Clinical Case Conference: Unobserved "Home" Induction Onto Buprenorphine

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Unobserved or "home" buprenorphine induction has become a common clinical practice. Patients take the initial and subsequent doses of buprenorphine after, rather than during, an office visit. This clinical case summarizes an unobserved induction onto buprenorphine in a typical new patient. We review the core issues surrounding patient selection, feasibility, logistics, safety, and effectiveness of unobserved buprenorphine induction. Prescribers, treatment providers, policy makers, and patients should weigh the benefits of observed induction (maximum clinical supervision) with the reduced resource burden, flexibility, and comparable safety of unobserved induction.

Key Words: buprenorphine, induction, medication adherence, opioid-related disorders, patient compliance, unobserved induction

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CASE DESCRIPTION

This case is a generic version of a typical new patient presenting to our center (JDL, JM, EG). A 37-year-old white female presented to a public hospital primary care office-based buprenorphine practice seeking treatment with buprenorphine (*The term "buprenorphine" refers throughout this report to buprenorphine mono and buprenorphine-naloxone products*). She stated that she was using 4 to 8 bags/d of heroin and was "tired" and wanted to quit. She was specifically interested in buprenorphine therapy and had been referred to the clinic by another patient. She reported significant withdrawal symptoms after a few hours of nonuse of opioids, not being able to quit or cut down on her own, and feeling that her health and life were unmanageable.

The patient was living with a boyfriend who did not use opioids and wanted her to stop. She was a high school graduate and an unemployed hairdresser and had active New York Medicaid insurance, which covers both primary care visits and buprenorphine prescriptions. She reported a greater than 15-year history of mixed prescription drug and heroin use. Her current use was heroin 4 to 8 bags/d, both intravenous (IV) and intranasal, occasionally using oxycodone and "street" methadone when available.

Over the last 10 years, she reported several treatment episodes, including hospital-based inpatient detoxifications using methadone tapers, one court-mandated residential "drug free" treatment stay of 28 days, and several years ago 6 months of methadone maintenance at a dose of 90 mg/d. She had tried buprenorphine-naloxone a year ago when given several tablets by a friend. She took the medication sublingually after a few hours off of heroin and felt that the medication helped her "stay straight" for a week or so, using up to two 8-mg tablets a day and then resuming heroin use. She says that she has a friend who had a "bad reaction" to "bup" when he took it right after using heroin. She reported occasional heavy drinking and cocaine and alprazolam misuse, but stated that she used primarily only heroin and no other drugs or alcohol the last few weeks. Her goals for recovery included "finally getting straight," reconciling with her 2 young children living with her parents, and finding stable employment. She was not considering a return to methadone maintenance or intensive outpatient programs and stated that she strongly preferred buprenorphine office-based treatment.

Her medical history was notable for hepatitis C-positive status, a recent negative human immunodeficiency virus test, and previous brief treatment for depressed mood with no

history of suicidal ideation or psychiatric hospitalizations. She reported no current medications or allergies. Her last menstrual period was 1 week ago. A physical examination was notable for poor dentition, and upper arm puncture marks and venous scarring with no erythema, swelling, or pain. Labs were sent for liver function, complete blood cell count, hepatitis serologies, and urine pregnancy. A urine toxicology test was positive only for opiates.

The physician documented a diagnosis of opioid use disorder—severe (opioid dependence). Buprenorphine-naloxone treatment was discussed in detail. The physician described the parameters of her office-based group practice: regular visit attendance and scheduled refills by a team of buprenorphine-certified providers, routine urine toxicology, including urine buprenorphine testing, as-needed telephone support, random pill counts on demand, an overall goal of opioid, drug, alcohol, and tobacco abstinence, the risk of oversedation and overdose when buprenorphine was used with alcohol and benzodiazepines, and strong recommendations, but not mandates, in favor of complimentary psychosocial addiction treatment, and 12-step involvement. The patient consented and signed a patient-practice agreement outlining these conditions.

