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Factors associated with complicated buprenorphine inductions

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Abstract

Despite data supporting its efficacy, barriers to implementation of buprenorphine for office-based treatment are present. Complications can occur during buprenorphine inductions, yet few published studies have examined this phase of treatment. To examine factors associated with complications during buprenorphine induction, we conducted a retrospective chart review of the first 107 patients receiving buprenorphine treatment in an urban community health center. The primary outcome, defined as complicated induction (precipitated or protracted withdrawal), was observed in 18 (16.8%) patients. Complicated inductions were associated with poorer treatment retention (than routine inductions) and decreased over time. Factors independently associated with complicated inductions included recent use of prescribed methadone, recent benzodiazepine use, no prior experience with buprenorphine, and a low initial dose of buprenorphine/naloxone. Findings from this study and further investigation of patient characteristics and treatment characteristics associated with complicated inductions can help guide buprenorphine treatment strategies.

Keywords

Opioid dependence; Buprenorphine; Buprenorphine induction

1. Introduction

Opioid abuse and dependence are a growing problem, yet in 2007, of the nearly 2 million Americans abusing or are dependent on opioids, less than 5% received pharmacologic treatment (Substance Abuse and Mental Health Services Administration [SAMHSA], 2008, 2009). The Drug Addiction Treatment Act of 2000 creates an opportunity to move treatment

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of opioid dependence out of the traditional methadone maintenance clinic and expand access to care. The Food and Drug Administration approved buprenorphine, a partial opioid agonist, in 2002, and ample data support its efficacy. Although access to treatment has expanded, many barriers to implementation continue to be identified (Fiellin, 2007).

Several studies indicate that providers' concern about managing the logistics of buprenorphine induction is a barrier to prescribing buprenorphine for the treatment of opioid addiction (Kissin, McLeod, Sonnefeld, & Stanton, 2006; Netherland et al., 2009; Walley et al., 2008). Buprenorphine induction, the first few days in which treatment is initiated, can be the most challenging phase of treatment for both providers and patients. For these reasons and because induction outcomes are likely predictors of long-term treatment outcomes, including retention and abstinence, careful attention to this phase of treatment is warranted (Soyka, Zingg, Koller, & Kuefher, 2008).

Potential complications of buprenorphine inductions include precipitated and protracted withdrawal. Precipitated withdrawal, an acute worsening of symptoms after taking the first dose of buprenorphine, is well defined and emphasized in buprenorphine trainings and treatment guidelines (Center for Substance Abuse Treatment [CSAT], 2004). Precipitated withdrawal can occur if an individual who is physically dependent on opioids and has opioids currently occupying mu-opioid receptors receives a dose of buprenorphine. Because of its high affinity for the mu-opioid receptor, buprenorphine can displace the existing full agonist (e.g., heroin, methadone) resulting in an abrupt decrease in net agonist effect. This can be expected to occur within 30 minutes after the buprenorphine dose is administered. Although symptoms are usually mild and easily tolerated by the patient (Strain, Preston, Liebson, & Bigelow, 1995), this possibility remains a major focus of concern for providers and patients. Patients experiencing precipitated withdrawal can require additional time and resources including telephone calls, office visits, and rarely emergency room visits.

To avoid precipitated withdrawal, opioid-dependent individuals must be in mild to moderate opioid withdrawal at the time that the first dose of buprenorphine is administered. Treatment guidelines suggest that precipitated withdrawal can be minimized by reducing the dose of the opioid of abuse prior to initiating treatment, allowing sufficient time between the last dose of opioid of abuse and first dose of buprenorphine, and starting treatment using a lower buprenorphine dose (CSAT, 2004). Treatment guidelines further recommend that inductions occur in the office of a qualified physician to assess for opioid withdrawal, gradually titrate buprenorphine doses, and monitor patients' responses to buprenorphine.

