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A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist Opioids To Buprenorphine/Naloxone Sublingual In Both Community and Acute Care Settings

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ABSTRACT

Background: Converting methadone to buprenorphine/naloxone sublingual (SL) is desirable for reasons including ease of prescribing, carries to improving function, decreased drug interactions, and decreased overdose risk. The process of conversion can be difficult given methadone's long half-life and concerns regarding the need for withdrawal before initiation.

Purpose: We aim to present several unique methods of converting individuals from methadone and other full opioid agonists (prescribed and illicit) to buprenorphine/naloxone SL as well as describe novel buprenorphine induction protocols to use in community and acute care settings.

Methods: A review was conducted using key search databases. Review of publications in peer reviewed journals as well as expert opinions and protocols were used to synthesize this article.

Discussion: A description of various protocols, their pros and cons, best setting of use, ease of use, and costs are detailed in the document.

Conclusion: Several methods of conversion will provide clinicians with more tools to support transitioning people from methadone and other full agonist opioids to buprenorphine/naloxone SL, as well as reduce withdrawal concerns for buprenorphine induction.

Keywords: Methadone, Buprenorphine, withdrawal avoidance, transitions

Contexte: La conversion de la méthadone en buprénorphine / naloxone sublinguale (SL) est souhaitable pour des raisons telles que la facilité de prescription, entraîne une amélioration du fonctionnement; diminution des interactions médicamenteuses et diminution du risque de surdosage. Le processus de conversion peut être difficile compte tenu de la longévité des effets de la méthadone et des craintes reliées à la nécessité de s'extraire avant l'initiation.

Objectif: Nous visons à présenter plusieurs méthodes uniques d'aider des individus à se convertir face à l'utilisation de la méthadone et d'autres agonistes opioïdes complets (prescrits et illicites) en buprénorphine / naloxone SL, et décrivons de nouveaux protocoles d'induction de la buprénorphine à utiliser en milieu communautaire et en milieu de soins de courte durée.

Méthodes: Un examen a été effectué à l'aide de recherche clés sur des bases de données. L'examen des publications dans des revues évaluées par des pairs, ainsi que des opinions et protocoles d'experts, ont été utilisés pour synthétiser cet article.

Discussion: Le document décrit en détail les divers protocoles, leurs avantages et inconvénients, les meilleurs paramètres d'utilisation, la facilité d'utilisation et les coÛts.

Conclusion: Plusieurs méthodes de conversion fourniront aux cliniciens davantage d'outils pour aider les personnes en transition de la méthadone et d'autres opioïdes agonistes complets à la buprénorphine / naloxone SL, ainsi que pour réduire les problèmes de sevrage liés à l'induction de la buprénorphine.

Mots clés: Méthadone, buprénorphine, évitement du sevrage, transitions

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INTRODUCTION

Best practice guidelines suggest the most effective means of treating opioid use disorder (OUD), is with opioid replacement therapy (ORT).[1] Types of ORT include full agonist treatments like methadone and slow release oral morphine (SROM), partial agonist treatment like buprenorphine, and antagonist treatment with naltrexone. Each therapy has unique advantages, disadvantages, and safety profiles. Consensus suggests that due to the ceiling effect of buprenorphine, and thus limited risk of overdose, buprenorphine should be the first line treatment for OUD. Buprenorphine is almost 6 times safer than methadone for risk for accidental overdose with other opioids.[2] Other full agonist opioids, including SROM, are thought to have comparable increases in overdose risk.[3] Individuals continue to take illicit substances even while on ORT, making the protective factor provided by buprenorphine appealing. Indeed, methadone is related to 1/3 of all deaths related to opioids in the United States,[4] and 25% of all opioid-related deaths in British Columbia.[5]

Many methadone patients who request buprenorphine/naloxone sublingual (SL) remain on methadone due to difficulties in transitioning to buprenorphine given methadone's extended half-life of and high potency, as well as the withdrawal requirement for buprenorphine initiation. Several organizations have published guidelines for methadone to buprenorphine transfers however, there is little consensus between protocols.[6–12] While techniques to transfer patients on low doses of methadone (<50 mg) and other full agonists are routine and clear-cut, those for moderate dosing (between 50 and 100 mg methadone), and high dosing (>100 mg methadone) are more complex and challenging. Of note, 70% of individuals on methadone treatment are on doses within the moderate to high dosing level.[13]

This article reviews novel methods for the transition of individuals from full agonists, including methadone, to buprenorphine from all levels of dosing. This can be applied to opioids for pain and illicit opioids. This article examined various published found through MEDLINE/OVID, and unpublished protocols shared and obtained from colleagues. As a cautionary note, these methods are considered off label and do not have ample evidence validating them. In addition, caution should be exercised in youth, the elderly or in debilitated patients. The authors of this paper strongly suggest that these methods are utilized in conjunction with a high level of clinical acumen, judicious knowledge of opiate pharmacology, and sound experience of ORT.

