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# Methadone to Buprenorphine/naloxone Induction without Withdrawal Utilizing Transdermal Fentanyl Bridge in an Inpatient Setting—Azar Method

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**Background and Objectives:** Although buprenorphine/naloxone is widely recognized as first-line therapy for opioid use disorder, the requirement for moderate withdrawal prior to initiation in efforts to avoid precipitated withdrawal can be a barrier to its initiation.
**Methods:** We present a case utilizing transdermal fentanyl as a bridging treatment to eliminate withdrawal during the transition from methadone to buprenorphine/naloxone in a patient who had ongoing significant intravenous heroin use while on methadone.
**Results:** Patient was successfully transitioned from methadone to buprenorphine/naloxone without a period of withdrawal utilizing transdermal fentanyl as a bridge in an inpatient setting.
**Discussion and Conclusions:** Our experience indicates a transdermal depot of fentanyl allows for slow release and elimination while buprenorphine doses are introduced during an induction without presence of withdrawal, as quantified by serial clinical opiate withdrawal score.
**Scientific Significance:** This case report highlights ways to minimize barriers to induction of first-line opioid substitution therapy, buprenorphine/naloxone, by eliminating withdrawal during induction phase utilizing a fentanyl bridge within the limitations of a transdermal fentanyl bridge in an inpatient setting. (Am J Addict 2018;27:601–604)

## INTRODUCTION

Rates of opioid-related overdose deaths have been increasing at an alarming rate in British Columbia.[1] Opioid substitution therapy, such as buprenorphine/naloxone and methadone, have been shown to reduce morbidity and mortality.[2–7] Buprenorphine/naloxone has been recommended as first-line therapy for opioid use disorder.[8–9]

Buprenorphine is a partial mu agonist, with high receptor affinity resulting in a slow dissociation from the receptor and prolonged activity. Oral intake of naloxone yields minimal antagonistic activity due to poor bioavailability and was introduced into this compound to minimize diversion exerting its antagonistic activity on mu receptor if injected. The pharmacokinetics of buprenorphine/naloxone result in a favorable safety profile due to a ceiling effect on respiratory depression and the permitting of rapid titration. However, precipitated withdrawal can result if introduced in the presence of other opiates with lesser binding affinities, such as heroin or methadone; therefore, patients are required to be in moderate withdrawal prior to induction. The timing of patients entering sufficient withdrawal in clinic settings can be challenging, however, home buprenorphine/naloxone induction strategies has essentially minimized this concern in large part. There however remains a selected patient population for whom the requirement for moderate withdrawal prior to initiation will remain a barrier regardless of the setting.[10]

Fentanyl has been shown to have a similar binding affinity profile as buprenorphine.[11] From a hypothetical standpoint, due to its equal competition for mu opioid receptor sites, it would not lead to large shifts in opioid receptor occupancy with an introduction of buprenorphine. Rather, it would create the opportunity for cross-tapering.

We present a case utilizing transdermal fentanyl as a bridge between methadone to buprenorphine/naloxone induction in an effort to minimize withdrawal during the induction phase in an inpatient setting. To our knowledge, this method of bridging using fentanyl has not been described previously in literature.

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## CASE HISTORY

The patient was a 54-year-old male who presented to hospital on November 10, 2016 with a 5-day history of flu like symptoms, including shortness of breath, fever, and productive cough. He was admitted on November 11, 2016 with a community-acquired pneumonia, treated with antibiotics and requiring supplemental oxygen. It was noted that he had previously required recurrent admissions for pneumonias. His past medical history included chronic obstructive pulmonary disease, human immunodeficiency virus, and polysubstance use including nicotine (cigarettes), intranasal cocaine and intravenous heroin. Medications administered while in hospital included alendronate, antiretroviral medications, ceftriaxone, doxycycline, cotrimoxazole, dalteparin, ferrous fumarate, acetaminophen as needed, and methadone. The complex pain and addiction consult service was asked to see him in the context of his active polysubstance use despite opioid substitution therapy (i.e., methadone). Initial bloodwork revealed normal liver function tests, including ALT, AST, and normal renal function. Urine drug screen was positive for methadone metabolites and opiates on admission.

With regards to his substance use history, he reported smoking cigarettes most of his life at approximately half a pack a day, and using intranasal cocaine for 20 years. He had also been using intravenous heroin for 20 years, injecting around 30 dollars worth of heroin daily, with his last use on November 10, 2016. He had previously been admitted for treatment of epidural abscess and osteomyelitis in 2006 in the context of active intravenous drug use. He had been on methadone intermittently for several years but never higher than 45 mg/day due to ongoing side effects primarily fatigue. His current dose was 30 mg/day with his last dose dispensed on November 10, 2016, but continued to experience cravings and withdrawal, leading to daily intravenous heroin use. Prior to admission to the hospital he had been in the process of tapering methadone with his community provider due to fatigue and during this admission he refused up titration of his dose for the same reason despite education regarding the benefits of methadone in treatment of opioid use disorder.

