who cannot or do not wish to access medical treatment use it to treat withdrawal symptoms. This reduces their risk of overdose from full agonists, and positive experiences with the medication can lead to eventual treatment seeking. When used sublingually, this is lower risk than when using by the IV or IN route, something more likely when people are not trying to 'stretch' the effect of the compound (Lowfall and Walsh, 2014; Bozinoff et al., 2022), and possibly with less reinforcing versions of buprenorphine (ie, combination product).

Allergy

Though infrequent, (SAMHSA, 2021) most agree that naloxone allergy is an indication to prescribe BUP, but the lengths to which a patient is asked to verify that history varies (e.g., previous records, allergy testing, on site administration). Clinical experience suggests that pursuing documentation can be time consuming and often unrevealing. Testing and on-site administration carry the risk of severe allergic reactions, and there is a lack of guidance for approaching this evaluation (SAMHSA, 2021; ASAM, 2020). Some providers requiring greater verification with patients who have inconsistent histories or more unstable presentations, or offer the option of long acting injectable monotherapy. Other providers are concerned that by requesting this additional information they are impacting rapport and stigmatizing the patient and so prescribe BUP based solely upon the patient's history. Some practice with the mindset that even if they are prescribing a medication that is misused, it is safer to prescribe a partial agonist than take any risk of the patient not engaging in care.

Adverse effects data

Adverse effects of small amounts of naloxone are cited primarily as headache and nausea but others have been reported. (Gregg et al., 2023, Grande, 2022). Prevalence for this is unclear as provider selection may play a role, and because symptoms abate over time. In one study on forced transitioning of patients in Finland, 50% initially reported adverse effects and 25% at 4 months. (Simojoki et al., 2008) In a US based study, 4% of patients at a low threshold clinic were transitioned to BUP within the first 16 months because of adverse effects. In this study, BUP was readily available and prescribing culture appeared more flexible than average given willingness to consider atypical symptoms as a reason to transition to BUP. (Grande, 2022)

There is burden associated with restricting BUP (Newcomb, 2023) but the long-term impact of readily making medication changes for these common complaints (headache, nausea) is not known. There is the potential to increase visit demand to evaluate potential side effects, and for increased prescribing of BUP more generally due to impact on prescribing culture/norms.

No quality evidence for a mortality benefit of monoproduct

One observational study linking treatment data to mortality records showed higher mortality after treatment cessation of BUP-N than after cessation of BUP, however, this effect missed statistical significance when adjusted for gender and prior hospitalizations (HR 1.6, p=0.055) (Kelty et al., 2018). The finding was theorized as possibly due to naloxone induced opioid receptor upregulation (Blazes and Morrow, 2020). This upregulation concept has been important for long term safety concerns related to medications including long acting beta agonists (e.g., salmeterol and increased asthma exacerbation death) and dopamine antagonists (e.g., haloperidol and tardive dyskinesia). However, here, confounding is likely, where BUP was perhaps prescribed to lower risk individuals, a factor not sufficiently corrected for in the analysis (factors adjusted for were gender and pretreatment hospitalization). In this same study there was a higher risk of hospitalizations for skin and soft tissue infection in the BUP-N group, again suggesting that the BUP group was indeed lower risk. Thus, while a signal to monitor, better evidence is needed to embrace receptor upregulation as a reason for practice change.

Considerations if monoproduct prescribing were to become more widespread

Child poisonings

While relatively uncommon, 85% of childhood poisonings with buprenorphine were in children under six (Post et al., 2018). Approximately half of poisonings require hospitalization and there were 68 deaths between 2000-2015. Unit dose packaging has been shown helpful in reducing inadvertent exposure in children, ie for iron. Films have been associated with the lowest rates of poisonings, perhaps because of the nature of their packaging. Poisoning rates were 2.5 poisonings /100k prescriptions for BUP-N films single dose packaging, 23/100k for BUP-N tabs multi-dose packaging, 6/100k for BUP-N tabs single dose packaging (comprising 38% of BUP-N), and 8/100k for BUP multi-dose packaging. It is curious that fatality rates were lower with BUP despite multidose packaging compared with BUP-N multidose packaging. This could be due to confounding, ie patients who are perceived more reliable may be more likely to be prescribed BUP vs BUP-N and more likely to store medication away from children. Overall, the film packaging may be protective, something available only for combination product at this time. (Wang, et al 2010; Hampp et al., 2020)

Provider patient relationship and treatment impact

Some providers aim to be more open to prescribing BUP to patients who request it because they believe it will impact care engagement. While the question has not been prospectively evaluated, there is no evidence that substantial numbers of people are not engaging in or are dropping out of treatment because they have adverse effects to naloxone that are not evaluated. Indeed, the impact may be more subtle, perhaps an interaction about the restriction makes a patient feel stigmatized – a factor that can deter treatment engagement (Falgas-Bague et al, 2023). Care with these conversations is warranted, and discussed further below.

If monoproduct prescribing were to increase in popularity, it has the potential to enhance nocebo effects among those prescribed combination product. The evaluation of these side effects may increase visits, and shift their focus from safety and recovery to low yield evaluations of medication intolerance. And, because of clinical uncertainty, will lead to some people being prescribed a higher risk medication that they don't need. Further, this raises a question of equity, as nocebo effects tend to be disproportionately borne by more stigmatized populations (Yetman et al., 2021).

