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CASE SERIES: LIMITED OPIOID WITHDRAWAL WITH USE OF TRANSDERMAL BUPRENORPHINE TO BRIDGE TO SUBLINGUAL BUPRENORPHINE IN HOSPITALIZED PATIENTS

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Abstract

Background—Prerequisite opioid withdrawal symptoms prior to buprenorphine induction are unacceptable to many patients. We assessed whether transdermal buprenorphine minimized withdrawal while bridging to sublingual therapy among hospital inpatients.

Methods—Retrospective chart review of (n = 23) inpatients with opioid use disorder or opioid dependence due to chronic pain.

Results—Of 23 inpatients, 65% transitioned without symptoms, while 35% experienced mild withdrawal. Ninety-six percent completed planned hospitalizations, with 83% engaged in treatment 4 weeks post-discharge.

Discussion and Conclusions—Bridging to sublingual therapy with transdermal buprenorphine patches was feasible without withdrawal symptoms.

Scientific Significance—This strategy may facilitate buprenorphine therapy in hospital inpatients.

INTRODUCTION

Leaving hospital against medical advice (AMA) is common in patients with untreated opioid use disorders (OUD) or opioid dependence due to chronic pain.¹ Inpatient management of substance use disorders contributes to hospitalization retention and reduces addiction

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Declaration of Interest

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

severity.² When patients with OUD are admitted to hospital for medical, surgical, or psychiatric reasons, this presents an opportunity to engage patients and offer opioid agonist therapy (OAT).³ Inpatient OAT initiation with buprenorphine or methadone leads to entry into maintenance therapy⁴ and reduces hospital discharges AMA and readmissions.⁵

Standard induction of sublingual buprenorphine requires at least moderate opioid withdrawal symptoms, which is unacceptable to many patients (particularly those with chronic pain)⁶ and is associated with high rates of discontinuation in the first week of treatment.^{7, 8} Complicated inductions with precipitated or prolonged withdrawal⁹ contribute to reluctance toward buprenorphine by patients and clinicians.¹⁰

With ongoing barriers to buprenorphine induction, novel strategies are needed. One proposed method is initiating with much lower “microdoses” of sublingual buprenorphine, allowing for less precipitated withdrawal and a more tolerable transition to therapeutic doses of sublingual buprenorphine.^{11, 12} Low doses of buprenorphine are also available in transdermal formulations, which offer an alternative method to gradually introduce “microdosing” levels of buprenorphine before titrating to therapeutic dosages of sublingual buprenorphine.

Initiation protocols using transdermal buprenorphine to bridge to sublingual therapy have been successfully reported among outpatients.^{13, 14} However, according to the Drug Addiction Treatment Act of 2000 (DATA 2000) it is currently illegal to use transdermal buprenorphine in the outpatient treatment of OUD. Any opioid can be used to treat withdrawal in patients hospitalized for other reasons, and so this approach could be viable in hospital settings. In Canada, no legal restrictions exist on the transdermal buprenorphine patch.

We present a case series of 23 hospital inpatients who were bridged to sublingual buprenorphine therapy with transdermal buprenorphine “microdosing”. The purpose of this study was to evaluate the feasibility of this approach in hospitalized inpatients, particularly whether it minimized withdrawal symptoms during induction. We hypothesized that transdermal buprenorphine was associated with limited withdrawal prior to initiation of sublingual buprenorphine, hospital retention, and post-discharge OAT retention. As a secondary objective, we were also interested in whether there were differences between patients with OUD and those with opioid dependence associated with chronic pain.

METHODS

Setting and Sample

We performed a retrospective chart review in a sample of inpatients treated from January 1, 2015 to December 29, 2016 at an academic medical center. We identified potential cases via hospital pharmacy records of all patients dispensed transdermal buprenorphine. Inclusion criteria included (1) inpatient admission for a primary medical, surgical or psychiatric indication, (2) assessment by the Inpatient Addiction Medicine Consultation Service, (3) confirmed diagnosis of current OUD or opioid dependence related to chronic pain by the assessing physician, and (4) dispensed transdermal buprenorphine as a method of

transitioning patients to sublingual buprenorphine therapy. The study was approved by the Research Ethics Board of the Toronto Academic Health Sciences Network.

Transdermal Buprenorphine Bridging Protocol

Short-acting opioid agonists were discontinued, approximately 12 hours prior to patch initiation. We applied transdermal buprenorphine 5 or 20 mcg/h patch for at least 12 hours (up to 24–48 hours on average; buprenorphine 0.24–0.48 mg daily) prior to sublingual buprenorphine initiation. The duration of continuing transdermal buprenorphine treatment prior was based on the clinical judgment, with some patients having an overlapping period with both transdermal and sublingual buprenorphine therapy. Sublingual buprenorphine was initiated at 2 to 4 mg, based on opioid tolerance, followed by a rapid up-titration of 2 to 4 mg increments until there was a stable resolution of any opioid withdrawal symptoms. For our patients, the titration period was between 2 and 6 days. There were no pre-determined target dose ranges or maximum daily dosages for sublingual buprenorphine. Patients who were on methadone were rotated to short-acting morphine prior to transdermal buprenorphine application.