He was contemplative of cessation from all substances, and expressed interest in pursuing buprenorphine/naloxone as an alternative opioid substitution therapy, but strongly identified withdrawal as a trigger. He met diagnostic and statistical manual of mental version 5 criteria for opioid use disorder, severe and active, despite opioid substitution therapy in the form of methadone.

Given that the patient continued to use illicit opioids while refusing to increase his dose of methadone and his ongoing risk of death by overdose the decision was made to switch the patient to buprenorphine. However, as withdrawal was identified as a significant barrier and he was admitted to a stable, monitored setting, a transition from methadone to buprenorphine/naloxone utilizing transdermal fentanyl was considered the best option for the patient.

His total dose of opiates was calculated based on his confirmed amount of daily opiate consumption, which totaled to methadone 30 mg daily. His illicit opioid use was not included in this calculation as it was not possible to know precisely the dose he was using. This was converted to total daily morphine via a 2:1 ratio, accounting for the variabilities in methadone to morphine and known unpredictable pharmacokinetics. Thus, daily methadone at 30 mg equaled 60 mg of total daily oral morphine. Utilizing the conversion of total daily oral morphine to transdermal fentanyl patch outlined in the Vancouver Coastal Health Community Palliative Care Clinical Practice Guidelines 2007,[12] he required a 25 mcg/h fentanyl patch.

He was started on a fentanyl patch on November 11, 2016 at 25 mcg/h transdermal every 3 days. All other opiates, including methadone, were discontinued on this day too. His fentanyl patch was discontinued the morning of November 16, 2016, and he denied any cravings or withdrawal during this transition period. At the time of discontinuation of the fentanyl patch, his initial clinical opiate withdrawal score (COWS) was 0.[13] At induction at 11:30, his initial COWS was 0, and he was dosed with 1 mg/0.25 mg of buprenorphine/naloxone sublingual. At 1-hour post initial induction dose at 12:20, his repeat COWS was 0, and a second 1 mg/0.25 mg sublingual dose of buprenorphine/naloxone was given. His subsequent COWS 2 h later at 14:15 remained at 0, and an increased dose of buprenorphine/naloxone of 2 mg/0.5 mg was given. At 2-hour intervals thereafter, he was given two additional doses of buprenorphine/naloxone at 2 mg/0.5 mg sublingual, and his COWS score remained at 0. Overall, his total buprenorphine/naloxone dose on induction was 8 mg/2 mg. Interdisciplinary notes completed by registered nurses managing his care noted no withdrawal symptoms during induction. On November 17th, 2016, he denied any symptoms of withdrawal, cravings or pain and reported an improved mood. He was discharged on November 22, 2016 with a total dose of 8 mg/2 mg of buprenorphine/naloxone sublingual daily reporting no pain or cravings (Fig. 1). He remained on buprenorphine/naloxone after his discharge on November 22, 2016 and continued to be managed by his community addiction provider thereafter. On November 30, 2016 he tested positive for opioids, buprenorphine and methamphetamine. On December 24, 2016 he had a buprenorphine/naloxone dose increase to 14 mg/3.5 mg sublingual daily. On January 19, 2017 the patient died due to mixed drug toxicity with Buprenorphine, Cocaine, Fentanyl, and Morphine as per British Columbia Coroner's Service report.

## DISCUSSION

We present a case of a patient in an inpatient setting successfully being transitioned from methadone to buprenorphine/naloxone without a period of withdrawal utilizing transdermal fentanyl as a bridge.