The physician issued a written 1-week buprenorphine-naloxone 16 mg/d sublingual tablet prescription (fourteen 8-mg to 2-mg tablets) to be filled at a community pharmacy (the patient's Medicaid managed care provider had added generic buprenorphine-naloxone tablets to its preferred formulary). The patient was instructed to call the clinic within 24 hours of starting the medication to trouble-shoot any problems, and to return to the clinic in 7 days, the primary care team's weekly clinical session for patients receiving buprenorphine. A patient pamphlet with instructions for unobserved buprenorphine induction was reviewed with the patient, which further detailed how to cease heroin use, wait at least 12 and preferably 24 hours until significant opioid withdrawal symptoms manifested ("get good and dope sick, then wait even longer, as long as you can"), begin induction with one 4-mg sublingual half of a tablet, repeat the 4-mg SL dose every 1 to 2 hours if withdrawal symptoms persisted, and aim not to exceed a 16-mg total first-day dose. The physician instructed the patient that exceeding 16 mg/d on average would exhaust the medication supply earlier than planned, and that she should be in contact with the provider if this proved likely. The pamphlet described the risk of precipitated withdrawal. The patient was instructed to begin day 2 with a single morning dose of the total milligrams taken the day before, and thereafter to aim for a single dose of 8 to 16 mg/d. Telephone clinical support was emphasized to support the unobserved induction process and first week maintenance dose titration.

Despite instructions, there was no phone contact with the patient between visits. She did not return a voice mail from the provider. The patient returned the following week, generally enthused and stating that the induction went, "really well, though I did run out of tabs 2 days ago and used 2 bags [of heroin] yesterday." The patient stated that she re-read the induction pamphlet when leaving the office, but did not refer to it thereafter. She filled the buprenorphine-naloxone prescription at a community pharmacy with no difficulty and did not use heroin after the visit. Later that evening (day 1), she felt withdrawal symptoms, including yawning, aches, and irritability, and took a 4-mg SL half-tablet. After approximately 30 minutes, she felt improved and described no acute worsening of withdrawal symptoms, but was also not completely relieved of all symptoms, and took another 4-mg half-tablet. One hour later, she took an entire 8-mg tablet, for a total of 16 mg, and stated that she then slept "OK." The following morning (day 2) she took one 8-mg tablet, a second 8-mg tablet midday, and due to trouble falling asleep, a further 8-mg tablet for a total of 24 mg on day 2. Days 3 to 5 she took between 16 and 24 mg in divided doses and, as reported, ran out of the initial supply by day 5. Day 6 she felt mild withdrawal symptoms and used 1 to 2 bags of intranasal heroin ("I didn't really feel anything but I wasn't as sick"). The day of the follow-up visit she had not used any heroin or buprenorphine and was eager for a refill and continued treatment.

DISCUSSION

Joshua D. Lee, MD, MSc; Jennifer McNeely, MD, MS; and Ellie Grossman, MD

Buprenorphine is an evidence-based intervention for opioid use disorders (heroin and prescription opioid dependence) of comparable effectiveness to methadone maintenance, and now the most commonly prescribed opioid treatment medication in the United States (Substance Abuse and Mental Health Service Administration, 2013). Along with extended-release and oral naltrexone, it is the only Food and Drug Administration–approved treatment for opioid use disorders available to an office-based physician. This patient's opioid use disorder diagnosis is clear, she has presented to a buprenorphine-waivered physician with a strong preference for office-based treatment, and inducing her onto buprenorphine seems to be well justified.

