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**Low and High Dose Initiation of Buprenorphine for the Treatment of Opioid Use Disorder:
A Review of the Evidence from the New York State Office of Addiction Services and Supports (OASAS)
Medical Advisory Panel**

According to provisional data published by the Centers for Disease Control (CDC), an estimated 107,622 people died of a drug overdose in the United States during the 12-month period ending in December 2021.¹ Opioids, including illicitly manufactured fentanyl (IMF) and its analogues (which shall be termed “fentanyl” for the purposes of this document), are the most common cause of overdose deaths, making the treatment of opioid use disorder (OUD) a critical aspect of combating the overdose epidemic. Two approved medications for opioid use disorder (MOUD), buprenorphine and methadone, have been shown to reduce the risk of overdose death by 66-80% while patients receive treatment² but the rates of initiation of these medications and retention of patients in treatment have been low.³

Buprenorphine is a particularly appealing treatment option for OUD because it is not subject to the same federal and state regulations as methadone. A qualified practitioner who has a waiver from the Drug Enforcement Agency (DEA) can prescribe buprenorphine in an office setting and patients can fill prescriptions for buprenorphine in community-based pharmacies. The pharmacologic advantages of buprenorphine are its opioid receptor partial agonist activity, high affinity for mu-opioid receptors, and long duration of action that effectively suppresses opioid withdrawal symptoms and opioid cravings while preventing overdose by blocking opioid full agonists from binding to the receptors.⁴ These same pharmacologic properties, however, are associated with precipitated opioid withdrawal when buprenorphine is started by an individual who has been taking an opioid full agonists regularly. Preventing precipitated opioid withdrawal is important not only for the patient’s physical and psychological comfort but also for long term treatment outcomes. Indeed, Whitley and colleagues found that individuals who had a complicated buprenorphine induction where they experienced precipitated or protracted opioid withdrawal had lower 30-day treatment retention rates than those with uncomplicated inductions.⁵

To minimize the risk of precipitated opioid withdrawal, it is recommended that buprenorphine is initiated only when an individual taking opioids regularly is in mild-to-moderate opioid withdrawal, which, for short-acting opioids, corresponds to 12 to 24 hours after the last dose,⁶ (although mild-to-moderate opioid withdrawal may occur as soon as 6 to 8 hours after the last dose of some short acting opioids such as heroin) and/or a Clinical Opiate Withdrawal Scale (COWS) score of at least 8.⁷ Yet these recommendations present challenges for individuals who want to transition from methadone to buprenorphine because clinical guidelines recommend that methadone is tapered to 20-30mg each day for at least one week or until the individual is comfortable on the lower dose of methadone before initiating buprenorphine 36 hours or longer after the last methadone dose.⁸ The time needed to taper methadone to a daily dose of 20-30mg coupled with the long wait to start buprenorphine after the last methadone dose may increase the risk of a return to opioid use and overdose during the transition period.⁹ It should be noted that NYS OASAS and the OASAS Medical Advisory Panel (MAP) recommend both methadone and buprenorphine for the treatment of OUD and do not recommend that individuals who are stable on methadone be transitioned routinely to buprenorphine.

Another challenge with buprenorphine induction occurs when individuals use fentanyl alone or fentanyl mixed with other opioids. Fentanyl has a relatively short duration of action, but it remains in the body for extended periods of time because it is highly lipophilic and sequestered rapidly in adipose tissue.¹⁰ As a result, fentanyl is cleared from the body more slowly than other opioids that also have a short duration of action. This was

demonstrated in a recent study of twelve treatment-seeking individuals with OUD where the time since their last opioid use and the average median time between the last positive and first negative fentanyl urine toxicology screen was 7.3 days.¹¹ This prolonged presence of fentanyl in the body likely contributes to the delayed appearance of opioid withdrawal symptoms after cessation of use and an increased risk of precipitated opioid withdrawal.^{11,12} In a published study of qualitative interviews with individuals using illicit opioids, two subjects reported experiencing precipitated opioid withdrawal after taking buprenorphine/naloxone 72 and 80 hours after last fentanyl use, respectively.¹³