BACKGROUND

Reasons for transitioning from methadone to buprenorphine

Several pharmacological features of buprenorphine make superior for treatment of both OUD and, off label, chronic pain. The respiratory suppression ceiling effect is particularly highlighted.[14] These variables are important in deciding which drug to use for initiation, and also deciding why to switch an individual from one opioid to another. Reasons for switching can be due to medical reasons such as drug to drug interactions and organizational reasons such as ease of access to carries especially in circumstances such as residential treatment facilities, rural communities, and work camps.

A study examining reasons for patients switching from methadone to buprenorphine found the ease of access to carries of buprenorphine, ease of coming off of buprenorphine, side effects of methadone, and a suggestion by a prescriber to be key.[15] When given the opportunity, 10% to 20% of individuals would choose to convert from methadone to buprenorphine,[16] although many experts suggest this is even higher.

Key principals and a brief review of pharmacology

Buprenorphine's partial agonism can induce precipitated withdrawal for individuals using a full agonist, due to the rapid decreased activation of opioid μ-receptors from full agonist activation to partial agonist activation over a very short period of time (Fig. 1). This rapid change is felt dramatically by clients, and is interpreted by clients as severe withdrawal. Methadone's extended half-life makes it particularly arduous to switch patients, as it can take up to 96 hours to reach adequate levels of withdrawal to start buprenorphine.[17] Indeed, patients who have precipitated withdrawal or significant withdrawal during the induction process, may have decrease retention rates in treatment within the first 2 weeks.[18]

One study suggests that patients who receive moderate to high doses of methadone demonstrated more intense withdrawal and required higher quantities of alpha-2 adrenergic medication (i.e., Clonidine) during transfer, compared to those on lower doses.[19] In addition, methadone not only affects μ-receptors but can act as an antagonist to the *N*-methyl-D-aspartate system as well.[20] Removal of methadone may lead to disruption of the glutamate–gamma-aminobutyric acid balance leading to unopposed glutaminergic hyperactivity, similar to what is seen in withdrawal from alcohol, benzodiazepines, and barbiturates. This would explain the increase in anxiety, uneasiness, feelings of panic, and confusion shared between these substances and methadone withdrawal.[21]