How to safely and most effectively induce the patient onto buprenorphine maintenance? Unobserved or "home" buprenorphine induction, in which patients take the initial doses of buprenorphine after, rather than during, an office visit, is now a common practice, but one not addressed in national treatment guidelines and that diverges from buprenorphine's Food and Drug Administration label that specifies observed induction (Reckitt Benckiser, 2011). Observed induction would typically include more time and effort by the physician or support staff, per guidelines, including a screening visit, an induction visit, and close follow-up after induction, though many variations on these procedures have been described. An observed induction visit consists of confirming that the patient is in opioid withdrawal, providing an initial induction dose, and observing for symptom improvement or adverse events, principally precipitated withdrawal. The choice of induction methods, then, depends largely on the physician and practice's preferences and capabilities, induction waiting room logistics and support staff, and the patient's own attitudes and preferences.

In this particular case, the individual physician and team of buprenorphine providers are not available in-clinic throughout the week but have established a busy once-weekly buprenorphine clinic session. The physician has 2 years' experience as a buprenorphine provider, and the group has

developed an unobserved induction protocol, using a patient pamphlet and telephone support. The patient has already taken buprenorphine as informal brief treatment and seems to have no difficulty understanding the basic induction procedures and the risks of precipitated withdrawal. The physician offered unobserved induction instructions and a 1-week buprenorphine-naloxone prescription, which the patient started and titrated with no difficulty. Within a 1-week period and over 2 standard office visits, the patient had begun buprenorphine treatment with no induction-related adverse events and reduced her opioid misuse from 56 bags of heroin per week to 2. Less successfully, the patient had been out of contact for 1 week, exceeded buprenorphine maintenance dose targets, and resumed heroin use by week's end. The following discussion considers the key issues surrounding unobserved buprenorphine induction and possible approaches to this case.

Patient Selection and Baseline Characteristics: Are Some Patients More Appropriate for Unobserved Induction?

What predicts good safety and effectiveness outcomes during the induction week? In brief and as reviewed elsewhere in this issue of *Journal of Addiction Medicine*, there is no evidence to date that either approach, observed or unobserved induction, is associated with superior safety, tolerability, retention, or opioid misuse outcomes (Lee, Vocci, Fiellin, 2014). The induction literature does point to several key patient and treatment characteristics as possibly predictive of difficult inductions but to date finds no difference between observed and unobserved methods. Previous use of buprenorphine by the patient seems to predict fewer induction adverse events (Lee et al., 2009; Whitley et al., 2010). This is entirely reasonable, as these patients are "re-inducing" onto a familiar and well-tolerated treatment and would presumably be less likely to do so had they previously experienced precipitated withdrawal or other adverse effects. Prior use of buprenorphine seems to characterize a substantial proportion of patients presenting for buprenorphine treatment and induction and may predict better long-term treatment retention (Cunningham et al., 2013).

Higher recommended buprenorphine induction doses may also reduce induction adverse events, with some evidence indicating that a day 1 total dose of 8 to 16 mg is better tolerated than the labeled recommendation of 8 mg maximum (Whitley et al., 2010). Conversely, switching from methadone to buprenorphine is a much more difficult induction process, and rates of protracted opioid withdrawal, defined as withdrawal symptoms not relieved by initial buprenorphine dosing and persisting over several days after buprenorphine induction, appear much more likely in patients recently receiving a maintenance dose of methadone (Lee et al., 2009; Whitley et al., 2010). This patient had reportedly used illicit methadone recently and had been in methadone maintenance previously, but not in the last few weeks by self-report and urine toxicology, leaving her at low risk for methadone-associated withdrawal complications. There is to date no evidence that other baseline characteristics (sex, age, IV vs other misuse, duration of opioid use, human immunodeficiency virus, or HCV+ status) predict rates of short-term induction success. In contrast, baseline characteristics, including age, treatment history and previous buprenorphine use, IV misuse, and major depression, may predict overall buprenorphine maintenance treatment success/failure over a longer period (Subramaniam et al., 2011; Weiss RD et al., 2011; Cunningham et al., 2013; Dreifuss et al., 2013).

