

## Buprenorphine with, or without, Naloxone for Pregnant Women? – Review of Current Evidence and Practice in Massachusetts

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### Abstract

Opioid use disorder has reached the level of an epidemic. Potential complications of unsafe injections, lifestyle, overdose and withdrawal are particularly concerning in pregnant women as the risk therein extends also to the foetus. The main medications in treatment of opioid use disorder are methadone, naltrexone and buprenorphine products. Naloxone (pregnancy class: B) was carefully selected to be a part of Suboxone<sup>®</sup> in 4:1 ratio to buprenorphine (pregnancy class: C) as a deterrent for intravenous use. Naloxone's bioavailability, delivered sublingually, is minimal (<10%) yet there is a theoretical concern that a potential precipitated withdrawal could incite premature labor and fetal demise. For this reason, it is recommended that buprenorphine be used alone in this setting. However, a limited amount of data exists, showing relative safety of this combination in pregnant women when compared to other alternatives. Furthermore, current evidence in non-pregnant individuals shows that the risk of withdrawal due to naloxone is in most instances insignificant. The merit of adding naloxone as a disincentive for injecting opioids has been debated, yet the significance of preventing maternal and fetal exposures to the risk of blood stream infections, sepsis, blood-borne pathogens, bleeding and other complications is clear and warrants focused consideration. In Massachusetts, the state health insurer requires prior authorization for all forms of buprenorphine other than buprenorphine/naloxone combination films, which further complicates access to care specifically in pregnancy. Waiting periods and treatment interruptions rather than naloxone are thus much more likely to cause adverse outcomes in this population.

**Keywords:** Pregnancy; Opioid use disorder; Substance use disorder; Drug abuse; Buprenorphine; Naloxone

### Introduction

Opioid use disorder, especially via intravenous administration, has reached the level of an epidemic [1,2]. The overuse of opioids, with the potential for both, overdose and withdrawal, as well as the potential complications of intravenous administration, is of particular concern and nuanced by unique challenges in the pregnant population [3]. Among the many known adverse complications of opioid use in pregnancy, including impeded fetal growth, withdrawal poses an additional unique risk as it may cause uterine contractions resulting in miscarriage or premature birth. Because of these potential adverse events, current consensus states that, beyond trying to reduce the harm caused by unsafe injection practices and the potential for overdose, abrupt opioid withdrawal should also be avoided in pregnant women [4-6]. Methadone (pregnancy category: C) has been the standard of care for the maintenance of opioid use disorder in pregnancy. Recently, buprenorphine has started to attract more attention for this indication due to its favorable pharmacological profile and relative ease of access [6,7].

Buprenorphine was first synthesized in the 1960's, and the early studies regarding its use in the 1970 are reported mostly on its analgesic properties. Due to its favorable pharmacokinetic and pharmacodynamics profile, in the 1990's buprenorphine was

considered for the treatment of severe opioid use disorder. Buprenorphine is a partial opiate  $\mu$ -receptor agonist and  $\kappa$ -receptor antagonist. The partial agonist activity creates a "ceiling effect", where administration of more buprenorphine, past a certain dose, does not produce more effect, which limits its acute toxicity and overdose potential [8]. In addition to having a ceiling on its own effects, buprenorphine also has a relatively high affinity for the  $\mu$ -opioid receptor compared to most opioids, making it capable of blocking the euphoric and potential overdosing effects of other opioids if co-administered [9,10]. Buprenorphine has an exceptionally long half-life (estimates range from 3-44 h for buprenorphine and up to 176 h for nor-buprenorphine, its main active metabolite), and clinical case reports describing difficulty overcoming buprenorphine's effects to achieve adequate analgesia confirm that the effect of buprenorphine and its metabolites can remain clinically significant for up to 72 h [9]. Other unique properties of buprenorphine include that it may produce milder withdrawal symptoms than full agonists if abruptly discontinued [11]. Buprenorphine does not require adjustment for renal impairment. Patients with advanced liver disease may have impaired metabolism of buprenorphine due to lower activity of Cytochrome P450 3A4 (CYP3A4) activity.

