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A Retrospective Study of Concurrent Non-Prescribed Medicinal and Illicit Drug Use by Opioid Dependent Patients Prescribed with Buprenorphine

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Research Article

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Abstract

Buprenorphine being a partial opioid agonist of the μ-receptor is widely preferred for managing opioid addiction. This retrospective study was conducted at a tertiary care de-addiction centre of North India. The laboratory records of all consecutive urine samples send for drug analysis over a period of 5 years were reviewed. The most prevalent illicit drug used in both the groups (prescribed and non-prescribed buprenorphine) was morphine followed by cannabis. The most prevalent controlled drug used by both the group was benzodiazepines. The overall prevalence of illicit and medicinal drug use was significantly higher in subjects who were prescribed with buprenorphine versus the non-prescribed use. Due to the increase in concurrent consumption of drugs along with buprenorphine in opioid dependent patients, it is recommended that health professionals prescribing buprenorphine should be well versed about the potential harm of concomitant usage of buprenorphine. This would reduce the risk of potential toxicity or fatal drug interaction among patients.

Keywords: Buprenorphine; Opioid; Illicit Drug; Prescribed

Introduction

Buprenorphine is a semi- synthetic derivative of a naturally occurring opioid alkaloid thebaine. It is a partial opioid receptor agonist and a κ- opioid receptor antagonist [1]. Buprenorphine has a significantly increased sublingual bioavailability but poor gastrointestinal bioavailability. It is metabolised in the liver via the cytochrome P-450 3A4 and 2C8 into nor-buprenorphine and its conjugate [2]. Nor-buprenorphine, however, has little ability to cross the blood brain barrier and so its effects are negligible [2,3]. Its terminal half-life ranges from 28 to 37 hours after sublingual administration [1,2]. Majority of its metabolites are

eliminated in the faeces, with approximately 10 to 30 percent excreted via urine [1].

Buprenorphine is more potent than morphine as an analgesic and hence it is preferred at low doses for effective treatment of acute and chronic pain [4]. Because of its low intrinsic activity and partial agonist properties, buprenorphine is used for the maintenance therapy of opiate addiction [5]. Buprenorphine derived sublingual tablets such as Subetex or Suboxone (in combination with naloxone) is widely used for treatment of opioid dependence [6]. Buprenorphine, itself has a high abuse potential and may cause dependency [1]. Opioid dependent patients being treated with buprenorphine also have a potency of abusing non-prescribed or illicit drugs [7,8]. It is reported to have higher efficacy in treatment of opioid dependence as compared to methadone [5]. Also, illicit self-administration of buprenorphine to treat opioid dependence, reduce withdrawal symptoms, decrease the illicit use of other opioids, and decrease injection drug use have all been commonly reported [9]. Therefore, with an overall increase in the number of buprenorphine patients worldwide, there is a gradual demand to investigate the concurrent drug use pattern associated with buprenorphine.

Keeping this in view, a study was conducted at a tertiary care de- addiction treatment centre in North India. The purpose of this retrospective study was to observe the non-prescribed medicinal and illicit drug use pattern associated with buprenorphine use. This study also attempts to examine the abuse pattern of buprenorphine in the substance use patient's population by observing the data collected from urine drug testing.

Methods

A retrospective chart review of all patients' urine samples sent for drug testing was done at National Drug Dependence Treatment Centre, a tertiary care centre, All India Institute of Medical Sciences, New Delhi (AIIMS) between the period of January 2013 and December 2017. The urine samples of patients' who tested positive for buprenorphine with or without buprenorphine prescription for Opioid Substitution Therapy (OST) were included.

At this centre, a standardized protocol was used for the detection of commonly abused drugs as well as prescribed medication in urine specimens of subjects who took buprenorphine with or without a prescription [10]. A modified hydrolysis method followed by Thin Layer Chromatography (TLC) was used for the detection of buprenorphine, morphine, benzodiazepines, pheniramine, pentazocine, proxyvon and tramadol in the urine samples as per methods described earlier [11]. Cassette test (Alfa scientific Designs, Inc. Poway, CA, USA), a test based on qualitative immunoassay, was used for the detection of cannabis (THC) and cocaine. It detects Δ9-THC-9-carboxylic acid (THC), a major metabolite of cannabis in human urine with a cut-off level of 50ng/ml and benzoylecgonine, a metabolite of cocaine, in human urine at a cut-off level of 300ng/ml [7,11].