An important baseline factor to consider is, of course, patient preference. The physician in this case worked in a tertiary public hospital with multiple opioid treatment options, including emergency detoxification, intensive outpatient, and methadone maintenance, but her own practice, the only office-based buprenorphine clinic in the hospital, offered only unobserved induction. The patient's induction preferences were, therefore, not deeply explored. The patient clearly preferred office-based buprenorphine and readily accepted the unobserved induction prescription. What if there had been a choice between unobserved and observed inductions? Studies have demonstrated that in patients similar to this one, predominantly heroin users seeking buprenorphine treatment in an urban public sector office-based setting, when given a choice, and with provider support and agreement, were more likely to select unobserved induction, 56% unobserved versus 44% observed (Sohler et al., 2010) and 95% versus 5% in a later cohort (Cunningham et al., 2011).

Feasibility and Logistics

The patient was initially assessed and diagnosed with opioid dependence, the plan of buprenorphine induction was agreed to and reviewed by the physician and patient, and some type of patient education and remote induction support was provided in the form of a handout and telephone contact. Follow-up for buprenorphine induction typically occurs within a few days or 1 week, and this schedule may vary depending on physician comfort and availability. Although this minimizes the number of in-person visits needed for induction, it potentially increases the staff time required for phone support or prompts unscheduled postinduction visits in the event of adverse events or other difficulties (we have not experienced this at our center and there are no such reports in the literature). It is generally more difficult to obtain reimbursement for phone support, and unobserved induction may be ineligible for enhanced billing codes applicable to lengthy observed buprenorphine induction visits (Clinical Tools, Inc, 2013). Per guidelines, observed induction would add at least 1 prolonged visit, after an initial assessment, when the patient returns in opioid withdrawal.

Studies have demonstrated variable use of provider-patient telephone support (Lee et al., 2009; Sohler et al., 2010; Gunderson et al., 2010; Cunningham et al., 2011). In our practice, few patients call the provider or clinic during induction days 1 to 3, despite routine instructions and strong encouragement to do this and often after providing the physician's direct mobile number. This likely relates to an initial unfamiliarity between physician and patient as treatment begins, the overall safety and nonevent of a typical buprenorphine induction, patients' own previous experience with buprenorphine and informal support from experienced friends or family, written patient education materials, and a largely passive contact approach depending on the patient.

Patient unobserved induction pamphlets and toolkits have been described and published by several sites (Lee et al., 2009; Sohler et al., 2010; Cunningham et al., 2011). Our own home induction pamphlet remains available as an online resource accompanying the manuscript and is freely adaptable with proper citation (Lee et al., 2009). Generally, patients and providers consider these helpful guides, although our pamphlet has within it an induction day 1 to 3 dosing worksheet that few patients describe completing or bring back for review. At the least, it is a helpful in-clinic guide that the physician and the patient review together before the initial induction prescription.

Another persistent issue in public sector buprenorphine treatment is patient health insurance and Medicaid status, copays and prior authorization barriers, and to date the high retail cost of buprenorphine. We found in our first 103 unobserved inductions that first week dropout was heavily correlated with reported insurance problems and self-pay status (Lee et al., 2009). This was the most common reason for patients to leave the initial visit with a written prescription and not return 1 week later. Observed induction wherein the provider has a supply of medication available for dispensing is clearly superior in this regard. However, some providers prescribe small amounts (eg, a 1-day supply) and instruct patients to fill at a nearby pharmacy and return for observed induction, which involves the same insurance and cost barriers.