Overdose with buprenorphine has been reported, but has been largely limited to young children [12] and those injecting buprenorphine while concurrently using other central nervous system depressants [13,14]. Notably, buprenorphine is most often co-formulated with naloxone specifically to avoid intravenous abuse [15].

This deterrence has been demonstrated in the users of full opioid agonists, and is due to the early reversal of full opioid agonists by naloxone. However, naloxone's effect is relatively short lived (approximately 20-90 min) [16,17].

Buprenorphine/naloxone combinations are currently not recommended in pregnancy, yet such prohibition may not be justified by currently available evidence. We reviewed the evidence regarding the choice between methadone and buprenorphine-based products, and the safety, risks and benefits of using buprenorphine with naloxone in pregnancy. The effectiveness of buprenorphine with naloxone as a deterrent of intravenous use and diversion is reviewed as well.

### **Buprenorphine versus Methadone (And Naltrexone) in Pregnancy**

Opioid agonist therapies are the standard of care for pregnant patients with an opioid use disorder. Methadone has, historically, been the preferred agent. This preference largely stems from longer experience with this medication. Several studies have shown improved retention in care with methadone compared to buprenorphine, both in the general population (though this effect may not be seen with fixed high doses of buprenorphine) [18] and specifically within the pregnant population [19]. Despite these distinctions, buprenorphine offers several advantages over methadone, which can be broadly categorized into those based on the medication's intrinsic properties and those based on its delivery system.

Importantly, buprenorphine's ceiling effect decreases the risk of overdose [8,12,13]. Buprenorphine has been associated with improved outcomes in fetal growth, while causing less neonatal abstinence syndrome when compared to methadone [20-23]. In 2012, a randomized clinical trial, observed better surrogate measures of fetal well-being via non-stress test and biophysical profile post-dosing of buprenorphine versus methadone [24]. Although, buprenorphine still undergoes metabolism by the CYP450 system in the liver, fewer specific enzymatic systems are involved in its metabolism as compared to methadone, offering the advantage of fewer potential drug-drug interactions than methadone [25]. Additionally, there are fewer reports of cardiac toxicity and QT interval prolongation with buprenorphine as compared to methadone [26].

Perhaps more importantly, buprenorphine is more readily available as a treatment option for many people. Under current federal regulations, the complex restrictions on participation in specialized methadone maintenance programs and the limited distribution of these programs compared to buprenorphine providers within the country disrupts the ease of access to care. Though historically opioid use disorder has been thought of as an urban problem, recent epidemiological shift shows opioid misuse increasing in the suburban and rural communities, where treatment with methadone is often not readily available [27]. Most individuals are particularly vulnerable to relapse during the detoxification and early phase of recovery, and a delay in linkage to care could lead to relapse and related health complications. The risk of early relapse is particularly evident among pregnant women where an additional concern includes risk to the foetus. Additionally, proper and close monitoring by knowledgeable staff is key to positive outcomes [28]. The frequency of follow up as well as the dosing changes and recommended participation in supportive therapy can be appropriately titrated in outpatient-based buprenorphine maintenance programs with more individualized approach than in specialized, heavily regulated methadone

maintenance programs. Buprenorphine's relative safety is the main reason for less stringent prescribing regulations, making it more accessible as a treatment option for many people.

Buprenorphine does have some unique challenges associated with its use. Buprenorphine's high affinity for opioid receptors can present a challenge in certain unique circumstances demanding urgent or emergent analgesia and anaesthesia [9,10,12]. a property which methadone, with its weaker receptor binding, does not share. At much higher doses, full opioid agonists with a higher receptor affinity such as fentanyl [29], may be able to displace buprenorphine from the mu-receptor [14]. It is important to note, however, that an older study showed the receptor-affinity of buprenorphine to be approximately 1.7-times more powerful than fentanyl [30]. The use of potent opioids at high doses consequently comes with its own inherent risks and adjuvant non-opioid analgesia is generally also required, typically making the perioperative care more complex.