A second complication associated with the induction process is protracted opioid withdrawal, defined here as experiencing symptoms of opioid withdrawal that persist beyond the first 24 hours of the initial buprenorphine dose. Protracted withdrawal is not well defined in treatment guidelines, but clinically, it is observed in a small proportion of patients. A similar condition, prolonged withdrawal, has been described in the literature and defined as opioid withdrawal symptoms that persisted until or past Day 2 of treatment (Lee, Grossman, DiRocco, & Gourevitch, 2009). Patients experiencing protracted withdrawal typically necessitate additional time and intervention from providers, thus complicating the induction process.

We are not aware of any studies that have specifically focused on complications during induction. Examining factors associated with complicated inductions can assist providers to identify appropriate candidates for buprenorphine treatment, allow providers to better prevent and manage complicated inductions, and suggest revisions to current buprenorphine treatment guidelines. Furthermore, improving understanding of the induction process may encourage more widespread adoption of buprenorphine treatment, which might address the problematic unmet treatment need for individuals with opioid addiction. Thus, we evaluated the induction process of the first 107 people who initiated buprenorphine treatment at an inner-city community health center.

2. Materials and methods

2.1. Setting

This analysis included all patients who initiated buprenorphine treatment from 2005 to 2008 in a South Bronx community health center. The buprenorphine treatment program, which has been described in detail previously (Cunningham et al., 2008), provides treatment with buprenorphine/naloxone for opioid dependence in the context of general primary care within a South Bronx community that has been devastated by drug use (Olson, Van Wye, Kerker, Thorpe, & Frieden, 2006).

2.2. Patients

In accordance with national guidelines (CSAT, 2004), five general internists in collaboration with a clinical pharmacist provide buprenorphine treatment to patients requesting opioid addiction treatment if they meet the following clinical eligibility criteria: (a) at least 18 years of age; (b) opioid dependence per *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria (American Psychiatric Association [APA], 2000); and (c) insured by a health plan accepted at the health center or ability to pay for treatment on a sliding scale fee. (Typically, uninsured patients paid $25 per visit, including laboratory and radiology tests, and $5 per month for buprenorphine prescriptions.) Patients are not considered for buprenorphine treatment at the health center if they are (a) hypersensitive to buprenorphine or naloxone; (b) pregnant; (c) alcohol-dependent by *DSM-IV* criteria (APA, 2000); (d) benzodiazepine-dependent by *DSM-IV* criteria (APA, 2000); (e) found to have serum aspartate aminotransferase or alanine aminotransferase levels greater than five times normal; (f) diagnosed with severe, untreated psychiatric illness; or (g) taking more than 60 mg of methadone daily during the past month. The Albert Einstein College of Medicine Committee on Clinical Investigations and Montefiore Medical Center reviewed and granted this investigation exempt status; informed consent was not required.

2.3. Buprenorphine induction procedures

Prior to induction, all patients were informed about the buprenorphine treatment program, and interested patients were screened for clinical eligibility as described above. For the first 2 years of the program, all clinically eligible patients underwent office-based inductions. For the second 2 years, eligible patients were offered home-based inductions or office-based inductions. The decision about induction type was made through mutual agreements between the patients and their providers.

All patients receiving buprenorphine treatment had a preparatory visit to plan the induction process. Those induced in the office were scheduled to return to the office in opioid withdrawal and were assessed using the Clinical Opiate Withdrawal Scale (COWS; Wesson & Ling, 2003) to ensure adequate opioid withdrawal. Those in mild to moderate withdrawal, generally a COWS score of 10 or greater, were administered buprenorphine/naloxone, observed for several hours, and administered additional doses of buprenorphine/naloxone if necessary. Patients were dosed with adjunctive medications (e.g., ibuprofen, clonidine, and/or loperamide hydrochloride) per clinical judgment. Patients who underwent home-based inductions received a home-induction kit, which included buprenorphine/naloxone, adjunctive medications mentioned above, and an instruction sheet with information about when and how to initiate buprenorphine treatment. It was expected that they would initiate treatment on their own, contacting providers at the health center if needed. Details about both types of inductions have been published previously (Sohler et al., 2009).