Although conventional buprenorphine induction strategies typically are successful for most individuals, treatment providers increasingly are discovering that alternative induction approaches may be necessary for those needing or choosing to transition from methadone to buprenorphine, and for those knowingly or unknowingly using fentanyl regularly. In these situations, precipitated opioid withdrawal may be avoided and opioid withdrawal symptoms minimized by introducing buprenorphine at a nonstandard low dose and gradually increasing the dose over several days while continuing an opioid full agonist.¹⁴ The opioid full agonist is tapered or stopped only after a therapeutic dose of buprenorphine has been reached. Increasingly, protocols for initiating low dose buprenorphine, also referred to as buprenorphine “micro-dosing” or the Bernese method,¹⁵ are being adopted in inpatient and outpatient settings to facilitate a transfer from methadone, fentanyl (both prescribed and IMF), and other short- and long-acting opioids to buprenorphine without precipitating opioid withdrawal.¹⁶

Lastly, high dose rapid buprenorphine induction with extended-release buprenorphine, a monthly injectable depot formulation of buprenorphine, during a single day in the outpatient setting was the focus of a recently published research study.¹⁷ In this model, treatment with standard doses of SL buprenorphine, which is required prior to administering extended-release buprenorphine to ensure an individual has an adequate opioid tolerance to tolerate the extended-release formulation, occurred when individuals using heroin and fentanyl experienced mild-to-moderate opioid withdrawal. If the individual tolerated SL buprenorphine, an injection of extended-release buprenorphine was administered. According to the study authors, the rationales for using injectable extended-release buprenorphine were improved treatment adherence since daily dosing of SL buprenorphine would no longer be necessary and the rapid achievement of a consistent therapeutic blood level of buprenorphine.¹⁷

The New York State Office of Addiction Services and Supports (OASAS) Medical Advisory Panel (MAP) convened a meeting on January 19, 2022, to discuss strategies for low and high dose initiation of buprenorphine and offers the following evidence review to clinical providers and local public health and mental hygiene authorities in New York. It should be noted that there are no randomized controlled trials or standardized protocols for low or high dose buprenorphine induction. The evidence is based on case reports, case series, and clinical experiences. Because of this, caution must be exercised when considering low or high dose buprenorphine inductions. Nothing in this document should be interpreted as an official endorsement on the part of NYS OASAS or the OASAS Medical Advisory Panel of any protocols for low dose or high dose buprenorphine induction.

Of note, most publications used the term “sublingual (SL) buprenorphine” when describing the inpatient or outpatient induction protocols and usually did not specify if SL mono formulation buprenorphine or SL dual formulation buprenorphine/naloxone was used. The terms “mono formulation buprenorphine” and “dual formulation buprenorphine/naloxone” will be used in this review when the formulation used was specified in the published protocols.

Inpatient Low Dose Buprenorphine Induction Protocols

- The four published case reports and series¹⁸⁻²¹ from the United States (US) describing inpatient low dose buprenorphine induction protocols presented at the MAP meeting utilized sublingual (SL),¹⁸ intravenous (IV),¹⁹ buccal,²⁰ and transdermal (TD)²¹ formulations of buprenorphine.