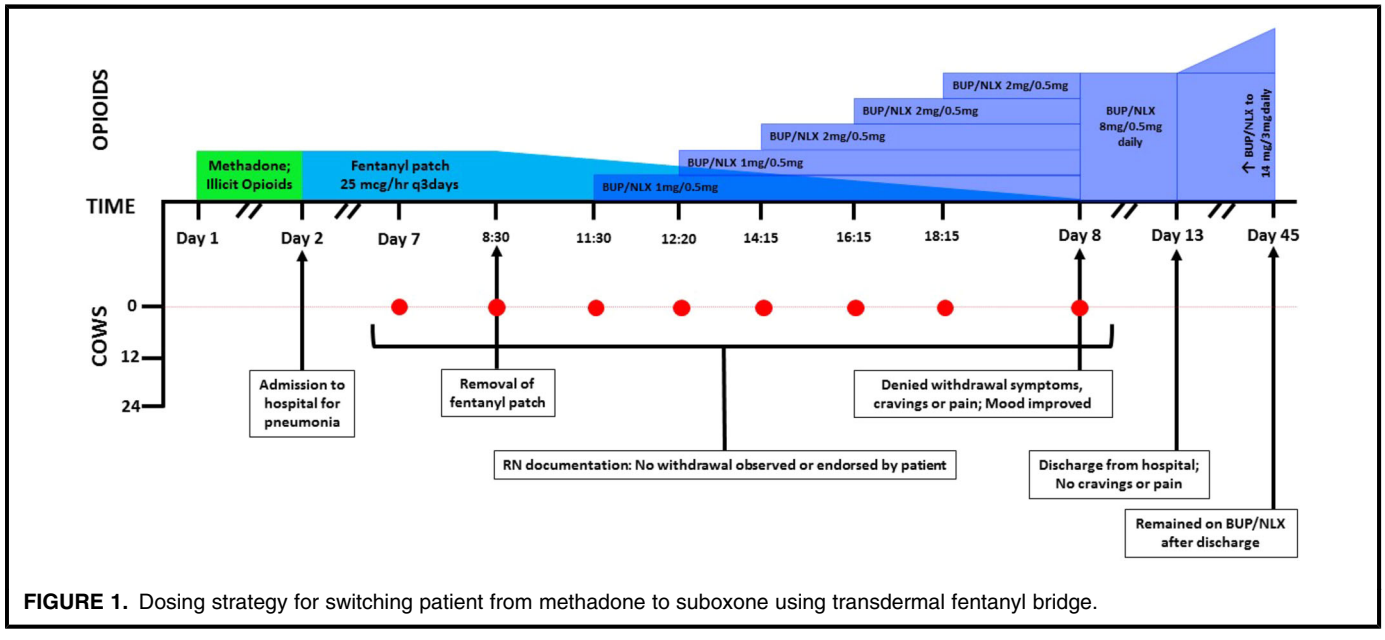


**FIGURE 1.** Dosing strategy for switching patient from methadone to suboxone using transdermal fentanyl bridge.

Methadone is a full mu agonist, and its prolonged half-life necessitates a prolonged induction phase over several weeks to avoid risk for respiratory depression. Due to the prolonged induction phase, many individuals continue to use opioids to treat withdrawal and cravings, and this puts them at risk of overdose. Buprenorphine/naloxone has the advantage of a rapid induction phase over a few days due to its advantageous safety profile, but requires moderate withdrawal prior to induction to minimize the risk of precipitated withdrawal.[8] This can exclude it as a viable option for many patients. Previous protocols for transition from methadone to buprenorphine/naloxone have utilized a buprenorphine patch. Although the withdrawal experience may be less significant, it still remains present.[14,15]

Fentanyl and buprenorphine have similar binding affinities for the mu receptor.[11] Compared to other opiates, fentanyl may compete equally with the receptor in the presence of buprenorphine. Rather than creating large shifts in opioid occupancy at the receptor when buprenorphine is introduced in the presence of other opiates such as methadone, their similar affinity profiles may create an environment for slow-cross taper at the receptor. In doing so, there would be no need for moderate withdrawal prior to induction to avoid precipitated withdrawal despite the presence of another opiate (i.e., fentanyl). Our experience indicates a transdermal depot of fentanyl allows for slow release and elimination while buprenorphine doses are introduced during an induction without presence of withdrawal, as quantified by serial COWS score.[13] The reported case's death was due to a polypharmacy which included fentanyl. Although British Columbia is currently in the midst of a public health crisis due to overdose of drugs which are contaminated with fentanyl in the majority of cases (75.5%); mentioning the possible connection between patient's overdose due to a polypharmacy including fentanyl and our utilization of fentanyl bridge as a cautionary tale is important.

One limitation to consider with this protocol is the variability of methadone conversion. Conversion rates of methadone to morphine vary between 2:1 to 20:1 in the literature, and are often dose dependent.[16–18] Additionally, illicit opiates such as heroin have a variable potency which can adversely impact the conversion calculation and estimated daily opiate use become unreliable. Another limitation is the risk of diversion of fentanyl patches which could increase the risk of overdose and death if combined with illicit opioids. Given these concerns, this type of induction should not be considered the standard of care and requires further study to determine efficacy and safety. A small pilot controlled trial comparing this transition with or without fentanyl bridge might be a reasonable next step. If it is to be utilized it must be completed in an inpatient setting, where total daily opiate consumption can be monitored precisely and diversion can be minimized. Use in outpatient settings yet remained to be explored in future studies as a possibility only with carefully selected patients.

This case report highlights ways to minimize barriers to induction of first-line opioid substitution therapy, buprenorphine/naloxone, by eliminating withdrawal during induction phase utilizing a fentanyl bridge within the limitations of a transdermal fentanyl bridge.

### *Declaration of Interest*

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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