Patients were generally scheduled for a follow-up visit within 7 days of initiating the induction process. During this visit, providers adjusted the buprenorphine/naloxone dose as needed and reviewed patients' induction course, which included collecting details about the timing and amount of buprenorphine/naloxone taken, the use of adjunctive medications, and response to medications.

2.4. Data collection

One provider extracted data from patients' medical records. A detailed drug use history was documented for every patient in the buprenorphine treatment program using standardized clinical forms. If patients had more than one induction, only the first induction was included in this analysis.

We extracted data on patient characteristics, including age (continuous), gender (male vs. female), race/ethnicity (Hispanic, non-Hispanic Black, and non-Hispanic White), employment (employed vs. unemployed), insurance status (public, private, and none), substance use in the 30 days prior to evaluation (including any vs. no use of heroin, prescribed and nonprescribed methadone, prescribed and nonprescribed opioid analgesics, cocaine, benzodiazepines, and alcohol), history of injection drug use (ever vs. never), history of prior methadone treatment (ever vs. never), and prior experience with buprenorphine (including any buprenorphine, prescribed buprenorphine, and nonprescribed buprenorphine). We also extracted data on treatment characteristics, including date of induction (categorized in quartiles), location of induction (office- vs. home-based), initial dose of buprenorphine/naloxone (2 vs. >2 mg), use of adjunctive medications (any vs. none), and retention in treatment at 30 days (continuing to take buprenorphine/naloxone and at least one visit 30 days or more after the induction date vs. not continuing to take buprenorphine and/or no visits beyond 30 days).

We conducted a rigorous process for extracting charts and reviewing data on the course of induction to determine whether patients experienced “complicated” versus “routine” inductions. Complicated inductions were defined as inductions in which patients experienced precipitated or protracted withdrawal. Precipitated withdrawal was defined as acute worsening of opioid withdrawal symptoms immediately following the initial dose of

buprenorphine. Protracted withdrawal was defined as opioid withdrawal symptoms persisting greater than 24 hours after the initial dose of buprenorphine. All other inductions were coded as “routine.”

To classify inductions as precipitated, protracted, or routine, a member of our clinical research team reviewed each chart extraction form and presented information relevant to the induction outcome to at least three experienced buprenorphine providers on our team. Team members discussed the case and reached a consensus decision about the appropriate induction classification. In eight cases, there were insufficient data for the team to classify the induction, and these cases were not included in the analyses.

2.5. Analysis

We conducted bivariate analyses to identify patient and treatment factors that were associated with complicated induction using Fisher exact tests.

3. Results

Of 107 patients who initiated buprenorphine treatment during the study period, the mean age was 45 years. Most were male (75.7%), Hispanic (66.4%), unemployed (66.4%), and insured by Medicaid (76.6%; Table 1). In the 30-day period prior to induction, the most common opioid of abuse was heroin (68.2%). Other opioids commonly used included nonprescribed methadone (30.8%), prescribed methadone (29.9%), prescribed opioid analgesics (16.8%), and nonprescribed opioid analgesics (11.2%). Alcohol (40.8%), cocaine (38.3%), and benzodiazepines (14.7%) use were common in the 30 days prior to induction, along with a history of injection drug use (60.0%). Many patients reported prior experience with buprenorphine either prescribed or obtained illicitly (27.1%) or with methadone treatment (72.0%).

Of the 107 inductions, 60 (56.1%) were office-based and 47 (43.9%) were home-based. Most patients received an initial buprenorphine/naloxone dose of 2/0.5 mg. Of the 18 (16.8%) complicated inductions, 10 (55.6%) experienced precipitated withdrawal, 8 (44.4%) protracted withdrawal. One patient experienced both precipitated and protracted withdrawal and was included in both groups for analysis.

Of the 10 patients who experienced precipitated withdrawal, 9 reported taking methadone (prescribed or nonprescribed) prior to initiating buprenorphine treatment. The most common symptom experienced during precipitated withdrawal was worsening anxiety (reported by 7 patients). Two patients initially misrepresented their current substance use, which significantly contributed to their complicated clinical course. Of the 9 patients who experienced protracted withdrawal, 7 reported taking methadone prior to initiating buprenorphine treatment. Prolonged withdrawal symptoms remained problematic for patients for 2–28 days after the initial buprenorphine dose.