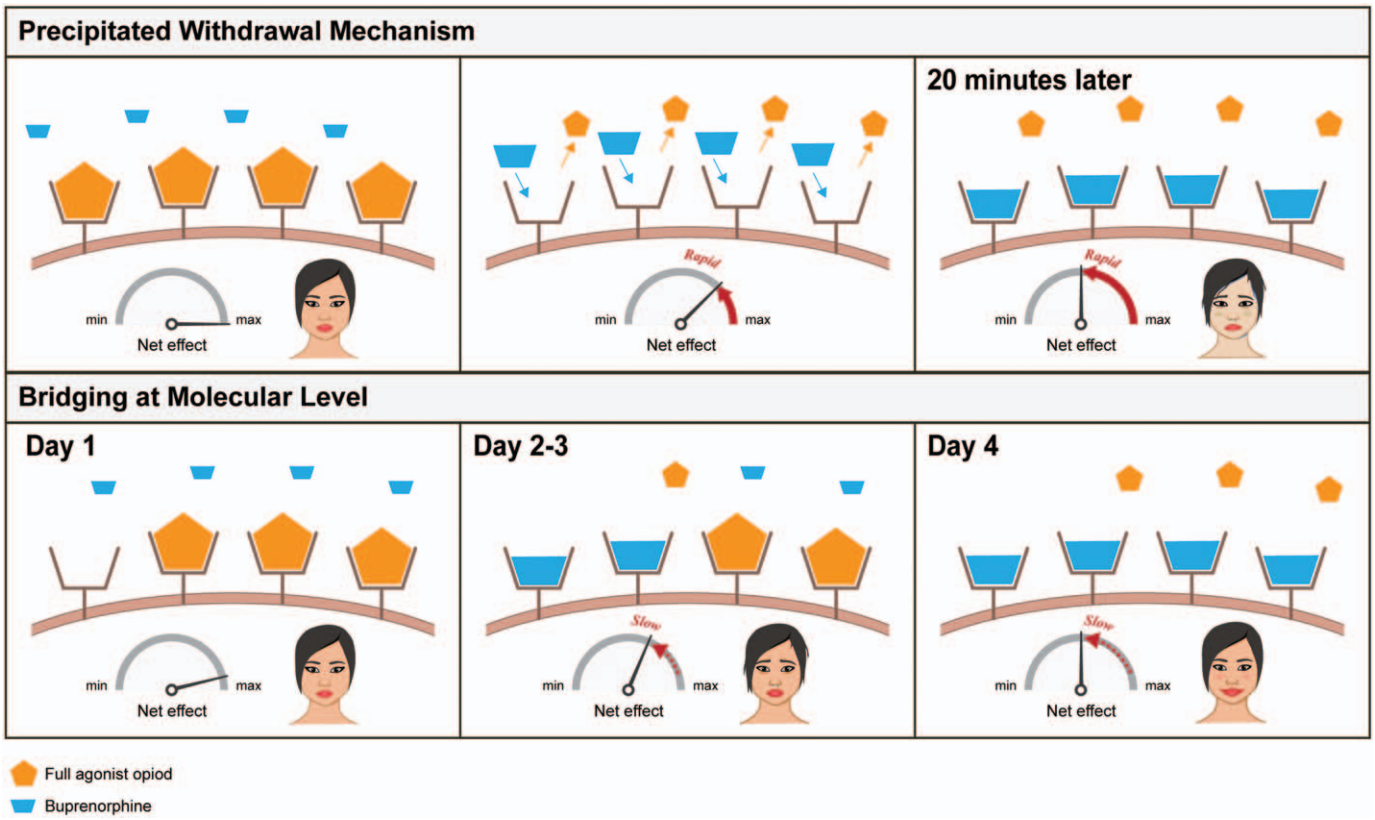


Fig. 1.

Mechanism behind precipitated withdrawal mechanism as well as bridging: Partial agonist opioid with high affinity for μ-receptors replaces the full opioid agonist rapidly over a short period of time causing a massive change in the net μ-receptor activation leading to rapid precipitated withdrawal. This can be mitigated by bridging, where the gradual introduction of higher affinity partial agonist opioids can help minimize withdrawal symptoms.

Risk factors for difficult and severe withdrawal during transition include high methadone doses (up to 100 mg), a shorter time to buprenorphine induction, and the female gender.[22] In addition, before the transition, certain characteristics increase the risk of unsuccessful transfer including[6]

- the patient experiencing withdrawal with their current methadone dose and methadone doses less than 60 mg/day;
- unsanctioned opioid use or unstable use of other drugs;
- severe medical or psychiatric conditions that may be destabilized during transfer;
- unstable social conditions;
- previous complications during previous transfer attempts; and
- poor understanding by the patient of the transfer process.

METHODS

Between the period of June 2018 and March 2019, we had searched the Cochrane Central Register of Controlled Trials, OVID MEDLINE and PubMed, and Embase, as well as hand searched references from found relevant articles.

Selection criteria

Randomized controlled trials, review articles, case series, and case reports examining interventions looking at transitions from any full agonist opioid to buprenorphine/naloxone was identified and used. Internal protocols which have been used at various sites were included based on merit discussions between the authors. The most useful protocols were added to this paper.

REVIEW OF TECHNIQUES

Methadone reduction followed by standard buprenorphine/naloxone SL switch

At this time, Canadian, Australian, and American[1,6,7] guidelines suggest the following key elements when transferring patients from methadone to buprenorphine (Fig. 2):

(a) Gradual reduction of methadone dose until the patient starts to feel mild to moderate withdrawal between doses.
(b) Tapering to 30 mg or less of daily methadone before the switch.[6]

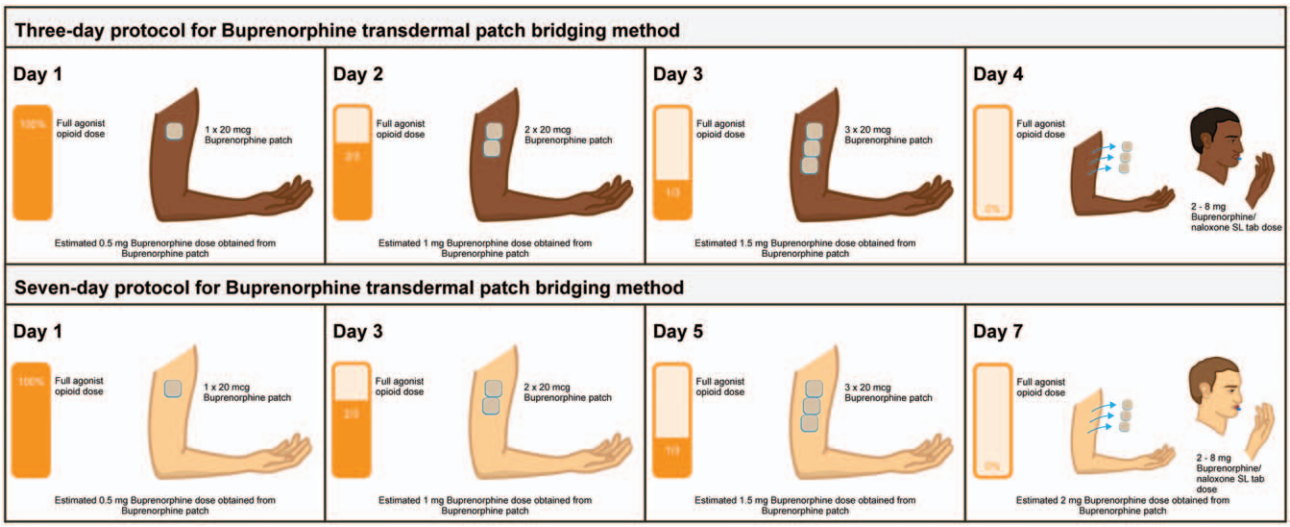


Fig. 2.

