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Buprenorphine – Induced Urinary Hesitancy is Common and Managed with Ease: A Retrospective Chart Review

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Abstract

Buprenorphine is a partial agonist at the mu opioid receptor. As compared to methadone, it has the advantage of being used in office based treatment setting, making this a preferred treatment option for opioid dependence. While opioid-induced urinary retention and hesitancy are well known, urinary hesitancy in patients who receive buprenorphine treatment may go unrecognized and untreated.

Objectives: The current study is a retrospective chart review of 104 charts of patients with a diagnosis of opioid dependence who received buprenorphine/naloxone treatment to examine the incidence of urinary hesitancy and identify the relationship of symptoms, if any, with the dose and duration of treatment and other patient and treatment factors.

Results: Forty-five percent of patients reported no side effects, while 26% of the subjects reported urinary hesitancy symptoms at some point in treatment. Urinary symptoms were reported as early as one day and predominantly in the first 2 weeks after initiation of bup/nlx treatment.

Conclusion: Urinary hesitancy occurs with buprenorphine is often under reported and may go untreated. It may lead to significant discomfort and could possibly interfere with patient compliance to buprenorphine treatment. In most cases the symptoms are mild and transient and can easily be treated with increased fluid intake and use of bethanechol, a cholinergic drug that has long been used for non-obstructive urinary hesitancy or retention, at low doses. Education of providers and patients regarding this early and transient side effect is likely to enhance compliance and lower risk of relapse in this highly vulnerable population.

Keywords: Analgesics; Opioid bethanechol; Buprenorphine; Cholinergic agents; Patient compliance; Receptors; Opioid; Urinary retention

Introduction

Opioid dependence is a chronic relapsing disorder that profoundly impacts the lives of those afflicted. Recently the Center for Disease Control declared that the United States was in midst of an opioid epidemic with an estimated 2.0 million adults in the Unites States who are opioid dependent and an estimated 30,000 deaths annually related to overdose of prescription pain medications and heroin combined [1]. Opioid maintenance is the most effective way to decrease illicit drug use in this population per Department of Veterans Affairs Veterans Health Administration [2]. Methadone has been the treatment of choice in the United States since the 1970s. The Drug Addiction Treatment Act 2000 enabled physicians to provide office based treatment of opioid addiction. Buprenorphine, a partial-agonist at the mu opioid receptor, was approved by Food and Drug Administration in 2002 for treatment of opioid dependence.

After the 2008 National mandate for provision of Opioid Agonist Treatment at all Veteran Affairs (VA) facilities [2]. Buprenorphine has been increasingly used for treatment of opioid dependence in the veteran population. Buprenorphine is preferred by patients and facilities because it can be administered in office based settings, as compared to methadone which can be given only in licensed clinical settings of an opioid treatment program [3].

Urinary hesitancy is a known side effect of opioids because of the receptor binding profile. The postulated mechanism of opioid-induced urinary retention is decreased parasympathetic activity of nerves, which innervate the bladder and the increased sympathetic tone may also have a role in increasing sphincter tonicity [4]. Agonism at the mu opioid receptor leads the detrusor and urinary sphincter muscle to contract [5]. This action is more robust when opioids are given parenterally.

In a self-reported study of heroin addicts 40% of the subjects reported urination problems on methadone maintenance which was lower than 55% that was reported during heroin use [6]. In a Swedish study urination problems were found in 25.4% during the previous week of methadone treatment [7]. It would be reasonable to think that

buprenorphine could have similar effect, considering that buprenorphine is a partial mu agonist. Urinary retention has been reported to have occurred in less than 1% of the patients who used buprenorphine and milder symptoms of hesitancy are often not mentioned in clinical trials [8]. Our group has previously reported a case series noting urinary hesitancy symptoms in male veterans maintained on buprenorphine/naloxone for opioid dependence [9].

The aim of this retrospective study was to review the Computerized Electronic Medical Records to examine the prevalence of urinary hesitancy and other symptoms in veterans being treated with buprenorphine/naloxone (bup/nlx) for maintenance treatment of opioid dependence and explore the relationship between these symptoms and various patient and treatment factors.

Methods

This study was approved by the Institutional Review Board committee and Research and Development committee of the Veterans Affairs Medical Center, Salem, VA. A review of medical records of all outpatients with a diagnosis of opioid dependence who have received treatment with buprenorphine between September 2009 to March 2012 was conducted by the Principal Investigator and 2 sub-investigators using a standardized structured data collection sheet to ensure uniformity in data collection.