In comparison to other easily accessible options such as naltrexone [31] (pregnancy category: C), agonist therapy is generally considered preferable to pure antagonist therapy [18]. Agonist therapy retains patients better in care than antagonist therapy, and the risk of relapse and overdose is significantly less [28,32]. Additionally, agonist therapy does not require a prolonged period of abstinence in order to initiate, which antagonist therapy does. This initial abstinence period makes antagonist therapy difficult to initiate for many people, and can potentially lead to withdrawal, which is generally best avoided in pregnancy [5,18,28]. Moreover, long-acting naltrexone injections present similar problems with adequate emergent analgesia and anaesthesia as buprenorphine. Notwithstanding the detoxification and withdrawal, the pure opiate antagonist naltrexone otherwise appears to be reasonably safe for foetal development [33].

### **Why not Buprenorphine with Naloxone in Pregnancy?**

As previously mentioned, most buprenorphine available in the United States is available as a co-formulation of buprenorphine (pregnancy category: C) and naloxone (pregnancy category: B). Naloxone was carefully selected to be a part of this combination in a 4:1 ratio to buprenorphine as a deterrent for intravenous use [16]. Naloxone's bioavailability, delivered sublingually in this form, is minimal (<10%) yet some are concerned that if it is used in pregnancy, the fetus may be exposed to the risk of opiate withdrawal and the effects of maternal withdrawal on the pregnant uterus. Specifically for this reason, the current recommendation is that buprenorphine alone be used in this setting [5,7]. Naloxone's potential for teratogenicity has also been questioned but to our knowledge, never corroborated by evidence [34]. The exact physiologic effects of various opioid receptor agonists and antagonists, especially in long-term use have not been fully elucidated either in pregnancy or in addiction treatment in general [33,35].

### **Can Buprenorphine with Naloxone be Actually Safer than Buprenorphine alone in Pregnancy?**

#### **Pharmacological reasoning**

Naloxone is a pregnancy class B drug. No studies to date have, to our knowledge, reported naloxone's potential for teratogenicity in animals or humans. A 2003 literature review of antidote use in pregnant women found no data linking naloxone to fetal harm [36]. A 1985 study in mice reported that naloxone prevented malformations

caused by opiate agonists [37]. Limited but growing amounts of data show relative safety of this combination directly in pregnant women [22,23]. Pharmacokinetic studies reporting on absorption of sublingual naloxone from the co-formulated products demonstrate that at commonly prescribed doses, the levels of naloxone remain insignificant [38]. A study looking at the levels of naloxone in the newborns of mothers receiving buprenorphine with naloxone during pregnancy showed undetectable levels in nearly half of the infants, as well as the mothers, and minimal concentrations in the remainder [39]. While some data showed that parenterally administered combination of naloxone with buprenorphine only partially attenuates the effects of buprenorphine in opiate agonist-dependent subjects, this effect was not significant in non-dependent individuals [16]. With respect to naloxone's potential for inducing a severe withdrawal when the co-formulation is injected, there are reports indicating that, in individuals whose symptoms are stable on buprenorphine maintenance, the injected combination including naloxone seems to lack the capacity to significantly displace buprenorphine from well saturated receptors [16,40].

### Pharmaco-economical reasoning

The scientific community continues to be engaged in a valid discussion regarding the effectiveness of adding naloxone to the co-formulation as a deterrent of intravenous use and, by extension, also of diversion [11,40,41]. However, the risks of intravenous drug use cannot be underestimated, especially in pregnancy (discussed further in this article). From the financial perspective, the use of simpler, less costly products is frequently more cost-effective, particularly when the evidence justifying the alternatives does not clearly overcome scientific equipoise [41]. Massachusetts Department of Health and Human Services, however, put out a statement requiring prior authorization for any buprenorphine products other than buprenorphine/naloxone co-formulated films [42]. All pregnant female customers of the state run health insurer, Mass Health, who are the primary buprenorphine mono-product using subgroup of patients with opioid use disorder, thus face additional obstacles, waiting periods and/or disruption in treatment risking withdrawal which, as previously stated, should be avoided in pregnancy.