Three- and 7-day buprenorphine patch protocol.

(c) Cease methadone and monitor the patient regularly for evidence of withdrawal. Initiate treatment when patient has a Clinical Opioid Withdrawal Scale score greater than 12, which may take as long as 24 to 72 hours.

A systematic review of this method of transfer was conducted by Mannelli et al[23] and individuals at doses less than 70 mg per day could benefit from this method in outpatient settings. One study suggested that transferring individuals from doses of methadone greater than 50 mg are associated with higher risk of precipitated withdrawal.[22] At high doses, inpatient support with withdrawal mitigation therapies such as clonidine, acetaminophen, trazodone, and dimenhydrinate is recommended within most guidelines.[1,6,7]

Another systematic review reported that the transfer completion rate was greatest for methadone doses less than 40 mg, and the least for those greater than 60 mg (NL review). Interestingly, and perhaps counter-intuitively, while there was no statistical significance in transfer rate success, there was a trend for greater transfer completion rate when SL buprenorphine/naloxone initiation was less than 24 hours since the last dose of methadone, during which patients were only in mild withdrawal. Transfer completion rates were also higher when the first-day dose of buprenorphine/naloxone SL was less than 4 mg. These results suggest the following initiating doses for this method which is not reflected in current guidelines[26]:

(a) First-day dosing of buprenorphine/naloxone SL should be less than 4 mg.
(b) Second-day dosing should be less than 8 mg.
(c) Rapid escalated up-titration and dose stabilization should be performed thereafter.

Rapid up-titration to a stable dose compared to slow and medium rate titrations demonstrated statistical superiority. Reasons for transition failure using this standard method included withdrawal, precipitated withdrawal, alcohol intoxication during initiation day, relapse to illicit opioids, and incarceration.

Micro induction and Bernese method

The concept of bridging

The key principle in the transition from methadone to buprenorphine is the idea of *bridging*. The pharmacologic principle of bridging incorporates an as-slow-as-possible introduction of buprenorphine onto the opioid receptors, facilitating a gentle loading of the high binding affinity and long half-life buprenorphine, without significant displacement of the full agonist opioid. This can involve a slow titration down of the full agonist opioid. As lower binding affinity opioid occupying the μ-receptors is slowly displaced or metabolized, up-titration of the newly introduced buprenorphine will steadily bind to the newly free μ-receptors. This slow titration helps creates a smooth transition from full agonist to partial agonist activity eliminating the potential precipitated withdrawal effects (Fig. 1). Because of buprenorphine's higher opioid receptor affinity, even if additional methadone is added, it is less likely to attach to μ-receptors which are occupied by buprenorphine. Eventually, the buprenorphine molecule will occupy more and more opioid receptors than the full agonist until the receptors are saturated with buprenorphine.

While there are a variety of microinduction protocols presented as case series and reports, it is the underlying principle of bridging that makes them effective. Essentially, any protocol which allows the slow induction of

buprenorphine would work provided the principles above are followed. The duration of this bridge will be the total time required for complete clearance of the full agonist opioids used before induction, approximately equal to 4 to 5 half-lives of the acting opioid.

The Bernese method

The Bernese method has been the basis of many unique methods of starting buprenorphine. The authors of this method determined the following[24]:

(1) Repetitive administration of very small buprenorphine doses with sufficient dosing intervals (e.g., 12 hours) should not precipitate opioid withdrawal.
(2) Because of the long receptor binding time due to higher affinity, buprenorphine will accumulate at the receptor.
(3) Over time, a greater percentage of the full μ-agonist will be replaced by buprenorphine at the opioid receptor as the dominant opioid.

The goal is to taper the opioid of choice while titrating the buprenorphine. This method involves dividing the 2 mg tablets of buprenorphine into eighths or quarters and slowly titrating this until it reaches a sufficient level, followed by the discontinuation of the full agonist opioid. Common concerns with this method include difficulties dividing the tablets into small doses as well as concerns with missed doses disrupting the tapering plan. Most individuals feel very mild forms of withdrawal during this transition if any at all.

The buprenorphine transdermal patch method

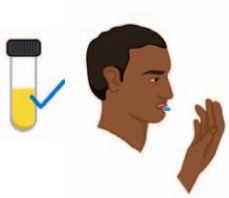
Dividing the 2 mg buprenorphine tablets to minute portions can result in uneven distribution of the buprenorphine molecule due to the friability and size of tablets. The transdermal formulation of buprenorphine provides small doses of buprenorphine as a continuous delivery of medication with consistent plasma drug concentrations with a peak plasma volume at 48 hours.[14] This offers a stable and easy-to-titrate alternative with consistent dosing. Patches of 20 μg/h patch of Butrans (Stamford, CT) contain 0.48 or ~0.5 mg of buprenorphine, creating a delivery system that simplifies induction dosing.