Inclusion criteria: Charts of subjects included in the study met Diagnostic and Statistical Manual IV (DSM IV) criteria for opioid dependence and were treated with bup/nlx combination product as an outpatient in an office based setting of a Veterans Affairs Medical Center and received at least one follow up.

Exclusion criteria: Charts of subjects who were evaluated in the buprenorphine outpatient clinic but were considered unfit for office based treatment due to concomitant use of benzodiazepines, being suicidal or actively psychotic and hence did not receive a single dose of buprenorphine/naloxone were excluded from the study.

Charts of subjects who failed to follow up after first dose treatment were also excluded from this chart review.

Charts were reviewed for side effect checklist in the medical record which the clinicians complete at the time of each visit. The checklist is in the form of review of systems with specific items to inquire about common opioid side effects such as headaches, sedation, constipation, urinary symptoms, sexual side effects, dryness of mouth and others.

Charts of patients who were evaluated in the buprenorphine clinic but did not receive treatment with bup/nlx due to reasons such as acute safety concerns, acute psychosis, current prescription for benzodiazepines or patients who declined treatment were excluded from this study. Of the 117 charts reviewed, 104 met inclusion criteria for the study.

Data analysis

We used log-rank test to compare the distribution of age between those who did and did not develop urinary hesitancy because it was not normally distributed. Additionally we used chi–square and fisher exact tests as appropriate to compare categorical variables between individuals who did and did not develop urinary hesitancy. An alpha of 0.05 was considered significant. We used STATA 11.2 (College Station, Texas) to conduct statistical analysis.

Results

Table 1 shows the sociodemographic profile, pattern of drug use, onset and nature of side effects that emerged as a result of from the treatment with bup/nlx and concomitant medications as well as medical and psychiatric comorbidity. We did not note any statistical difference in the sociodemographic profile between the subjects who reported urinary symptoms and those who did not. Forty-five percent of patients reported no side effects, while 26% of the subjects reported urinary hesitancy symptoms at some point in treatment. Urinary symptoms were reported as early as one day and predominantly in the first 2 weeks after initiation of bup/nlx treatment.

	All Patients (N=104)	Urinary Hesitancy (N=27)	No Urinary Hesitancy (N=77)	p-value
Characteristic				
Age (median, IQR)	38.5 (30-50.5)	38 (30-50)	39 (30-52)	0.76
Male	93%	93%	93%	0.47
>High school education	36%	22%	40%	0.084
Living situation				
Alone	29%	41%	25%	0.3
With partner	48%	41%	51%	-
With parents	22%	19%	23%	-
Marital status				
Single	25%	19%	27%	0.39
Married	39%	37%	40%	-

Divorced	34%	44%	30%	-
Income <$1,000/month	48%	48%	48%	0.92
Employment				
Employed	38%	41%	36%	0.82
Unemployed	49%	44%	51%	-
Retired/disabled	13%	15%	12%	-
Opioid of choice				
Heroin	11%	11%	10%	0.95
Prescription narcotics	88%	89%	87%	-
Route of drug use				
Oral	52%	48%	53%	0.65
Intravenous	33%	33%	32%	0.93
Snorting	41%	48%	39%	0.4
Peak drug use				
>100 mg of oxycontin or equivalent	75%	81%	73%	0.61
<100 mg of oxycontin or equivalent	21%	19%	22%	-
Side effects reported				
None	45%	NA	NA	-
Any	55%	-	-	-
Urinary hesitancy	26%	-	-	-
Headaches	10%	4%	12%	0.45
Constipation	34%	59%	25%	0.001
Sexual side effects	9%	22%	4%	0.009
Others	7%	11%	5%	0.37
Buprenorphine dose				
≤8	4%	11%	1%	0.1
Sep-16	27%	30%	26%	
17-24	49%	37%	53%	
25-32	20%	22%	19%	-
Other psychotropic medications	16%	63%	0%	<0.001
Coexisting major medical conditions				
Hypertension	7%	26%	0%	<0.001
Diabetes	1%	4%	0%	0.26
Benign prostatic hyperplasia	1%	4%	0%	0.26
Buprenorphine suspended	54%	52%	55%	0.81

Table 1: Characteristics of the sample.