### Associated health and socio-economic risks

The known risks of naloxone in pregnancy are, in fact, few and they appear to lack clinical significance. Our understanding of current evidence leads us to believe that naloxone does not play an important role, particularly when administered concurrently with buprenorphine in patients on long-term buprenorphine maintenance [16,40]. The aversive effect with parenteral, but much less so with sublingual buprenorphine/naloxone combination for individuals dependent on full opiate receptor agonists, has been reported to decrease the desirability of the combination for parenteral use but the extent of the deterrent effect in practice remains controversial [11,41,43]. On the other hand, the significance of unsafe intravenous substance use is overwhelming, both from the perspective of the pregnant woman and her unborn foetus. The risks include: blood stream infections, sepsis, skin and soft tissue infections at injection sites, deep seated infections by haematogenous spread - most commonly infective endocarditis, internal abscesses and osteomyelitis; transmission of blood-borne pathogens (i.e., HIV, HCV, HBV/HDV); thrombophlebitis due to toxic additives; frequently severe systemic auto-immune reactions caused by hyper-sensitivity to various components of the injected substances;

higher likelihood of overdose due to direct intravenous delivery [44]. The potential for diversion of easily injectable substances itself poses a risk for erratic dosing in the individuals with legitimate prescriptions paradoxically creating room for withdrawal and subsequent self-medication with more dangerous substances if too much of the supply gets diverted for financial gain. Participation in illegal activity and black-market networks amplifies the potential for further exposure to unsafe and harmful behaviour frequently leading to physical and emotional trauma, spread of sexually transmitted diseases, polysubstance use as well as stress related to the disruption of social support networks and problems with the legal system (i.e., criminal charges; Department of Children and Families) [14,28,45]. Seemingly, one of the benefits of the buprenorphine mono-product would be easier access for patients in need, which is typically due to prohibitive cost of the more complex and/or newer patented medications. Paradoxically, Massachusetts currently provides unrestricted access only to the buprenorphine/naloxone co-formulated films for Mass Health beneficiaries [42]. Available reviews show the challenges the anaesthesiologists face to achieve appropriate anaesthesia/analgesia in buprenorphine treated individuals [9,10]. Naloxone, with its short-half-life, however, plays no role in this aspect.

### Conclusion

A significant gap certainly remains and more investigation is needed to optimize the way we treat opiate use disorders in general and particularly in pregnant women. We find current evidence supportive of buprenorphine with naloxone as a safe alternative to both methadone and buprenorphine alone. Pregnancy makes women a particularly captive audience when it comes to treatment of their opioid use disorder. In this respect, the foetal outcome advantage seems particularly attractive, and likely outweighs the possible disadvantage in treatment retention, particularly because pregnant women are frequently encouraged to seek care because of pregnancy itself, and often have six or fewer months to delivery after their pregnancy is confirmed.

- In general, just like buprenorphine alone, buprenorphine/naloxone offers certain advantages over methadone, particularly pertinent to overall safety and to intrauterine foetal growth and neonatal abstinence syndrome.
- The linkage to care under current federal regulations is much less complicated with buprenorphine products, which also have lower potential to cause drug-drug interactions and overdose.
- The potential for deterrence of intravenous use and diversion is greater for the combined buprenorphine/naloxone products in comparison to buprenorphine alone. The combination product should thus be preferred over the monoproduct even in pregnancy as the real risk of significant adverse outcomes outweighs the theoretical risk of withdrawal. The evidence of withdrawal precipitation in subjects stable on buprenorphine maintenance seems to be lacking even when the combination product is injected.
- Informed policy support - if compelling data is found to support the continued use of buprenorphine rather than the combination with naloxone, then the buprenorphine mono-products should be exempt from formulary restrictions so that pregnant women are not exposed to withdrawal symptoms due to frequently days' long waiting for approvals rather than due to the effects of naloxone.

## Declaration of Interest

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## Co-author Contributions

All co-authors, Martin Krsak, Paul Trowbridge, Nancy Regan and Ken Freedman, declare that they do not have any potential conflicts of interest.

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