Data analysis was carried out using SPSS® version 22. The pattern of prescription and non-prescription buprenorphine use was assessed using frequency distribution. Also the medicinal and illicit drug use pattern associated with prescribed and non-prescribed buprenorphine use was assessed using frequency distribution. Extended Mantel-Haenszel chi square for linear trend was applied to study the trend of occurrence of various drugs.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki (1975), and complete confidentiality has been ensured.

Results

A total of 5151 consecutive urine samples received over a period of 5 years tested positive for buprenorphine. 71.6% of the patients were tested positive for prescribed buprenorphineuse (Figure 1). Hence, the rate of non-prescribed buprenorphine use was 28.3% (Figure 1). Also the highest rate of recorded prescribed buprenorphine use was 88.4% at the year 2015 while the rate of recorded non-prescribed buprenorphine use was 48.6% at the year 2014 (Figure2).

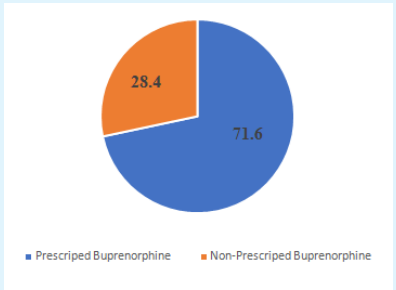


Figure 1: The percentage of subjects that tested positive for Buprenorphine in both prescription and non prescription buprenorphine use (n=5151).

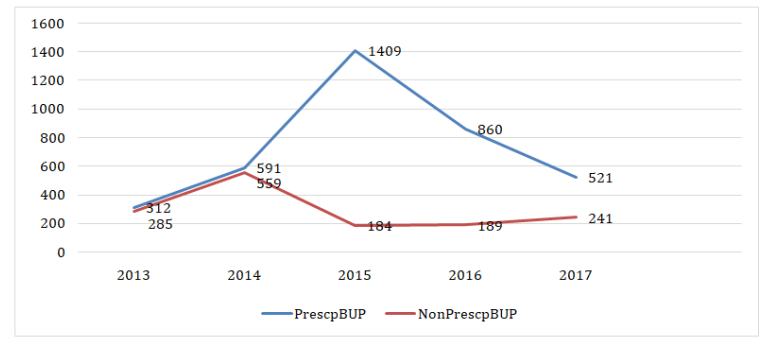


Figure 2: Five years record showing the percentage of subjects that tested positive for Buprenorphine in both prescription buprenorphine uses (n=3693) and non-prescription buprenorphine use (n=1458).

Figure 3 shows the illicit drug use pattern in subjects who were prescribed buprenorphine and those who used the drug without a prescription. The most prevalent drug used in both the group was morphine, followed by THC (marijuana). Sixteen percent (16.1%) of subjects who were prescribed with buprenorphine tested positive for morphine, whereas 19.8% of subjects who used buprenorphine without prescription tested positive for morphine. Subjects who were prescribed with buprenorphine were 2.8 times more likely to abuse morphine than THC. Subjects who used buprenorphine without prescription were 2.3 times more likely to abuse morphine than THC.

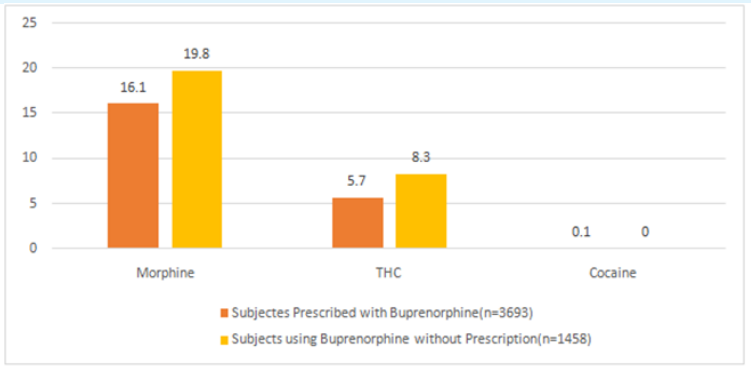


Figure 3: The percentage of subjects in each population that tested positive for each illicit drug.