Conclusion and recommendations

Overall, multiple lines of evidence, including experimental and survey data from people who use drugs, support that injection and insufflation are more likely with BUP (monotherapy) vs BUP-N. The higher risk of BUP vs BUP-N is further supported by knowledge of the neurobiology of addiction where faster onset and greater peak effect, as occurs when BUP is unmitigated by naloxone, confers higher potential for nonmedical use and addiction. The impact of this increased risk varies by circumstance. In particular, in areas where treatment access is limited, there will be more un- and under-treated people with OUD, driving non-medical use including use through the IV or IN route**. Access to MOUD for those who need it is therefore one of the best ways to limit non-medical use and diversion of any form of buprenorphine**. And though of lesser impact, preference for BUP-N vs BUP in most patients is another. This said, the minor amounts of naloxone absorbed sublingually cause side effects in some patients. Blanket prohibition of monoproduct can have unintended harmful consequences in those cases.

What follows are recommendations to providers based upon the writers' clinical experience and interpretation of the evidence discussed above. This includes ideas developed during the Maine Medical Center Addiction Medicine Whirlwind Journal Club session on 1/19/2024 in which the majority of the core references cited here were reviewed.

1. Generally, prescribe combination product (BUP-N) given the increased risk for nonmedical use of monoproduct (BUP).
2. Naloxone allergy is a clear reason to use BUP in lieu of BUP-N. Less clear is knowing whether a true allergy is present. Described above are a variety of approaches used in clinical practice to address the question of allergy. It would be unusual to have more than a small percentage of patients with naloxone allergy in a given geographic area.
3. Adverse effects to naloxone often dissipate over weeks to months. A trial of monoproduct should be considered if a) the onset of suspected AEs is linked to the start of combination product or significant dose increase b) other common causes for the AE have been considered and c) if not severe, the AE persists over 1-2 months of consistent dosing. Close follow up to determine the effect of a switch to monoproduct should be conducted, and effect documented clearly to justify continued therapy with this formulation and to provide informative history in the case of care transition. If initial symptoms resume while on monoproduct, patients should be switched back to combination therapy. As with allergy, monoproduct for AEs would not be expected to comprise a substantial portion of a provider's practice. Recall that one low barrier program with ready availability of BUP cited a rate of 4% for those ultimately requiring monoproduct for AEs including allergy (Grande 2022) and that 25% of people reported AEs after forced BUP to BUP-N transition (Simojoki, 2008).

4. Monoproduct may be considered in stable people planning pregnancy, however combination therapy is preferred due to logistical concerns with switching formulations, pressure from others to divert monoproduct, and increased risk if there is IV use during pregnancy. See the on this subject for more comprehensive information and recommendations.
5. Do not prescribe monoproduct with the aim of better controlling cravings or reducing use, as evidence does not support impact on treatment efficacy.
6. While it is beyond the scope of this review to clearly define the benefits and risks of monoproduct in buprenorphine initiation/withdrawal management, temporary use of monoproduct for induction may be warranted while inducing from methadone, and potentially with long acting fentanyls.
7. For those individuals who request monoproduct but who are high risk for IV/IN use consider prescribing injectable long acting buprenorphine.
8. Risk mitigation for patients who are newly prescribed monoproduct or who are not stable (ie, continued use of substances that impairs function, unstable employment, missed visits, chaotic relationships, or decrease in usual level of function) should including consistent monitoring with urine drug tests, examination for signs of injection, and medication counts. Given that naloxone is absorbed and present in most urine specimens, one consideration is to conduct urinary naloxone testing when there is concern for diversion or misuse. Transition to long acting injectable buprenorphine is warranted in unstable patients requiring long term monoproduct.
9. It is important that providers devote attention to communication so as to avoid making patients feel dismissed and stigmatized. Focus on this is especially needed in more challenging conversations such as with monoproduct prescribing. In addition to ensuring acknowledgement (ie, with active listening and appropriate evaluation), one can convey concern and respect while communicating a decision to not prescribe monoproduct. Helpful talking points may include
    a. Monoproduct is a medication that has a higher risk for injection than combination. I want to provide you with effective medication that is also the safest possible.
    b. I want to do my part to keep higher risk medications from 'catching on', as the more a higher risk medication is prescribed, the more it becomes a norm, increasing the amount circulating in the community.
    c. In pregnancy: Patients have reported that they have felt pressured to share their BUP and/or people have taken it without their consent because of the higher risk potential. I do not want to inadvertently put you in a difficult position, and want you to have access to the medication that you need for a safe and healthy pregnancy.

To further consider the concern about stigma, it may be helpful to think about this as parallel to antibiotic stewardship. Just as providers are sometimes in the uncomfortable position of not giving antibiotics that a patient feels are warranted, so we are in the position of considering the likelihood that naloxone is the cause of a

given complaint and effectively communicating a plan that may be counter to the patient's expectation. Sometimes that complaint is a true side effect, sometimes it is intent to obtain medication for nonmedical use, and sometimes it is a nocebo effect. In those situations we are thinking about the patient in front of us as well as the community adds complexity to the encounter. In any of these cases, except for life threatening allergy, time can be a useful tool, as it allows observation and information gathering. This is admittedly challenging, with the customer service pressures that abound in healthcare.

Finally, guidelines and policies can be restricting, but they can also be helpful. If they are clear in their rationale but provide some flexibility to veer from standard, they support providers in striking a balance between unnecessarily prescribing higher risk medication and being able to provide the best fit medication for an individual patient.

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