Safety and Effectiveness

Studies comparing unobserved versus observed induction have not shown differential rates of adverse events or serious adverse events, including precipitated or protracted opioid withdrawal, or other unfavorable outcomes such as pediatric exposure or diversion-related emergency department visits (Lee, Vocci, Fiellin, 2013). There is no definitive randomized comparative effectiveness trial to date with adequate power to model the equivalence or noninferiority of the 2 approaches in regard to infrequent safety events. The comparative trials to date, including a small randomized trial (Gunderson et al., 2010) and observational cohorts (Sohler et al., 2010; Cunningham et al., 2011), and a single-arm observational assessment of week 1 safety events from our center (Lee et al., 2009), indicate that providers should expect low rates of precipitated withdrawal ($\leq$10%) using either induction method. In contrast, methadone-to-buprenorphine inductions are more frequently complicated by protracted withdrawal, defined as opioid withdrawal symptoms continuing and not significantly improved after more than 24 hours of buprenorphine induction (protracted withdrawal rates of 21% for methadone-buprenorphine vs 2% for non–methadone-buprenorphine inductions at our center).

If effectiveness is defined as the proportion of patients successfully induced onto a maintenance dose of buprenorphine at 1 to 2 weeks, these same studies have not detected a difference in treatment retention between unobserved/observed induction approaches. After the first week and long term, when all doses of buprenorphine prescribed in a typical US office-based practice are unobserved, treatment outcomes likely have little to do with the initial induction procedures. The aforementioned studies and others with observed and unobserved induction cohorts examining 12- to 24-week retention and opioid misuse showed equivalent outcomes between the 2 approaches (Alford et al., 2007; Mintzer et al., 2007; Lee et al., 2012). Typical week 1 outcomes could be improved in office-based buprenorphine treatment overall, chief among them dropout. Across a number of naturalistic office-based buprenorphine studies, week 1 dropout ranges from 10% to 30%. Increasing the proportion of patients screened and in need of opioid medication who successfully return for induction and maintenance is a quality improvement priority, independent of induction method.

Frank Vocci, PhD

Induction with buprenorphine/naloxone products has been reported to be feasible and safe for many years (Fiellin et al., 2006; Moore et al., 2007; Ling et al., 2010). A recent labeling revision approved Suboxone-brand film for use during supervised induction (Reckitt Benckiser, 2014). The transition to unobserved dosing is then a clinical decision of the physician in concert with the patient. Patient education, especially for the induction period, is likely to be a primary reason for the success of unobserved and home-based inductions. Imparting knowledge on dosing and the timing of buprenorphine/naloxone administration since last opioid use can likely minimize the possibility of a negative outcome, for example, precipitated withdrawal. Giving patients access to the physician via their mobile phones during induction is a good idea but seems to be underutilized by the patients. Perhaps a more direct approach would help; that is, a physician or nurse from the practice or clinic could call the patient to see how the induction was proceeding, as in the Gunderson protocol (Gunderson et al., 2010). In fact, the notion of active (the physician or nurse initiates call) versus passive (the patient is given a phone number and instructions to call the physician) induction monitoring could be studied to see whether active monitoring of induction produces better outcomes. In this case, a better outcome could be defined as a greater proportion of patients completing induction with a stable dose of buprenorphine/naloxone and higher patient satisfaction. The construct of active versus passive monitoring of induction could also be assessed via a mobile phone application. Again, the application could allow initiation of the interaction by the physician or the patient to determine whether active monitoring improved outcomes compared with passive monitoring, respectively.

David A. Fiellin, MD

As buprenorphine treatment has entered its second decade in the United States, clinical experience has grown among providers and patients. Induction logistics, an often-cited concern among those new to providing buprenorphine treatment (Egan et al., 2010), typically ends up being among the less-complicated aspects of treatment. As providers have developed greater experience with the medication, and patients have been through their own treatment experiences (officially or unofficially), inductions become easier and unobserved inductions more routine (Netherland et al., 2009). The risks of adverse events during induction, however, are not theoretical and any provider who has witnessed and managed a precipitated withdrawal can attest to the substantial and prolonged

patient (and provider) discomfort involved in the process. What can we do then to minimize the likelihood of precipitated withdrawal with observed and unobserved buprenorphine inductions? The case discussion provides reminders as to the most essential components of patient education regarding induction: (1) adequate amount of time since intake of the last opioid full agonist and buprenorphine ingestion to allow for the development of mild to moderate withdrawal, (2) tailoring expectations regarding the time course of such withdrawal based on the recently ingested opioids (eg, oral methadone or sustained release oxycodone take longer than IN heroin or immediate release oxycodone), (3) monitoring of cardinal withdrawal signs and symptoms, and (4) divided doses of buprenorphine on the first day (Center for Substance Abuse Treatment, 2004; Rosado et al., 2007).