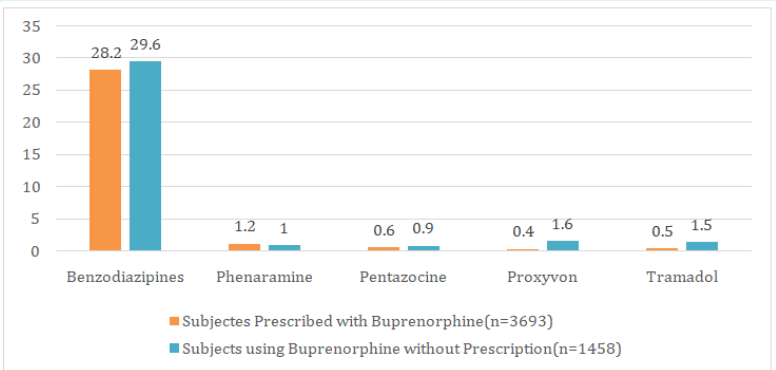


Figure 4: The percentage of subjects in each population that tested positive for each medicinal drug.

Figure 4 shows medicinal drug use pattern in both populations. The most prevalent medicinal drug was benzodiazepine in both the categories. The rate of consumption of benzodiazepines was greater among subjects who consumed buprenorphine without prescription.

For subjects prescribed with buprenorphine, Figure 5 shows a comparatively high rate of morphine (14.7%) consumption at the year 2014 which decreases gradually with passing years. However, 2016 shows a higher rate of THC (3.1%) consumption with cocaine being the least reported illicit drug of consumption. Extended Mantel-Haenszel chi square for linear trend was applied by keeping the year 2013 as the baseline, a significant increase in trend with p-value =<0.0000001was observed for morphine, THC. However cocaine showed no significant result.

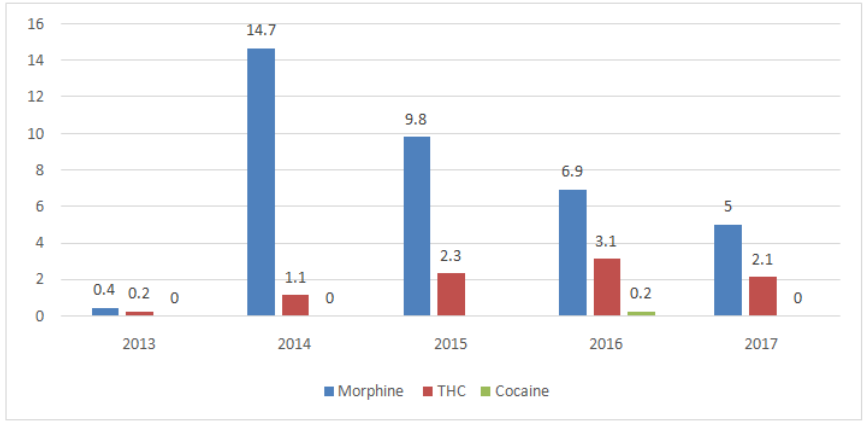
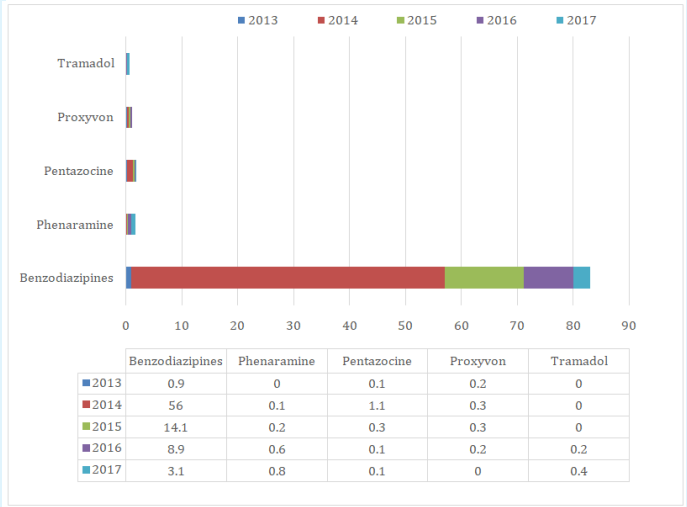


Figure 5: The percentage of subjects that tested positive for illicit drugs for subjects prescribed with buprenorphine (n=3693).

Figure 6 shows that among the medicinal drugs used in subjects prescribed with Buprenorphine, benzodiazepines was the most commonly abused drug reported in the year 2014 (56%) followed by other drugs. Extended Mantel-Haenszel chi square for linear trend was applied by keeping the year 2013 as the baseline, a significant increase in trend with p-value =<0.0000001was observed for benzodiazepines and pheniramine as shown Table1. However pentazocine, proxyvon and tramadol showed no significant result.