- Low dose SL, IV, buccal, and TD formulations were used to bridge the patients from a full opioid agonist to standard doses of SL buprenorphine.
- IV, buccal, and TD buprenorphine are FDA-approved only for the treatment of pain at this time.
- The number of inpatients initiated on low dose buprenorphine in each case report or series was low, ranging from one to fifteen.¹⁸⁻²¹
 - The total number of patients in the case reports and series was twenty-one.
- Four inpatients were taking methadone for OUD prior to low dose buprenorphine induction,^{18,19} two were receiving high doses of opioids parenterally for pain management,^{19,20} and fifteen were taking various named (i.e., “heroin”) and unnamed (i.e., “opioids”) opioids.²¹
- SL buprenorphine was the only formulation used in the case series of three subjects who were transitioned from methadone to buprenorphine.¹⁸
 - 0.5mg SL buprenorphine was administered on the first day and the dose was titrated to 12-16mg SL per day over the next 8 days.
- IV and buccal buprenorphine were used to transition one inpatient from methadone to SL buprenorphine,¹⁹ and one inpatient from high dose parenteral morphine to SL dual formulation buprenorphine/naloxone,²⁰ respectively, because the hospital pharmacies did not have nonstandard low doses of other buprenorphine formulations and did not allow for standard doses to be modified.
- The fifteen individuals who were treated with low dose TD buprenorphine as a bridge from a full opioid agonist to SL buprenorphine had pain syndromes.²¹
- Initial low doses of IV 0.15mg¹⁹, buccal 225µg²⁰, and TD 20µg per hour/480µg per day²¹ buprenorphine were used as an approximately equivalent dose of 0.5mg SL buprenorphine.
- During low dose buprenorphine inductions, opioid full agonists were either continued at their full dose and then discontinued after an adequate dose of SL buprenorphine had been achieved^{19,21} or tapered during the induction and discontinued after the induction was completed.^{18,20}
- The inpatients in all the case reports and series had minimal opioid withdrawal symptoms during the low dose induction and no patients experienced precipitated opioid withdrawal.¹⁸⁻²¹

Table 1 provides a summary of the case reports and series describing inpatient protocols for low dose buprenorphine induction.¹⁸⁻²¹

Outpatient Low Dose Buprenorphine Induction Protocols

- Five published case reports and series²²⁻²⁶ from the US presented at the MAP meeting described low dose buprenorphine induction protocols in outpatient settings that utilized low dose SL dual formulation buprenorphine/naloxone^{22,23} and TD²⁴⁻²⁶ formulations.
- Similar to the inpatient case reports and series from the US, the number of outpatients initiated on low dose buprenorphine in each published study was low, ranging from one to eight.²²⁻²⁶
 - The total number of outpatients in these case reports and series was twenty-three.
- Five outpatients were taking methadone (two for the treatment of OUD, three for pain management) prior to low dose buprenorphine induction,²²⁻²⁶ and seventeen were taking prescribed short- and/or long-acting opioids,^{22-24,26} including TD fentanyl,²⁶ for pain management. One outpatient was taking an opioid that is available by prescription for pain management but was purchasing the medication from an Internet supplier.²⁶
- SL dual formulation buprenorphine/naloxone was the only formulation used in low dose induction protocols for fourteen outpatients^{22,23} while the other nine received TD buprenorphine as a bridge medication from an opioid full agonist to standard doses of buprenorphine.²⁴⁻²⁶
- The outpatient low dose SL dual formulation buprenorphine/naloxone induction protocols utilized 0.5mg as the initial dose with dose titration to 12mg/day over five²² or six days.²³ Both protocols allowed for further adjustments in the daily SL dual formulation buprenorphine/naloxone dose after the induction phase in response to the patient’s symptoms.