Buprenorphine transdermal patch method 1

Two 20 μg/h patches are applied to the patient in a staggered method over 3 days to limit the risk of precipitated withdrawal. A urine screen is conducted 1 to 2 days after the second patch is added, and if it is positive for buprenorphine, cessation of the full agonist opioid and buprenorphine induction can begin.[25] This induction protocol is presented in Table 1.

In a modified induction method, 2 × 20 μg patches are applied for 24 hours. After 24 hours the client ceases the full agonist dosing. If the patient experiences no withdrawal then continue with the modified induction by adding 1 to 2 mg of buprenorphine/naloxone SL every hour until the patient reaches the 12 mg max for day 1 with a subsequent regular titration schedule. If the patient feels some withdrawal then hold the next 1 mg dose until

Table 1: Protocol for Buprenorphine Patch Conversion Method

At initiation 	If the methadone dose is: • > 60mg, reduce by ½ 2 days prior to start of buprenorphine/naloxone SL. • is < 60 mg, then the last dose should be given the morning prior to induction. Apply 40 mcg of transdermal buprenorphine (~1mg of buprenorphine/naloxone SL) for 3-6 days or until urine drug screen (UDS) is positive for buprenorphine.
Day 1 **Induction Day** 	Perform UDS. If urine screens positive for buprenorphine, stop the original opioid (ie. methadone). Administer 1mg SL Buprenorphine/naltrexone test dose. Observe 2 hours. If withdrawal symptoms emerge and COWS increases, hold further doses until COWS returns to baseline. Administer 1 mg test dose and observe two hours. Repeat if COWS increases. If COWS remains the same or decreases, administer 1-2mg SL buprenorphine, observe 2 hours. Repeat to a maximum of 8-12 mg buprenorphine SL on induction day, based on elimination of withdrawal symptoms Discontinue transdermal delivery.
Day 2	Administer induction day dose and up-titrate buprenorphine/naloxone SL up to 16 mg on Day 2 if pain or withdrawal symptoms persist.
Day 3	Administer Day 2 dose, up-titrate buprenorphine/naltrexone SL to 20-24 mg if pain or withdrawal symptoms persist.
Day 4	Continue established daily buprenorphine/naltrexone dose.

COWS = Clinical Opioid Withdrawal Scale, SL = sublingual, UDS = urine drug screen.

their Clinical Opioid Withdrawal Scale starts to increase, then continue with modified induction as before with 1 to 2 mg titrations every hour until the daily maximum dose is achieved.

The timing on when to stop the methadone, or any full agonist is dependent on the affinity, dose, and half-life of the full opioid agonist used. For example, higher doses of methadone (>60 mg/day) warrant a dose reduction 1 to 2 days before buprenorphine induction, whereas regular agonists with shorter half-lives can be continued right up to the night before induction. The transdermal patch can be worn up to and even through the day of induction as the overall quantity of buprenorphine from the patches is a fraction compared to the SL tablets.

Buprenorphine transdermal patch method 2: buprenorphine patch microdosing

The second method used for buprenorphine transdermal patches is a mix between micro dosing and bridging. While patches are titrated over the course of a few days, the methadone dose is tapered by thirds. The 3- and 7-day induction protocols are in Figure 2. The 3-day protocol is more appropriate for short-acting opioids and illicit opioids, and the 7-day induction protocol for methadone. This method has been most successful with low-to-moderate doses of methadone but has been successful in some of our high dose (>100 mg of methadone) patients as well.

All the buprenorphine transdermal patch methods are suitable for outpatient settings, easy to use, and can be used for low to high doses of methadone. Time to induction as well as cost are seen as barriers but are offset by the reduced need for withdrawal before induction.

Rapid microdosing induction protocol

While traditional microdosing protocols utilize doses given once or twice daily in an outpatient setting, rapid microinduction involves the administration of buprenorphine every 3 to 4 hours without requiring a period of withdrawal before initiation. Frequent dosing is possible because of buprenorphine's time to peak plasma concentration of approximately 1 hour.[26] This is particularly useful in an inpatient setting where discharges are generally delayed due to incomplete buprenorphine induction. Typically, a patient would receive doses of *0.5 mg SL q3h* on day 1, with this being doubled to *1.0 mg SL q3h* on day 2. On day 3, a consolidated dose of 12 mg SL is administered, with additional 2 mg PRN doses provided as needed like a traditional buprenorphine induction. A shortened 24-hour protocol is given in Table 2.

This method involves a rapid induction of buprenorphine on an hourly basis over an 8-hour time span. Rapid microdosing is low cost and is useful particularly for low to mid-range methadone dosing but is most suitable for inpatient settings.

Fentanyl patch transition method

An alternative technique of transitioning from methadone to buprenorphine/naloxone involves the use of fentanyl in the form of a transdermal patch. This method published as the Azar method,[27] begins with the calculation of an equipotent dose of fentanyl based on a patient's current methadone use. In the setting of pain that is being treated with additional opioids or ongoing illicit substance use, a single dose of fentanyl can be determined based on an estimation of the patient's total opioid requirements. Once the fentanyl patch is applied, all other opioids including methadone are discontinued. The duration of this bridge will be the total time required for complete clearance of opioids, that is, 4 to 5 half-lives of the acting opioid. Once this period is complete, the patch can be removed and a standard buprenorphine/naloxone induction can begin right away. An example of the protocol is shown in Figure 3.