When precipitated or protracted withdrawal occurred, physicians tended to increase the dose of buprenorphine fairly rapidly within the first 24–48 hours and prescribe ancillary medications such as clonidine, loperamide hydrochloride, or ibuprofen. Despite this, 6 of the

10 patients who experienced precipitated withdrawal discontinued treatment shortly thereafter. However, only 3 of the 9 patients experiencing protracted withdrawal discontinued treatment prior to 30 days. Most of the patients who experienced precipitated or protracted withdrawal and were not retained in treatment at 30 days dropped out of treatment within the first 3 days.

Compared with patients who experienced routine inductions, patients who experienced complicated inductions were more likely to report using prescribed methadone (61.1% vs. 23.6%, $p < .01$) or benzodiazepines (47.1% vs. 8.2%, $p < .001$) in the 30 days before induction, have had a low initial dose of buprenorphine/naloxone (2/0.5 mg; 94.4% vs. 67.1%, $p < .05$), and be in the first or second quartile of all inductions in the buprenorphine treatment program (trend test for quartiles, $p < .05$). Patients who experienced complicated inductions were also less likely to have a history of prior buprenorphine use (prescribed or nonprescribed; 0% vs. 32.6%, $p < .005$) compared with patients experiencing routine inductions. Finally, complicated inductions were associated with lower 30-day treatment retention than routine inductions (55.6% vs. 87.6%, $p < .01$).

4. Discussion

In this study of buprenorphine inductions in an urban community health center among primarily Hispanic men, 16.8% of patients experienced complicated inductions. Complicated inductions were significantly associated with treatment outcomes, as patients with complicated inductions had lower 30-day retention rates than those with routine inductions. Both patient characteristics and treatment characteristics were associated with difficult inductions. Specifically, patient characteristics associated with complicated inductions included recent use of prescribed methadone, recent benzodiazepine use, and no prior history of buprenorphine use. Treatment characteristics associated with complicated inductions included a low initial dose of buprenorphine/naloxone.

Not surprisingly, our study found that patients who experienced complicated inductions had poorer treatment outcomes when compared to those who had routine inductions. The induction phase, which can be difficult for providers and patients (Walley et al., 2008), is clearly a critical element in buprenorphine treatment. Although we are not aware of other studies that have specifically examined the role of complicated inductions and treatment outcomes, other studies have demonstrated significant dropout early in buprenorphine treatment during the induction period (Lee et al., 2009; O'Connor et al., 1998). It may be that early treatment failures are frequently associated with complicated induction; prospective research on factors associated with early treatment failures is needed. As it becomes clear that buprenorphine inductions play a key role in the successful treatment of opioid addiction, it is important to develop new strategies to improve induction outcomes and eliminate or reduce complicated inductions.

Although the prevalence of complicated inductions was nearly 17%, this decreased over time. The prevalence of complication induction was 38.9% during both the first and second quartiles, dropping to 16.7% in the third quartile and 5.6% in the fourth quartile. The substantial change over time suggests that as providers became more experienced in

buprenorphine inductions, complications decreased. It is also possible that patient characteristics evolved over time. For example, over time, more patients entering treatment reported having prior buprenorphine experience (data not shown). Providers with minimal buprenorphine treatment experience can benefit from mentorship or consultation with experienced buprenorphine treatment providers. Access to such mentorship is available through the federally funded Physician Clinical Support System for Buprenorphine (PCSSmentor.org).