The case also presents a number of other points to consider. The first of which is that some patients may have had prior experiences (or known others with prior experience) with buprenorphine either from the "street" or from a prior treatment episode. It is useful for the clinician to review that experience with the patient, especially the induction period, to educate the patient about any misconceptions they might have. The second relates to the time lag that is involved in arranging for observed inductions. Although not clearly relevant in this case, this delay can sometimes be useful in allowing the clinician time to receive and review laboratory tests, urine results, and records of prescription monitoring programs, and speak to prior and current medical or addiction treatment providers, although these same delays can also be associated with continued opioid-related adverse events. The third issue pertains to maximum doses during the first week of induction. The US treatment guidelines, developed to reflect the available evidence at the time, are likely too cautious in recommending a maximum of 8 mg of buprenorphine on the first day. Clinical experience reveals that some patients, though not all, benefit from higher doses, perhaps up to 16 mg on the first day of buprenorphine treatment as evidenced in this case. Patients may end up taking higher doses than needed, without clear indications, at any point during buprenorphine treatment. The case provides an example of this when the patient takes an additional 8 mg for a total of 24 mg on the second day of treatment for the inappropriate indication of insomnia. Treatment plans should include education strategies that avoid unnecessarily increasing the patient's level of opioid physical dependence (through dose escalations) and/or having the patient take the medication in unnecessary ways (eg, divided doses). This may mean limiting the amount of available medication early on in buprenorphine treatment until the provider has a better sense of how the patient uses his or her medication. Although this is not an obligate feature of observed inductions, more frequent contact early on in buprenorphine treatment allows for this type of patient evaluation and education. Barriers such as visit costs and copays should be structured to allow optimal patient outcomes, a process that may require clinicians to advocate with insurers and administrators on behalf of their patients. The fourth issue pertains to staffing of induction procedures. Although a physician is required to write a prescription for buprenorphine and should be involved and oversee all aspects of the patient's care, nurses and other ancillary health care professionals have proven invaluable to a number of practices providing buprenorphine, including patient education and the process of observed inductions (Fiellin et al., 2006; Center for Substance Abuse Treatment, 2009; Alford et al., 2011; Weiss L et al., 2011). Indeed, although inductions may not always need to be observed by the physician, some patients may benefit from having them observed by ancillary clinical staff.

CONCLUSIONS

This clinical case was a representative presentation of a heroin-dependent adult for office-based unobserved buprenorphine induction. The patient reported previous experience with buprenorphine and the induction was largely uneventful. However, several features indicated typical areas for improvement of early buprenorphine treatment, including patient-directed dose titration and between visit provider-patient support.

Unobserved induction is now grounded in a growing body of literature demonstrating feasibility, wide adoption, and reasonable and acceptable level of safety compared with that of observed induction, although definitive data on comparative effectiveness are lacking. The choice of unobserved versus observed induction methods is currently made along practical lines, taking into account patient and provider preference, levels of ancillary support, practice logistics, and overall treatment goals. Strategies emphasizing active remote induction support and multidisciplinary treatment teams may improve buprenorphine induction and maintenance outcomes independent of unobserved versus observed induction. The US guidelines should address this common approach to buprenorphine induction, as is the case with the guidance from the Provider Clinical Support System for Medication Assisted Therapy (Casadonte and Sullivan, 2013). Studies of comparative and optimal buprenorphine treatment strategies would further clarify the differences or lack thereof between unobserved and observed inductions.

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