Table 2: 24-Hour Rapid Microinduction Dosing Schedule For Buprenorphine/Naloxone SL Using 50 mg of Methadone

Day 1 time in hours from start of induction	Buprenorphine/Naloxone SL dosing (mg)	Cumulated total dose of buprenorphine over 24 hours	Methadone dose
1	0.5	0.5	50 mg
2	0.75	1.25	–
3	1	2.25	–
4	1	3.25	–
5	1	4.25	–
6	1	5.25	–
7	1	6.25	–
8	1	7.25	–
Day 2	12 and 1–2 mg q3h PRN	12 mg + additional doses	STOP all methadone

SL = sublingual.

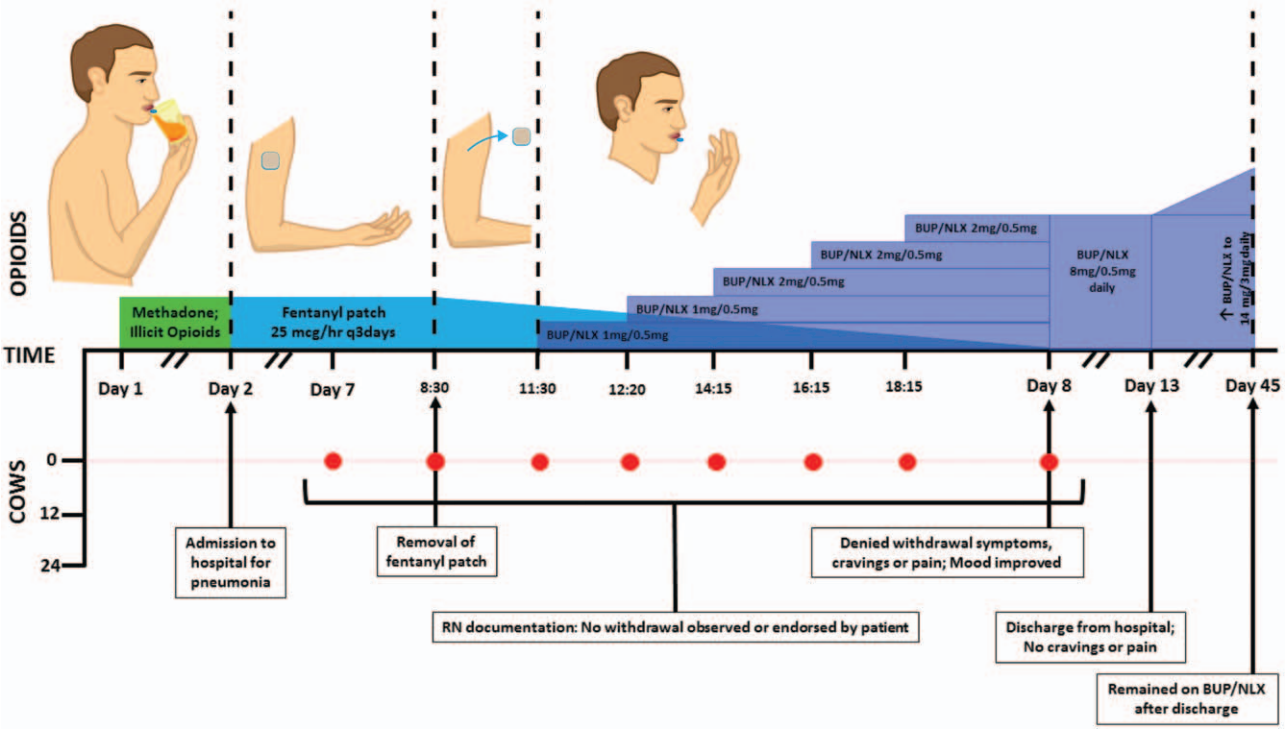


Fig. 3.

Fentanyl patch transition method.

The rationale for this approach is based on the similar binding affinities of fentanyl and buprenorphine to the μ-opioid receptor.[28] When it is initially introduced, fentanyl begins to occupy μ-opioid receptor sites while methadone dissipates. Due to its equal competition for receptor sites, when buprenorphine is administered it does not lead to large shifts in occupancy. Instead, it slowly accumulates at the receptor while fentanyl is metabolized. This prevents precipitation of withdrawal symptoms. One consideration of this protocol is the risk of opioid toxicity which can be avoided by judiciously calculating the starting dose of fentanyl and monitoring the patient during the initial stages. Should respiratory depression or other signs of opioid overdose occur, the transdermal patch can be removed.

The risk of diversion of fentanyl may limit this approach to the inpatient setting only. Other barriers such as cost and risk of precipitated withdrawal should be considered as well. The fentanyl patch method can be used for low to high doses of methadone, and is moderately easy to use, and leads to quick stabilization of the patient.