CASE DESCRIPTIONS

Two investigators reviewed each chart and collected information in a standardized data collection form. Variables collected included: demographics, opioid use history, confirmed OUD or opioid dependence diagnosis, pre-hospital and in-hospital opioid use in morphine equivalent daily dose (MEDD), addiction treatment history, a dose of transdermal and subsequent sublingual buprenorphine, discharge prescription, and outpatient addiction follow-up post-discharge. Disagreements between data abstractors were resolved by consensus. Outcome measures included symptoms during the transition, hospitalization retention for primary treatment (defined as discharge recommendation by the most responsible physician), discharge prescription for sublingual buprenorphine, and treatment retention in outpatient addiction medicine services at 4 weeks post-discharge.

Baseline prescribed pre-hospital and in-hospital opioid use was calculated using an oral opioid analgesic conversion table¹⁵ and a methadone-to-morphine conversion ratio of 1:4.7;^{16, 17} illicit opioid use was not included as it could not reliably be quantified. Clinical Opioid Withdrawal Scale (COWS) scores were available for nine patients. Information on the outcome measures of interest was derived from physician and nursing notes from the chart.

Analysis

We performed statistical comparisons between patients with OUD and those with opioid dependence related to chronic pain using χ^2 test for categorical variables and T test or Mann-Whitney U test for normally and nonnormally distributed continuous variables, respectively. Statistical power was not predetermined. Statistical significance was set as P .05.

RESULTS

The OUD and chronic pain groups were similar, except for higher rates of the previous OAT in the OUD group (Table 1). Nineteen patients (83%) were bridged with buprenorphine 20 mcg/h patch and four patients (17%) with 5 mcg/h patch. Twenty patients (87%) were initiated on sublingual buprenorphine within 12 to 48 hours of patch application. One patient declined initiation due to skin irritation. Transdermal buprenorphine patch initiation occurred at various points in the hospitalization due to variability in their primary treatment course and time to obtain informed consent.

Fifteen patients (65%) tolerated the transition without significant symptoms (Table 2). Five of eight patients (35%) that experienced mild and tolerable withdrawal symptoms were on high-dose opioid therapy pre-hospitalization. Of the three remaining patients, two had suboptimally treated primary psychiatric diagnoses and one cited skin irritation. Three of the eight mildly symptomatic patients were not discharged on sublingual therapy. All patients, except one who left AMA, completed their full intended hospitalization. COWS scores of nine patients revealed no appreciable worsening in COWS score during the transition. COWS scores were available at variable time points depending on the patient. Average (mean $\pm$ standard deviation) COWS scores in 24 hours prior to patch application was 7.0 ± 4.8 ($n = 4$), 24 hours after patch application was 8.9 ± 3.7 ($n = 6$), and 24–48 hours after patch application was 5.1 ± 5.0 ($n = 5$).

Seventeen patients were discharged on sublingual buprenorphine (mean dose 11.9 mg). Of six patients not discharged on buprenorphine, two switched to methadone due to uncontrolled opioid withdrawal despite buprenorphine titration, one left AMA, one declined initiation due to patch irritation, one patient expired, and for one information was unavailable. Five patients were lost to follow-up or referred back to addictions physicians not part of our institution and one patient was not continued on therapy due to medical comorbidities; these patients were not included in the outcome analysis. Twelve of 13 (92%) patients attended our institution's outpatient addictions services and 10 (83%) were still on therapy after 4 weeks.

DISCUSSION

In our series of 23 hospital inpatients initiating sublingual buprenorphine therapy, the use of transdermal buprenorphine as a “microdosing” bridge was feasible and associated with limited withdrawal symptoms. This clinical protocol can be used to decrease barriers to buprenorphine OAT in hospital inpatients. We did not find any significant differences in outcomes between OUD and opioid dependence related to chronic pain.

