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Buprenorphine Prescribing Flexibility: Buprenorphine Monoproduct for Adverse Effects from Buprenorphine/Naloxone

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Buprenorphine Prescribing Flexibility: Buprenorphine Monoproduct for Adverse Effects from Buprenorphine/Naloxone

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Clinical Question:

Is it appropriate to prescribe buprenorphine monoproduct on a case-by-case basis for the treatment of Opioid Use Disorder for management of patients who experience adverse effects from buprenorphine/naloxone (bup/nx; Suboxone, Zubsolv)?

Background

Opioid agonist treatment like buprenorphine is lifesaving[1] for patients suffering from Opioid Use Disorder (OUD) and is considered a gold-standard treatment. Although buprenorphine is available in multiple formulations, the conventional approach for sublingual treatment has been to prioritize the use of the combination product buprenorphine/naloxone (BNX) for maintenance therapy as it is the first-line recommendation in the absence of a clinical exception.[2,3] This longstanding recommendation is based on the inclusion of naloxone in the dual product, which is intended to deter misuse of buprenorphine by injection or insufflation given the rapid bioavailability of the antagonist, naloxone, with these routes of administration. However, some patients experience adverse effects (AE) from the dual product, which may be alleviated with the use of buprenorphine monoproduct (BUP) as an alternative. In this scenario, clinical discretion is required for decision-making since the topic is not addressed directly in national guidelines and publications.

Characterization of sublingual naloxone absorption as negligible based on the pharmacokinetic properties of sublingual buprenorphine and naloxone is a widely accepted viewpoint.[4] Yet clinically relevant levels of sublingual naloxone absorption have been demonstrated[5], contradicting this assumption. There is limited clinical research on AE from the absorption of sublingual naloxone to guide clinical decision-making. However, frequently reported side effects from the combination product include nausea and headaches.[5,6,7] Other reported side effects[6] include diaphoresis and dysphoria as well as idiopathic reactions like bilateral flank pain[8]. A retrospective study of patients forced to transfer from BUP to BNX identified adverse events of 50% at four weeks and 26.6% at four months, including nausea, gastrointestinal pain, fatigue, headache, hyperhidrosis, vomiting, and dyspepsia, which led some to drop out of treatment.[9]

Until recently, the problem of AE, presumably from the absorption of sublingual naloxone, has been overlooked almost entirely in academic literature and by professional societies. This lack of acknowledgment of AE coupled with a rigid understanding of the dual product as an adequate safeguard against misuse can lead to an insistence on BNX for sublingual treatment as the perceived standard of care. Implementing this line of reasoning into clinical practice, however, is incongruent with a patient-centered approach and risks compromising the ethical principle of beneficence when AE leads to undue hardships or treatment dropout. Published commentary[6] illustrates the potential harms of disregarding AE from BNX.

Acknowledging AE from BNX as authentic rather than presupposing a motive of misuse or diversion runs counter to intervention stigma, a factor that negatively impacts opioid agonist treatment.[10] Such acknowledgment, particularly for marginalized patients, can help build trust in the provider-patient relationship and unequivocally prioritizes patient welfare as paramount.

BUP, like BNX, is an FDA-approved and evidence-based treatment for OUD. [11] Based on the inclusion of naloxone, BNX is widely depicted as an effective abuse-deterrent formulation and recommended as first- line in most circumstances instead of BUP.[2,3] Indeed, there are studies[12,13] that suggest a reduced rate of buprenorphine misuse for BNX; however, recent studies[14,15] challenge the assumption that BUP is unambiguously less safe than BNX. In fact, BNX, like BUP, is subject to misuse[13,15] and diversion[16,17].