- The patients cut SL dual formulation buprenorphine/naloxone 2mg tablets or films to obtain the 0.5mg and 1mg doses needed for the induction protocols.^{22,23}
- TD buprenorphine was used for eleven outpatients as a bridge medication from an opioid full agonist to standard doses of SL buprenorphine²⁴ or SL dual formulation buprenorphine/naloxone^{25,26}
 - In two of the three case reports or series, TD buprenorphine initial doses were 20µg per hour/480mg per day^{24,26}, while one case report used a lower TD buprenorphine dose of 5µg per hour/120 µg per day.²⁵
 - The reason for using a lower bridging dose of 5µg per hour/120 µg per day for the one outpatient who was transitioned from methadone to SL dual buprenorphine/naloxone was not provided.²⁵
- Opioid full agonists were continued at their full dose during the induction and then discontinued after an adequate dose of SL dual buprenorphine/naloxone had been achieved^{22,23,25,26} or tapered from the full dose during the SL buprenorphine induction and discontinued when the induction was completed.²⁴
- Some outpatients in the case reports or series who were induced with only low dose SL dual formulation buprenorphine/naloxone,^{22,23} TD buprenorphine followed by SL buprenorphine²⁴ or SL dual formulation buprenorphine/naloxone,²⁵ and the one outpatient who was induced with the lower TD buprenorphine dose of 5µg per hour/120µg per day²⁶ experienced mild opioid withdrawal symptoms.
 - No outpatients experienced precipitated opioid withdrawal.²²⁻²⁶
- Although not discussed at the MAP meeting, a recently published cases series from San Francisco described a rapid low dose SL buprenorphine induction protocol for seven outpatients diagnosed with OUD who were using fentanyl and heroin.³³
 - Similar to other outpatient case reports and series, the patients continued to use opioid full agonists during the induction period.
 - 0.5mg SL mono formulation buprenorphine was the starting dose but instead of a slower increase in the daily SL dose over six to seven days, the protocol used more frequent administration of low doses of SL mono formulation buprenorphine (such as every three to six hours), to reach a SL mono formulation buprenorphine dose of 8mg by the end of day three with a switch to SL dual formulation buprenorphine/naloxone 12mg in a single dose on day four.
 - SL mono formulation buprenorphine was used in the initial days of the protocol because the authors found that mono formulation buprenorphine was easier to divide than the dual formulation buprenorphine/naloxone.
 - No patients experienced precipitated opioid withdrawal and only one patient experienced mild opioid withdrawal in the first twenty-four hours of the protocol.

Outpatient High Dose Buprenorphine Induction

- The final presentation at the MAP meeting was an open-label twelve-week trial of a single-day induction onto extended-release buprenorphine in the outpatient setting.¹⁷
 - On Day 1, five patients with OUD who used heroin and fentanyl were initiated on SL buprenorphine 2mg when their COWS score was greater than six.
 - Additional doses of SL buprenorphine were administered in divided doses until they had received a total of 24mg.
 - One hour after the last SL dose, patients received an injection of extended-release buprenorphine 300mg and were released from the research clinic one hour after the injection.
 - Four participants had COWS scores between four and eleven (mild range) at the end of the induction and one had a score of fifteen (moderate range).
 - COWS scores for all five participants were lower (range 0 to 7) during the follow-up visits on Days 2-4.
 - The five patients received all three, monthly injections of extended-release buprenorphine (300mg, 300mg and 100mg) and completed the twelve-week trial.

Table 2 provides a summary of case reports and series describing outpatient protocols for low and high dose buprenorphine induction^{17,23,24,27}

Key Take-Home Points

- Conventional buprenorphine induction protocols that are successful for most individuals with opioid use disorder may not be the best approach for individuals taking methadone or using fentanyl.
- Low dose buprenorphine inductions may circumvent the need for prolonged methadone tapers and reduce the risk of precipitated opioid withdrawal for individuals using fentanyl.
- Inpatient and outpatient case series and reports from the United States described low dose buprenorphine induction protocols that were used to transition a small number of patients from methadone, prescribed short- and long-acting opioids, or heroin to SL buprenorphine.
 - Protocols using IV or buccal buprenorphine as a bridge medication to SL buprenorphine only took place in inpatient settings.
 - Protocols using TD buprenorphine as a bridge medication and using only SL buprenorphine took place in inpatient and outpatient settings.
- Opioid full agonists were taken at a full dose or tapered during the induction period with discontinuation after an effective dose of SL buprenorphine had been achieved.
- One of the challenges with implementing low dose buprenorphine inductions is the lack of availability of SL buprenorphine in doses lower than 2mg.
 - Most inpatient protocols used doses of IV, buccal, and TD buprenorphine that were equivalent to 0.5mg SL and available on hospital formulary.
 - Outpatient protocols using only SL buprenorphine required individuals to cut 2mg SL buprenorphine films or tablets to obtain lower doses.
 - TD buprenorphine doses used in outpatient low dose buprenorphine protocols were the same as those used in inpatient protocols.
- Most individuals reported no or mild opioid withdrawal symptoms during low dose inductions and there were no reports of precipitated opioid withdrawal.
- Based on the finding of one small, open-label trial, a single-day induction onto extended-release buprenorphine in an outpatient setting may transition individuals more rapidly to a consistent buprenorphine blood level without causing precipitated opioid withdrawal. More research is needed on this novel approach.
- While low dose buprenorphine inductions appear to be a promising treatment approach for individuals with OUD, only case reports and case series with low numbers of participants are available to guide protocol development. More rigorous research is needed to examine efficacy, risk and benefits, and best practices of low and high dose buprenorphine induction approaches, in inpatient and outpatient settings.