	Benzodiazipines	Phenaramine	Pentazocine	Proxyvon	Tramadol
2013	0.9	0	0.1	0.2	0
2014	56	0.1	1.1	0.3	0
2015	14.1	0.2	0.3	0.3	0
2016	8.9	0.6	0.1	0.2	0.2
2017	3.1	0.8	0.1	0	0.4

Figure 6: The percentage of subjects that tested positive for medicinal drug for subjects prescribed with buprenorphine (n=3693).

Drugs under Prescribed Buprenorphine	Extended Mantel-Haenszel chi square for linear trend	p- value (1 degree of freedom)
Morphine	158.08	<0.0000001
THC	75.09	<0.0000001
Benzodiazepines	30.55	<0.0000001
Pheniramine	43.55	<0.0000001

Table1: Extended Mantel-Haenszel chi square statistical test for linear trend for Drugs under Prescribed Buprenorphine.

In Figure 7, subjects who consumed buprenorphine without prescription also showed increase morphine (25.4%) consumption at the year 2014. Likewise, THC (2.3%) too showed peak consumption on 2014 with cocaine being the least reported illicit drug of consumption. Extended Mantel-Haenszel chi square for linear trend was applied by keeping the year 2013 as the baseline, a significant increase in trend with p-value =<0.0000001was observed for morphine, THC. However cocaine showed no significant result.

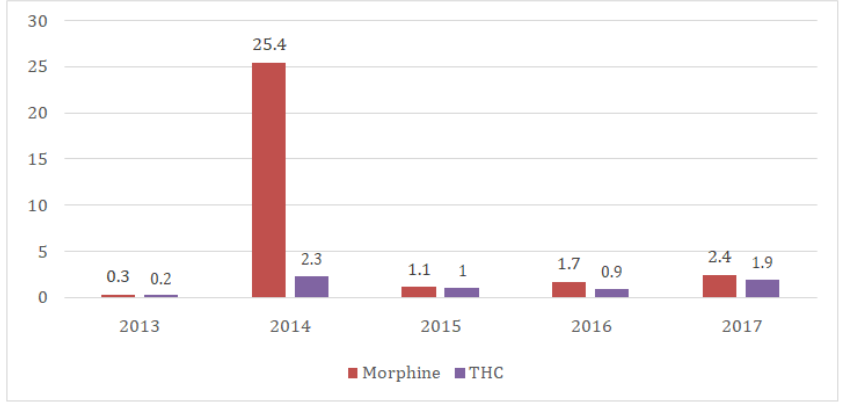
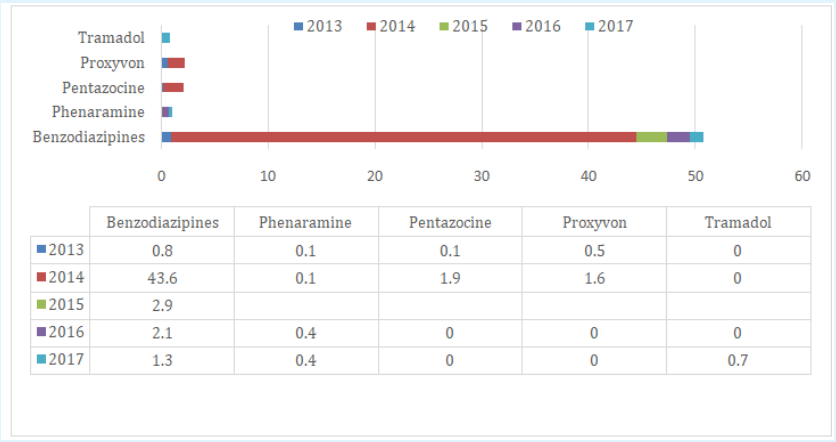


Figure 7: The percentage of subjects that tested positive for illicit drugs for subjects using buprenorphine without prescription (n=1458).

Figure 8 shows that among the medicinal drugs used in non-prescribed buprenorphine use subjects, benzodiazepines was the most commonly abused drug reported in the year 2014 (43.6%) followed by other drugs. Extended Mantel-Haenszel chi square for linear trend was applied by keeping the year 2013, but no significant result was observed (Table2).