This study identified specific substance use patterns that were associated with complicated inductions, which might help guide transitions to buprenorphine treatment. Patients in our study who used prescribed methadone were more likely to experience complicated inductions than patients using other opioids. This is consistent with treatment guidelines warning that the recent use of long-acting opioids, such as methadone, increases the risk of precipitated withdrawal (CSAT, 2004). We did not collect information about whether patients' prescribed methadone was for the purpose of pain management or opioid addiction treatment. However, from our clinical experience, most patients who were taking prescribed methadone during the time they presented for buprenorphine treatment were receiving methadone from opioid addiction treatment programs. Recent methadone treatment may increase the risk of experiencing complicated inductions because, in addition to being a long-acting opioid, the psychological effects of disrupting methadone treatment may make the transition from methadone to buprenorphine treatment more difficult.

Assessment of secondary drug use is recommended for all patients entering buprenorphine treatment, with specific concerns about overdose risk with simultaneous use of benzodiazepines and buprenorphine (CSAT, 2004; Reynaud, Petit, Potard, & Courty, 1998). Consistent with treatment guidelines (CSAT, 2004), patients who were dependent on benzodiazepines (per *DSM-IV* criteria) were excluded from receiving buprenorphine treatment at the health center. However, patients who used benzodiazepines and were not dependent did receive buprenorphine treatment. In this study, self-reported benzodiazepine use was associated with complicated inductions. Possible explanations for this include drug-specific effects, higher rates of psychiatric comorbidity, and/or cognitive dysfunction in patients using benzodiazepines. Benzodiazepine use has been correlated with higher rates of anxiety and depression in a population of buprenorphine maintained patients (Lavie, Fatseas, Denis, & Auriacombe, 2009). Impairment of memory and concentration are known adverse effects of benzodiazepine use (Moller, 1999). Further, exploration into complications associated with simultaneous benzodiazepine and buprenorphine use are warranted.

There were also treatment-related factors associated with experiencing a complicated induction. Patients who received a low initial dose of buprenorphine/naloxone (2/0.5 mg) were more likely to experience complicated inductions than those who received higher initial doses. This finding was unexpected, as treatment guidelines and literature suggest that a lower initial dose of buprenorphine reduces the risk of precipitated withdrawal (CSAT, 2004; Rosado, Walsh, Bigelow, & Strain, 2007). There are a few potential explanations for this paradoxical finding. Among those with low initial doses and complicated inductions, equal numbers of precipitated and protracted withdrawal were observed. First, providers may have predicted patients at high risk of precipitated withdrawal (e.g., patients on

methadone) and dosed more cautiously in this subgroup. Alternatively, prescribing low doses of buprenorphine/naloxone may reflect insufficient buprenorphine dosing during induction, which may result in increased risk of protracted withdrawal. As buprenorphine treatment becomes more widely implemented in various settings, it is important to closely follow whether initial buprenorphine doses are associated with complications during induction.

Patients with prior buprenorphine experience were less likely to experience complicated inductions. In fact, no patient who had prior buprenorphine use experienced either protracted or precipitated withdrawal during buprenorphine inductions. This likely reflects familiarity with the medication and increased knowledge about the risk of precipitated withdrawal. In addition, patients and providers may be more comfortable with rapid dose escalation resulting in quicker relief of withdrawal symptoms as compared to buprenorphine-naive patients, reducing the risk of protracted withdrawal. Interestingly, the absence of complicated inductions was observed in patients who used both prescribed and nonprescribed buprenorphine. We believe that as more patients are buprenorphine experienced, there will be fewer complicated inductions.

There are a number of limitations of this study. The sample size was modest; thus, we may have had insufficient power to detect other factors associated with complicated inductions. Our data were based on reviews of medical records of routine clinical care, rather than prospective data collected for the purpose of research, limiting the factors that we could examine. For example, information regarding dosing patterns was missing from many charts, especially in patients who had home-based inductions, limiting our ability to examine these factors in detail. In addition, our retrospective study design would not allow us to fully describe the range of potential adverse events associated with buprenorphine treatment (e.g., other than protracted or precipitated withdrawal). Future research should include these details and provide data regarding patients' comorbid medical and psychiatric illnesses and social context that are not consistently available in routine medical records. Finally, findings from this inner-city community health center with primarily male Hispanic patients may not be generalizeable to a larger population of opioid-dependent patients in other health centers or other cities.