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Table 1: Summary of Inpatient Protocols for Low Dose Buprenorphine Induction*

Full Opioid Agonist	N	Route of buprenorphine administration	Buprenorphine Dosing Schedule	Full opioid agonist taper schedule	Adverse Events During Induction	Comments
Methadone for OUD ¹⁸	3	Sublingual (SL)	Day 1, only: 0.5mg SL daily Increase to 12mg-16mg SL/day over a total of 8 days	7 days at full dose then discontinued on Day 8.	<i>Patient 1:</i> None <i>Patient 2:</i> Leg restlessness overnight on Day 1 <i>Patient 3:</i> Anxiety on Day 1	One patient received prn doses of oral oxycodone and IV hydromorphone, and one received oral oxycodone during the transition because they had been taking these opioids for pain management.
Methadone for OUD and opioid analgesics for pain ¹⁹	2	Intravenous (IV) then SL	<i>Patients 1 and 2:</i> Days 1-3: 0.15mg-0.6mg IV q6hr prn Day 4: 4-8mg SL q4hr prn Day 5: 12mg (<i>Patient 1</i>) or 16mg SL (<i>Patient 2</i>) twice a day	<i>Patient 1:</i> Methadone 65mg/day decreased to 20mg/day by Day 3, then discontinued on Day 4. <i>Patient 2:</i> Tapered over 28 days.	None reported	0.15mg IV buprenorphine was used as an approximate equivalent of 0.5mg SL buprenorphine.
High dose parenteral morphine via patient-controlled analgesia ²⁰	1	Buccal then SL	Day 1: 225µg buccal/day Day 2: 225µg buccal/twice daily Day 3: 450µg buccal/twice daily Days 4 to 7: 2mg SL/twice daily titrated to 12-16mg SL/daily in divided doses.	Full dose on Days 1-6 then discontinued on Day 7.	No opioid withdrawal symptoms reported by the patient during the transition and highest COWS score during transition was 3.	225µg buccal buprenorphine was used as an approximate equivalent to 0.5mg of SL buprenorphine.
Heroin and prescribed short- and long-acting opioid analgesics ²¹	15	Transdermal (TD) then SL	Day 1 and Day 2: 20µg TD/hour Day 2: 2mg SL buprenorphine, increase by 2-4mg q2-4hr as needed up to a total dose of 8mg/day. Day 3: Administer previous days total SL buprenorphine dose and increase by 2-4mg q2-4hrs as needed up to a total dose of 16mg/day. Day 4+: adjust dose to symptoms	Tapered slowly as tolerated with goal of discontinuing after induction completed.	Maximum COWS score for any patient during induction was 8. Average COWS score for all patients was 3.93.	20µg TD/hour (480µg TD/day) was used as an approximate equivalent of 0.5mg buprenorphine SL/day. 10µgTD/hour (240µg TD/day) was used for one patient who was receiving low doses of an opioid analgesic.