Despite these risks, evidence suggests that diverted buprenorphine products are primarily used for self- treatment and rarely as a drug of choice.[16,18]

Given the complex nature of buprenorphine misuse and diversion, it would be erroneous to conclude that misuse or diversion can be reliably prevented by prescribing BNX instead of BUP. Longitudinal clinical assessment, including measures like accessing prescription drug monitoring program (PDMP) data, toxicology testing, and/or recall visits for pill counts, along with dynamic adjustment of the treatment plan, is a recommended strategy to address risks of misuse and diversion[19], which can be accomplished while prescribing BNX or BUP.

Prescribing BUP as Second-Line Sublingual

Patients with AE from BNX typically report one or more symptoms consistent with adrenergic excess like those reported in the literature: nausea, vomiting, gastrointestinal pain, dyspepsia, headaches, diaphoresis, fatigue, and dysphoria. A patient with prior AE from BNX may have firsthand experience tolerating BUP without any side effects and a reluctance for treatment with BNX. Such patients would be good candidates for consideration of treatment with BUP. Similarly, BUP could also be considered for patients taking BNX who report one or more persistent symptoms consistent with adrenergic excess beyond the initiation phase (1-2 weeks) and who have limited or no prior experience with BUP.
A recent commentary describes the practical clinical strategy of prescribing a trial of BUP when AE of BNX jeopardize the management of OUD.[8] As suggested in this publication, a risk-benefit analysis on a case-by-case basis should be implemented when prescribing BUP instead of BNX, given the first-line recommendation for BNX. In many cases, the benefits of maintaining treatment engagement by eliminating AE from BNX with BUP, an alternative lifesaving, evidence-based treatment, outweigh the risks of using a second-line formulation. Monitoring strategies for treatment with BUP should be commensurate with the risks presented by a given case, and documentation of the decision-making process should be reflected in the medical record.

Low Risk:
In the case of a stable patient who properly secures and does not misuse their medication, there is not a compelling clinical reason for BNX instead of BUP. Although a level of uncertainty may exist regarding a given patient's stability, a lack of prior injection use or buprenorphine misuse, expected toxicology results demonstrating medication adherence, relative abstinence from drug use, and clinically stable follow-up are consistent with a relatively low risk for prescribing BUP instead of BNX. Management in this scenario would be relatively identical to prescribing BNX.

Risks Present:
Factors presenting elevated risks, like housing insecurity for diversion, ongoing substance use, or a recent history of injection drug use, require a careful ongoing risk-benefit assessment if prescribing BUP instead of BNX for AE. Alternative treatment options such as long-acting injectable buprenorphine or the structure of an Opioid Treatment Program may be more appropriate than BUP (or BNX) in some cases, however; the practicality of implementing such measures must be weighed against the potential for patient disengagement and treatment dropout given the markedly increased mortality risk immediately after discontinuation of buprenorphine treatment[20]. If a patient is benefiting from BUP instead of BNX without apparent problematic misuse of the medication, and adherence can be demonstrated with toxicology testing and/or medication callbacks, then appropriate treatment is validated despite the presence of risks. Closer monitoring (e.g. weekly or every other week encounters) is consistent with best practice for patients with treatment instability or ongoing risk factors when prescribing BUP (or BNX).

Unacceptably High Risk:
Repeatedly negative unexplained buprenorphine or buprenorphine metabolite toxicology tests, as well as recurring

lost, stolen, or shared medication supplies, necessitate a reassessment of the appropriateness of prescribing BUP. If feasible, implementing daily or thrice weekly pharmacy pick-up and observed dosing of BUP is a possible management strategy for unacceptably high-risk situations. However, unacceptably high diversion risks or medication nonadherence unresponsive to mitigation strategies are indications to discontinue take-home BUP (or BNX) and refer to a higher level of care to best meet patient needs. Long-acting injectable buprenorphine or the structure of an OTP are more appropriate treatment strategies than take-home BUP when unacceptably high diversion risks persist, or there is an inability to confirm medication adherence.