The Calgary SROM conversion strategy

SROM is a 24-hour formula of morphine (Kadian) which is a reasonable form of ORT improving treatment retention, quality of life, limit withdrawal symptoms, and decrease opioid cravings.[1,29] It comes in a crystalline powder with attached morphine components which are slowly released in a gradual fashion over 24 hours. Once released, morphine can function in an active form with typical morphine pharmacokinetics and usual half-life of 4 hours.[30] The goal of

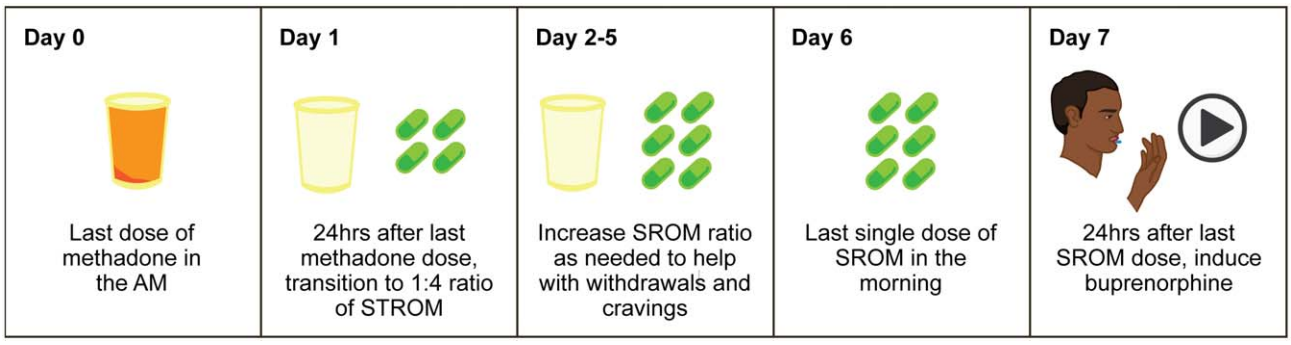


Fig. 4.

Calgary SROM conversion strategy. SROM = slow release oral morphine.

SROM transition is to wash out the methadone and replace it with the more predictable full μ-agonist morphine, with little withdrawal and risk of relapse.

The Calgary SROM conversion strategy highlights the principle of using SROM as a conversion tool from methadone to buprenorphine/naloxone SL and involves the following steps[31] (Fig. 4):

(1) Transfer methadone to SROM starting at a 1:4 ratio of methadone: SROM.
(2) Up titrate to avoid cravings and withdrawal eventually reaching 1:5 or 1:6 ratios of methadone to SROM.
(3) Maintain patient on a stable dose of SROM. Wait 1 week for patient to be off of methadone. One can consider switching from SROM to a dose equivalent of regular short-acting morphine right before buprenorphine induction.
(4) Discontinue SROM and allow the patient to reach reasonable withdrawal to start buprenorphine/naloxone SL which usually is around 24 to 36 hours.
(5) Perform usual induction method of buprenorphine/naloxone SL using standard or microinduction techniques.

A technique we use to estimate a potential ceiling dose of SROM from methadone involves the plonk equation to calculate an equivalent morphine dose followed by a 25% dose reduction.[32] The equation is as follows:

Step 1:

[(Methadone dose in mg − 15) × 15] = equivalent morphine dose

Step 2:

25% Dose reduction of this equivalent morphine dose as an estimate max SROM target dose.

We use this number only as an estimate of how high we can go, but we still begin at a 1:4 conversion and up titrate based on the patient's subjective amount of withdrawal and cravings.

In most cases the initiation of buprenorphine would be a simple home induction. As the morphine formulation is pharmaceutically designed to be used for 24 hours, the last of the morphine will be released around this time, allowing for more predictability for the prescriber. For individuals that have significant phobia of withdrawal, a conversion from sustained release to immediate release morphine forms can further reduce withdrawal time, although risk of diversion is high. Finally, a microinduction protocol can be added to the rotation to buprenorphine/naloxone, almost eliminating any withdrawal symptoms. The SROM strategy is reasonable for low to high doses of methadone, reasonably easy to use, but can be costly for clients.

Outpatient-based rapid microdosing with buprenorphine and SROM

This rapid microinduction method, while used more for illicit opioids can be used for low dose methadone as well. This method requires stopping either the opioid on day 1, and starting frequent microdoses of buprenorphine/naloxone SL and SROM simultaneously (Table 3). The SROM dose remains the same while there is slow titration of the buprenorphine. This method is particularly good for patients using variable and inconsistent daily doses of full agonist opioids in an outpatient setting especially illicit opioids, as it provides some stability to their withdrawal and cravings while up-titrating their buprenorphine/naloxone SL. Its ease of use is moderate, has a reasonably quick time to induction, but can be slightly expensive due to the cost of SROM.