*Only one case series²⁰ specified that SL dual formulation buprenorphine/naloxone was used in the induction protocol. All others^{18,19,21} used the term “SL buprenorphine” and did not specify if SL mono formulation buprenorphine or SL dual formulation buprenorphine/naloxone was used.

Table 2: Summary of Outpatient Protocols for Low and High Dose Buprenorphine Induction**

Full Opioid Agonist	N	Route of buprenorphine administration	Buprenorphine Dosing Schedule	Full opioid agonist taper schedule	Adverse Events During Induction	Comments
Prescribed short- and long-acting opioid analgesics including fentanyl patch and methadone ²³	8	SL (standard low dose overlap initiation protocol)	Day 1: 0.5mg SL once a day Day 2: 0.5mg SL twice a day Day 3: 1mg SL twice a day Day 4: 2mg SL twice a day Day 5: 2mg SL three times a day Day 6: 4mg SL three times a day Day 7+: adjust dose to symptoms	No change in opioid full agonist dose from Days 1 through 6, then a taper by 25% weekly.	None reported	Two patients were unable to continue buprenorphine after induction due to oversedation that did not respond to dose reductions, and nausea, respectively.
Fentanyl and heroin ²⁷	7	SL (rapid overlap initiation protocol)	Day 1: 0.5mg SL q6hr (total dose 2mg) Day 2: 1mg SL q6hr (total dose 4mg) Day 3: 2mg SL q6hr (total dose 8mg) Day 4: 12mg SL daily and follow-up with provider.	All patients continued to use opioid full agonists during the induction.	Mild opioid withdrawal symptoms reported by one patient in the first 24 hours.	Two patients discontinued buprenorphine after the induction period and returned to opioid use. Three of the remaining five switched to extended-release injectable buprenorphine.
Heroin and fentanyl ¹⁷	5	SL then extended-release injectable buprenorphine	Day 1: 2mg SL when COWS > 6, and administered in divided doses to a total 24mg SL. Extended-release buprenorphine 300mg injection given one hour after last SL dose.	Patients were instructed to abstain from opioid use at least 16hr.	Four patients experienced mild opioid withdrawal and one experienced moderate opioid withdrawal as measured by the COWS at the end of the induction.	COWS scores for all participants were low (range 0-7) during the follow-up visits on Days 2-4. All five participants received the three, monthly injections of extended-release buprenorphine during the 12-week trial.

<p>Prescribed short and long-acting opioid analgesics, including fentanyl patch and methadone²⁴</p>	<p>3</p>	<p>Transdermal (TD) then SL</p>	<p>Day 1 only: 20µg TD/hour Day 2: <i>Patient 1:</i> 2mg SL q6hr <i>Patient 2:</i> 0.125 or 0.25mg q2-4 hr <i>Patient 3:</i> 2mg SL q4hr Day 3+: <i>Patient 1:</i> Increased to 32mg SL daily over undefined period <i>Patient 2:</i> Stabilized at 0.75mg SL by day 5 <i>Patient 3:</i> Increased to 32mg SL daily over undefined period</p>	<p>Patients 1 and 3: Hydromorphone was substituted for their usual opioid analgesic regimens and tapered during the induction period. Patient 2: Took previously prescribed hydrocodone on Day 1, only.</p>	<p>Patient 1: No opioid withdrawal. Patient 2: No opioid withdrawal but had increased pain and discomfort on Days 1 and 2. Patient 3: No opioid withdrawal</p>	<p>SL doses of 0.125mg and 0.25mg were obtained by dividing gelatin tronches of buprenorphine made by a compounding pharmacist.</p>
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**One case series²³ specified that SL dual formulation buprenorphine/naloxone was used in the protocol, while another²⁷ specified that SL mono formulation buprenorphine was used initially before switching to SL dual formulation buprenorphine/naloxone. The others^{17,24} used the term “SL buprenorphine” and did not specify if SL mono formulation buprenorphine mono-product or SL dual formulation buprenorphine/naloxone was used.