Most symptoms of urinary hesitancy were reported in the two weeks of buprenorphine therapy (Figure 1). Of those who did report urinary symptoms, 30% increased fluid intake to treat symptoms while an additional 67% increased fluid and were offered bethanechol. It is interesting to note that on 6 month follow up of the charts 80% of the subjects who did receive bethanechol had either discontinued it themselves due to resolution of symptoms or were taking the medication.

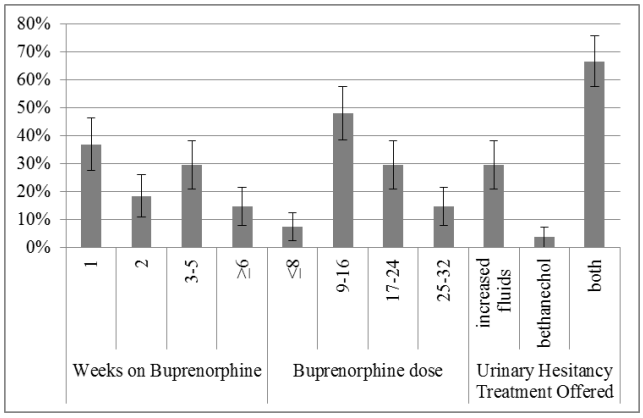

Figure 1: Timing, dose and treatment of those who develop urinary hesitancy.

Discussion

Literature extensively discusses Post-operative urinary retention as a common complication of opioid regional anesthesia [10]. Urinary retention with epidural/intrathecal delivery of buprenorphine is also a known effect on the lower urinary tract [11]. There are two case reports in literature reporting acute urinary retention with the use of sublingual buprenorphine/naloxone [5,12]. In the more recent case report by Edwards et al., the patient was 49 years old and had a history of BPH. This patient had two episodes of urinary retention on subsequent days and then refused a retrial of buprenorphine. This finding is in support of our study, these authors also emphasize that acute urinary symptoms could impact compliance and increased awareness among providers may be help prevent the same.

To our knowledge our current study is the first systematic study of the urinary symptoms of hesitancy/retention in patients receiving buprenorphine/naloxone treatment for the treatment of opioid dependence.

The prevalence of urinary symptoms noted in our study is much higher than that reported by the manufacturer of the drug. This is possibly attributable to an all-male sample; the age range includes some patients with prostatic hypertrophy and use of other concomitant psychotropic medications which could further worsen urinary symptoms. We also found a significant p value for hypertension which may have contributed to our results. Awareness among our team of providers from our earlier case series and use of a checklist in the medical record to specifically ask for and document in the medical record common side effects of the medication could also be a factor for the higher reports in our population 9.

Most patients are typically maintained on a dose of 8-24 mg/day. In our study we did not find a significant relation between dose of buprenorphine/naloxone and the occurrence of urinary symptoms. Nevertheless, the symptoms are noted to be short lived and easily treated using increase in fluid intake and bethanechol. Other common and expected side effects noted were constipation and sexual side effects which reached statistical significance.

Awareness among providers of this common, yet easy to treat side effect of buprenorphine/naloxone would enhance patient education regarding the early onset and transient nature of these symptoms. While mild symptoms may be treated with increased fluid intake alone, more disabling symptoms are better treated by bethanechol. This may obviate the need to switch to methadone, as was seen in the case reported by Edwards et al. Bethanechol is a cholinergic drug that has been in use for non-obstructive urinary retention or hesitancy. It has long been used for the more commonly reported urinary hesitancy with the pure opioid agonists such as methadone. Cholinergic action helps with contraction of the bladder musculature and ultimately bladder emptying.

Limitations

Out study have several limitations. Being a retrospective chart review the generalizability of the results is somewhat limited. Since the study was conducted in a single VA hospital, our study primarily included male subjects and may not represent the VA at large or people with more limited access to healthcare. Our sample size was relatively small and the side effect reported is not new but noted to be higher than expected.

Conclusion

Urinary hesitancy is a known side effect of buprenorphine due to the agonism at the mu opioid receptor leading to detrusor and urinary sphincter muscle contraction. However, this side effect is often under reported and may go untreated. It may lead to significant discomfort and could possibly interfere with patient compliance with buprenorphine treatment. In most cases the symptoms are mild and transient and can easily be treated with increased fluid intake and use of bethanechol, a cholinergic drug that has long been used for non-obstructive urinary hesitancy or retention, at low doses.

Since urinary hesitancy is typically an early and transient side effect, patients need to be educated about the symptoms being short lasting and treated as needed with fluids and bethanechol. This is likely to enhance compliance and lower risk of relapse in this highly vulnerable population.

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