	Benzodiazipines	Phenaramine	Pentazocine	Proxyvon	Tramadol
2013	0.8	0.1	0.1	0.5	0
2014	43.6	0.1	1.9	1.6	0
2015	2.9				
2016	2.1	0.4	0	0	0
2017	1.3	0.4	0	0	0.7

Figure: 8: The percentage of subjects that tested positive for medicinal drug for subjects using buprenorphine without prescription (n=1458).

Illicit Drugs under Non-Prescribed Buprenorphine	Extended Mantel-Haenszel chi square for linear trend	p- value (1 degree of freedom)
Morphine	28.84	<0.0000001
THC	95.44	<0.0000001

Table2: Extended Mantel-Haenszel chi square statistical test for linear trend for Illicit Drugs under Prescribed Buprenorphine.

In patients who were prescribed buprenorphine, 53.1% had at least one in all the drugs detected in their urine. And in patients who consumed buprenorphine without prescription, 63.4% had atleast one in all the drugs detected in their urine.

Discussion

The current study observed that buprenorphine is one of the most demanding medications in treatment for opioid addiction; the same was suggested in the study by Walter et al., [12]. The analysed data revealed that a fair number of subjects were involved in consumption of non-prescribed buprenorphine i.e. 28.3%. This trend agrees with the findings of Lofwall et al., which highlights the buprenorphine misuse to overcome opioid addiction [13]. With increasing opioid addiction worldwide, cases of illicit self-administration of buprenorphine to treat opioid addiction, reduce withdrawal symptoms, decrease illicit use of heroin or any other opioid is rapidly increasing.

This study reports the concurrent drug use pattern associated with buprenorphine. In context to illicit drug use, the highest prevalence in subjects prescribed or not prescribed with buprenorphine were morphine followed by THC. There is a growing need for the clinicians to be aware of this abuse pattern for better monitoring. Also these results further agrees with the statement made by Pesce, et al. which states that physicians prescribing opioids should consider urine testing in their patients as a routine procedure for presence of illicit drug [14].

The rate of polydrug use in patients prescribed with buprenorphine was found to be 31% with benzodiazepines being the most widely abused prescription drugs in subjects prescribed with buprenorphine and those taking buprenorphine without prescription. Subjects may have been consuming benzodiazepines without prescription to reduce withdrawal symptoms associated with opioid replacement therapy such as sleeplessness, anxiety [15]. A potential risk of excess sedation leading to respiratory depression may occur in concurrent use of benzodiazepines with buprenorphine [16]. A study conducted by Kintz reported about 75% of deaths due to concurrent use of benzodiazepines with buprenorphine [17]. In a study conducted by Lai, et al., benzodiazepines were detected in the autopsies of 19 out of 21 for subjects who were prescribed to buprenorphine for treatment for opioid dependence [18]. These studies highlight the potential lethal consequences of co-administration of the co-administration of benzodiazepines with buprenorphine. Our findings could support the existing literature that links buprenorphine related deaths with benzodiazepines.

The prevalence of other controlled drug usage along with buprenorphine indicates that clinicians should consider regular urine testing for all controlled drugs of all buprenorphine subjected patients for better monitoring and good outcome. Such steps can ensure appropriate use of a drug regimen while reducing drug diversion.

In this current study, one of the major limitation is the presence or absence of benzodiazepine in the urine sample of subjects mentioned is solely based on the urine reports recorded in the laboratory and not based on the medical records of patients. As a matter of fact, benzodiazepine are widely prescribed group of medicines used for treating psychiatric and neurological conditions as well as they are highly misused among patients to treat insomnia and anxiety disorders. Also, sometimes there is incomplete reporting of benzodiazepine being used by the patients during recording medical history by the clinician.

Conclusion

The crisis of nonmedical use of prescription opioids is an important public health priority. The results suggest that the pattern of drug use in the treatment seeking population may not be uniform. This study may not be generalizable to other health care facilities in the country, due to the geographic variation in drugs of abuse use and the type of population being studied. The findings from the current study provide important insights into the pattern of use of other non-prescribed opioids (including illicit heroin) along with other illicit drugs among

individuals on buprenorphine therapy. These findings support routine use of urine drug screening among individuals on OST. The findings also suggest that clinicians must educate their patients about the potential toxicity of buprenorphine and also the other illicit and non-illicit drugs when consumed concurrently. Taken together, these results might be used to contribute to some extent the estimates of illicit use of non-prescribed drugs for the epidemiological surveys related to public health and warrants future research.

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