COMPARISON BETWEEN THE VARIOUS METHODS

A complete comparison between the various methods of buprenorphine initiation can be seen in Table 4. Each method has its own distinct advantages and disadvantages based on transition settings (inpatient vs outpatient), starting dose of methadone (<50, 50–100 mg, and greater than 100 mg), risk of precipitated withdrawal, time to induction, ease of use as well as cost. In addition, some of these methods are better suited for illicit opioids, in comparison to methadone. Of note, especially with the

Table 3: Rapid Microdosing of Buprenorphine and SROM

Day 1	Stop methadone or illicit opioid and start 0.5 mg QID of buprenorphine/naloxone and start SROM at 200 mg PO Q daily
Day 2	1 mg QID of buprenorphine/naloxone SL and continue SROM dosing
Day 3	2 mg QID of buprenorphine/naloxone SL and continue SROM dosing
Day 4	12 mg DAILY of buprenorphine/naloxone SL + 2 mg PRN q3h Max 16 mg/24 hours and stop SROM Or Start at 16 mg of buprenorphine/naloxone SL and stop SROM
Day 5 and onwards	Consolidate buprenorphine to once a day dosing and up titrate as necessary, i.e., 16 mg Q daily buprenorphine/naloxone SL

SL = sublingual, SROM = slow release oral morphine.

Table 4: Comparison of Various Different Methods of Conversion

Variable	Classic induction method	Microinduction bernese method	Buprenorphine transdermal patch method	Rapid microinduction method	Fentanyl patch method	SROM conversion strategy	Microdosing with buprenorphine and SROM
Setting of treatment	Outpatient for methadone less than 70 mg. Inpatient setting for methadone doses greater than 70 mg	Outpatient	Outpatient	Inpatient	Inpatient	Outpatient	Outpatient
Dose of methadone most effective for <50 mg = low, 50–100 mg = moderate, >100 mg = high	Low	Low to moderate	Low to high	Low to moderate	Low to high	Low to high	Low to moderate
Risk of precipitated withdrawal	High	Low	Low	Moderate	Moderate	Low to moderate	Low to moderate
Time to induction	Typically 24–72 hours but sometimes as long as a week	A few days to a week	A few days to weeks	Hours	Hours to days	1 Week of SROM then 24 hours wait to start buprenorphine/naloxone SL	Days
Ease of use	Difficult	Moderate	Easy	Moderate	Moderate	Moderate	Moderate
Need for withdrawal during induction	Yes	No	No	No	No	Yes	No
Cost	Inexpensive	Inexpensive	Expensive due to high cost of patches	Inexpensive	Expensive due to cost of fentanyl patches	Expensive due to high cost of SROM	Slightly expensive for 4 days of SROM
Additional concerns		Dividing tablets into small portions. Missed doses makes it difficult for titration of buprenorphine and tapering of methadone	Risk of diversion with buprenorphine patches		Risk of diversion of fentanyl patches if patient is not observed carefully	Risk of diversion if short-acting morphine is used during last leg of SROM transfer	Mostly used for illicit opioids

SL = sublingual, SROM = slow release oral morphine.

microinduction protocols, patients may not require going into withdrawal before the initiation of buprenorphine.

These are not recommendations as would be contained in a guideline, but rather these are based on our group's collective discussion, evaluation, and debated recommendations. We advise that the risks and benefits of each method be discussed with the patient, and the protocol best suited for the patient be utilized.

LIMITATIONS

Outside of the standard treatment method outlined in the *Reasons for transitioning from methadone to buprenorphine section*, there is limited evidence to substantiate any of the novel methods described. There are no efficacy trials done, and there is limited data comparing one method to the other. Clinical trials are undeniably required to appropriately and firmly establish these protocols in our armamentarium. Future trials should examine the starting dose of methadone before transfer (low <50 mg, medium >50–100 mg, or high dose >100 mg), withdrawal risk, transfer completion rates, the efficacy of the speed of up-titration of buprenorphine, and retention rates.

Lastly, while these methods are focused on transitioning between methadone to buprenorphine, these methods have been utilized for both prescription opioids for pain, and illicit opioids with success. This involves similar mechanisms of management, particularly for microinduction.

CONCLUSION

The transfer of patients from methadone to buprenorphine/naloxone SL can be a difficult prospect due to the half-life of methadone, as well as other factors including gamma-aminobutyric acid–glutamate imbalance leading to withdrawal symptoms. Transitioning patients to buprenorphine/naloxone SL can benefit patients in multiple ways including less risk of overdose, increased capacity for take-home doses, improved functioning, and better side effect and drug interaction profile to name a few. Many guidelines strongly encourage buprenorphine as first-line treatment. The methods outlined in this paper offer multiple unique ways to transition patients and were established by the expertise of veteran ORT prescribers. Each method has its own unique benefits, as well as limits and challenges, knowledge of which can help with patient and method matching. The evidence supporting these methods, apart from case studies, is limited and require further studies including randomized controlled trials to determine its efficacy. These methods utilize medications in an off-label fashion and should be used with caution.

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