Despite these limitations, this study found that 16.8% of buprenorphine inductions were complicated, but complications occurred less frequently as both providers and patients gained experience with buprenorphine treatment. Complicated inductions were associated with important treatment outcomes, specifically lower treatment retention than routine inductions. Both patient characteristics (recent use of prescribed methadone, recent benzodiazepine use, and no prior buprenorphine experience) and treatment characteristics (low initial dose of buprenorphine/naloxone) were associated with complicated inductions. These findings suggest that some patients may benefit from closer monitoring and/or consultation with a more experienced buprenorphine treatment provider to prevent complicated inductions. As further research examines buprenorphine inductions, treatment guidelines should incorporate guidance about assessment of risk for and prevention of complicated inductions.

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Table 1

Patient and treatment characteristics associated with complicated buprenorphine inductions

Characteristics	Total (*n* = 107)	Complicated induction		*P*
		No (*n* = 89)	Yes (*n* = 18)	
Patient characteristics				
Age (mean ± SD)	44.9 ± 8.7	44.7 ± 9.2	46.4 ± 5.5	.29
Male	81 (75.7)	68 (76.4)	13 (72.2)	.76
Race/Ethnicity				
Black	24 (22.4)	21 (23.6)	3 (16.7)	
Hispanic	71 (66.4)	58 (65.2)	13 (72.2)	.92
Other	12 (11.2)	10 (11.2)	2 (11.1)	
Employed	36 (33.6)	29 (32.6)	7 (38.9)	.60
Have Medicaid	82 (76.6)	68 (76.4)	14 (77.8)	1.00
Substance use within 30 days				
Opioids				
Heroin	73 (68.2)	64 (71.9)	9 (50.0)	.07
Methadone, prescribed	32 (29.9)	21 (23.6)	11 (61.1)	<.01
Methadone, nonprescribed	33 (30.8)	29 (32.6)	4 (22.2)	.39
Opioid analgesic, prescribed	18 (16.8)	12 (13.5)	6 (33.3)	.08
Opioid analgesic, nonprescribed	12 (11.2)	9 (10.1)	3 (16.7)	.42
Alcohol	42 (40.8)	38 (44.2)	4 (23.5)	.11
Crack/Cocaine	41 (38.3)	36 (40.5)	5 (27.8)	.31
Benzodiazepines	15 (14.7)	7 (8.2)	8 (47.1)	<001
Ever injected drugs	63 (60.0)	54 (61.4)	9 (52.9)	.52
Ever took buprenorphine	29 (27.1)	29 (32.6)	0	.003
Ever took prescribed buprenorphine	10 (9.4)	10 (11.4)	0	.03
Ever took street buprenorphine	23 (21.5)	23 (25.8)	0	.02
Ever in methadone treatment	77 (72.0)	62 (69.7)	15 (83.3)	.239
Treatment characteristics				
Induction date relative to program development				
First quartile		19 (21.3)	7 (38.9)	
Second quartile		20 (22.5)	7 (38.9)	
Third quartile		25 (28.1)	3 (16.7)	.01[a]
Fourth quartile		25 (28.1)	1 (5.6)	
Home induction	47 (43.9)	39 (43.8)	8 (44.4)	.96
Low first buprenorphine/naloxone dose (2 mg)	70 (72.2)	53 (67.1)	17 (94.4)	.02
Total Day 1 buprenorphine/naloxone dose >8 mg	43 (45.7)	34 (44.2)	9 (52.9)	.51
Any adjunctive medication	25 (23.4)	18 (20.2)	7 (38.9)	.12
Retained in treatment at 30 days	88 (82.2)	78 (87.6)	10 (55.6)	.001

Note. All percentages denote column percentages. Missing data are as follows: 4 for alcohol use, 5 for benzodiazepine use, 2 for ever injected drugs, 10 for first buprenorphine/naloxone dose, and 13 for total day 1 buprenorphine/naloxone dose.

[a] Trend test.