Two case series report using transdermal buprenorphine to transition outpatients to sublingual buprenorphine without significant withdrawal symptoms. Hess et al. transitioned eleven patients with OUD on methadone.¹³ A 35 μ g/h buprenorphine patch was applied 12 hours after the last methadone dose for 96 hours. At 24 and 48 hours, mild withdrawal symptoms were observed but did not require treatment. Kornfeld and Reetz¹⁴ demonstrated similar findings during opioid rotation with transdermal buprenorphine in three outpatients

with chronic pain. Our patients' mean in-hospital opioid use (230.3 MEDD) is comparable with prior transdermal buprenorphine induction studies.^{13, 14}

Our study had a relatively small sample size and lacked a comparator standard induction group; however, the sample size was more than double that of previous studies on transdermal buprenorphine transitions. There was also variability in the protocol (patch strength, duration of application) and underestimation of opioid use (primarily due to illicit use), which both reflect real-world practice. Furthermore, OUD and chronic pain groups were separated based on preferred diagnosis by the addiction medicine physician, however, there remains no standard method of diagnosing opioid addiction in chronic pain.¹⁸ Other limitations included our lack of data on illicit drug use prior to initiation of this protocol and data on the length of stay of the intended hospitalizations, which varied between patients and could have influenced the outcomes for some of our patients.

Our data support prior buprenorphine “microdosing” induction protocol studies^{11, 12} and qualitative research on patient acceptability.⁶ “Microdosing” buprenorphine approaches appear to reduce risks of precipitated withdrawal and eliminate the prerequisite moderate withdrawal symptoms prior to initiating sublingual therapy; this may increase the acceptability of buprenorphine OAT. Transdermal formulations may have an added benefit of convenience and ease of use and may more gradually saturate the unoccupied mu-opioid receptors and slowly displace occupied mu-opioid receptors.

In conclusion, transdermal buprenorphine for hospital inpatients prior to sublingual buprenorphine was generally well-tolerated and associated with limited opioid withdrawal symptoms, even in patients on high-dose opioid therapy. This may have contributed to inpatient retention and outpatient follow-up. Further research into the use of transdermal buprenorphine may improve the treatment outcomes with OAT in patients with OUD and chronic pain.

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Table 1.

Baseline Characteristics

	CP and OUD N = 23	CP N = 9	OD N = 14	P value*
Age (mean years $\pm$ standard deviation)	51.2 $\pm$ 11.6	47.8 $\pm$ 12.7	53.9 $\pm$ 11.4	.2
Male	12 (52%)	4 (44%)	8 (57%)	.5
Previous OAT	12 (61%)	2 (22%)	10 (71%)	.02
Duration of opioid use (years)	11.7 ^a	7.2	14	.8
Mean pre-hospitalization opioid use (MEDD)	263.2 ^b	379.4	168	.5
Mean in-hospital opioid use (MEDD)	230.3 ^b	325.7	152.2	.6

CP = chronic pain; MEDD = Morphine Equivalent Daily Dose; OD = Opioid Use Disorder; OAT = Opioid Agonist Therapy.

^aExcluded eight unknown duration (4 CP, 4 OD).

^bExcluded three illicit heroin users, with unknown average daily doses (OD).

* P value refers to the results of χ^2 test, T test, or Mann-Whitney U test performed between OD and CP groups. Statistical significance was set at P .05.

Table 2.

Treatment Outcomes

	CP and OUD N = 23	CP N = 9	OD N = 14	P value [*]
Symptoms experienced during transition	8 (35%) ^a	3 (33%)	5 (36%)	0.9
Hospitalization retention	22 (96%)	9 (100%)	13 (93%)	0.4
Patients who left against medical advice	1 (4%)	0 (0%)	1 (7%)	
	N = 21 ^b	N = 8	N = 13	
Discharged on sublingual buprenorphine	17 (81%)	6 (75%)	11 (85%)	0.6
Mean discharge sublingual buprenorphine dose (mg/day)	11.9	11.7	13.1	1.0
	N = 13 ^c	N = 6	N = 7	
Outpatient addiction treatment within 4 weeks	12 (92%)	5 (83%)	7 (100%)	0.3
	N = 12 ^d	N = 6	N = 6	
Sublingual buprenorphine treatment in 4 weeks	10 (83%)	5 (83%)	5 (83%)	1.0

CP = chronic pain, OD = Opioid Use Disorder.

^aTwo patients had suboptimally treated psychiatric disorders (1 CP, 1 OD), one patient had concurrent alcohol withdrawal (OD), one patient had skin irritation (CP)

^bExcluded one patient missing information (OD) and one expired (CP); four patients not discharged on sublingual buprenorphine (2 CP, 2 OD)

^cExcluded five patients lost to follow-up (OD); five patients not discharged on sublingual buprenorphine (2 CP, 2 OD, 1 expired).

^dExcluded six patients lost to follow-up (OD); five patients not discharged on sublingual buprenorphine (2 CP, 2 OD, 1 expired).

^{*} P value refers to the results of χ^2 test, T test or Mann-Whitney U test performed between OD and CP groups. Statistical significance was set at P .05.