Regardless of the level of risk, it should be clear to the provider and anyone reviewing the medical record that ongoing treatment with BUP instead of BNX unequivocally benefits the patient and outweighs the risks presented by each case. Otherwise, BNX should be prescribed for sublingual treatment instead of BUP. Clear documentation of the benefits of BUP instead of BNX can help reduce potential misinterpretations by outside entities during chart reviews, such as a quality-of-care regulatory audit.

Prescribing BUP, on a case-by-case basis, for AE from BNX expands treatment flexibility within the framework of evidence-based medicine. It promotes shared decision-making, an underutilized provision in Substance Use Disorder care.[21] This type of strategy is emblematic of patient-centered care. Promoting engagement with flexibility in the selection of evidence-based medications is congruent with efforts to expand buprenorphine treatment access to help fulfill the needs of patients suffering from OUD, which is an important consideration given the ongoing[22] public health emergency.

General Principles:

1) Patient-centered care and treatment matching are fundamental aspects of Addiction Medicine.
2) Medications for Opioid Use Disorder (MOUD), such as the various formulations of buprenorphine, are evidence-based and highly effective, with clear benefits for reduced morbidity and mortality.
3) MOUD retention is crucial given the known risks, like overdose death, after treatment dropout.
4) BNX is considered the first-line sublingual formulation for treating OUD in the absence of a clinical exception like pregnancy or drug allergy. AE would be consistent with a clinical reason for an alternative MOUD option when adversely affecting care.
5) AE from sublingual naloxone is an under-appreciated patient experience. Acknowledging side effects from medications, like AE from BNX, is essential to a provider's ethical responsibility to the patient.
6) Alternative opioid agonist treatments for BNX include methadone as well as implantable and long-acting injectable buprenorphine; these options may be limited by the observed daily dosing requirement and potential out-of-pocket expenses of an Opioid Treatment Program (OTP) as well as the lofty cost of implantable and long-acting injectable formulations on the healthcare system and, in the case of a lack of healthcare coverage, for the patient.
7) BUP is an evidence-based and FDA-approved alternative to BNX for treating OUD.
8) A prescriber must balance risks and benefits in all aspects of healthcare delivery.
9) Treatment of OUD with opioid agonist treatment carries an inherent risk of harm to population health when diverted medication is misused. Maintaining the structural integrity of an office-based treatment program for buprenorphine prescribing with diversion mitigation strategies is recommended to reduce risks.

Recommendations:

Low – High: expert opinion/clinical experience, observational studies, and randomized controlled trials

1. Buprenorphine is a well-established, evidence-based treatment that should be offered to all patients with OUD.
2. Prioritize the use of a buprenorphine/naloxone formulation for sublingual medication treatment, given its first-line recommendations in guidelines and publications.
3. Acknowledge patient experiences such as AE from BNX to promote trust in the provider-patient relationship and provide ethical care.
4. If there are clinical reasons to avoid BNX, including AE, alternatives like methadone, long-acting buprenorphine injectables, or BUP should be considered and offered in an appropriate manner to help maintain a patient in treatment with MOUD.
5. A prescriber may consider and prescribe BUP on a case-by-case basis as a second-line treatment option when AE from BNX jeopardizes a patient's engagement in MOUD treatment.
6. The medical record should document the clinical reasons for using BUP instead of BNX to demonstrate the decision-making process.
7. BUP may be restricted in some states. Ensure the prescribing of BUP does not conflict with state regulations or laws before providing this MOUD treatment.
8. All take-home buprenorphine medications should be appropriately monitored clinically and managed with a diversion mitigation plan to help minimize risks.
9. More studies examining the AE of sublingual naloxone absorption would help in the clinical decision-making process of selecting the optimal buprenorphine formulation for patients.

PCSS-MOUD's Guidance's use the following levels of evidence*:

High = Further research is very unlikely to change our confidence in the estimate of effect
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low = Any estimate of effect is very uncertain.

Type of evidence:
Randomized trial = high
Observational study = **low**
Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations
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