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ORIGINAL RESEARCH

A Urinalysis-based Comparative Study of Treatment Adherence on Buprenorphine and Buprenorphine/Naloxone Combination Used as Opioid Substitution Therapy

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ABSTRACT

Objective: The objective of the current study was to explore the difference in treatment adherence to directly supervised buprenorphine and take-home buprenorphine/naloxone combination for opioid substitution therapy. Urinalysis findings have been used to check treatment adherence on opioid substitution therapy agent. Additionally the study aimed to explore the misuse rate of buprenorphine/naloxone combination based on urinalysis findings.

Design: Cross-sectional chart review

Setting: Laboratory of a tertiary care drug dependence treatment center

Participants: One-year laboratory urinalysis records of a tertiary care, drug-dependence treatment center in India were analyzed. All the urine samples of subjects on opioid substitution therapy with buprenorphine or buprenorphine/naloxone combination were included in the study.

Measurements: Urinalysis using thin layer chromatography for buprenorphine and naloxone. In between group difference for treatment adherence on buprenorphine and buprenorphine/naloxone combination was done using Mantel-Haenszel test.

Results: A higher proportion of samples from subjects on buprenorphine/naloxone tested positive for buprenorphine as compared to subjects on buprenorphine. Twelve (7.6%) urine samples from patients on buprenorphine/naloxone tested positive for naloxone.

Conclusions: The findings of the current study suggest that buprenorphine/naloxone combination has a higher adherence

rate as compared to buprenorphine when used for opioid substitution therapy.

INTRODUCTION

Abuse of illicit opioids is a major public health problem. According to World Drug Report 2010, 12.8 to 21.9 million people abused opiates over the past 12 months globally.[1] As per findings of a national survey, there were approximately two million heroin abusers in India.[2] Opioids are the most common illicit drugs of abuse among the individuals presenting to the treatment settings in the country.[2]

Effectiveness of opioid substitution therapy (OST) for opioid dependence and associated risk behaviors has been established.[3,4] Buprenorphine is one of the two most commonly used medications for OST. A better safety profile due to ceiling effect has helped in its dispensing from office-based practice.[5] Research has suggested that buprenorphine used for OST, if not administered supervised, is liable for diversion (bell). Possible misuse of prescribed buprenorphine through injecting route has limited its use to directly "supervised administration" in most settings.[6] This, however, means frequent visits of service users to the treatment center. Not only does this interfere with the vocational rehabilitation (as it requires taking time off from work), the frequency of visits has been found to be an important reason for treatment drop out. In fact, studies have reported it to be the key limitation of buprenorphine treatment.[7] Requirement of less frequent visits to the treatment center has been reported to be a desirable attribute of an OST center by service users.[8]

Buprenorphine/naloxone is a combination of buprenorphine and naloxone in a 4:1 ratio. Sublingually administered buprenorphine/naloxone has been found to be an effective OST.[9] Buprenorphine/naloxone combination was developed to avoid misuse of buprenorphine through injecting route. This property is imparted to the combination by poor bioavailability of naloxone through the sublingual route. However, if the combination tablets are injected, the effect of naloxone predominates. This prevents the subjective effect of the buprenorphine present in the combination for occurring. The combination offers an opportunity to dispense take-home doses to the patients, which may make the OST combination less demanding on the patients. The combination is expected to improve treatment adherence due to a reduced number of missed doses and drop-outs.

OST was introduced in India in the late 1980s. There are limited treatment facilities offering OST in the country.[10] Recently, OST was proposed for an extensive scale up in India. The buprenorphine tablet was introduced in India in 1989 for opioid dependence. The buprenorphine/naloxone combination was made available in the country in 2005.[11]

Our center provides both buprenorphine and buprenorphine/naloxone for OST. The choice of medication is based on suitability for each patient. The current study aimed at exploring the difference in adherence to directly supervised buprenorphine and take-home buprenorphine/naloxone combination for OST. Urinalysis findings were used to check the adherence to treatment. Additionally, the study aimed at exploring the misuse of buprenorphine/naloxone combination based on urinalysis findings.

METHODS

One-year laboratory urinalysis records of a tertiary care, drug-dependence treatment center in India were analyzed. The sample frame for the study comprised all consecutive urine samples sent for analysis over a period of one year.

Setting. The study was carried out in an apex drug dependence treatment center. The center provides services to individuals with substance abuse-related disorders. Opioids, alcohol, cannabis, and tobacco are the commonly used substances for which treatment is sought at the center. The center OST to individuals with opioid dependence. Buprenorphine and buprenorphine/naloxone combination are used for this purpose. Methadone has only recently been introduced as a pilot project in the country. Individuals seeking treatment from the center are assessed by a multidisciplinary team comprising a qualified psychiatrist, clinical psychologist, and medical social services officer.

Dispensing of buprenorphine and buprenorphine/naloxone combination at the center is done through a protocol adapted from the United Nations Office on Drugs and Crime Regional Office of South Asia (UNODC ROSA) and the World Health Organization (WHO).[12,13] Induction and stabilization of dose is done in accordance with these guidelines. This protocol is standard across the country and in other countries of the South Asian region as well. Individuals with opioid dependence, aged 21 years or older, using opioids for at least three years, consenting to take medication, and willing to provide urine sample for monitoring therapeutic adherence are deemed suitable for OST. Buprenorphine is prescribed as "supervised administration." Buprenorphine/naloxone is given as take-home medication for a period ranging from 1 to 2 weeks. Opioid-dependent individuals facing difficulty in daily supervised administration with buprenorphine and having good record of outpatient attendance are considered for take-home buprenorphine/naloxone combination.[14] Treatment adherence is checked objectively by urinalysis.

Sample collection and urinalysis. All urine samples of subjects who were on OST with buprenorphine or buprenorphine/naloxone combination were included

TABLE 1. In between group difference for buprenorphine and buprenorphine/naloxone combination prescribed as OST for adherence based on urinalysis findings

BUPRENORPHINE URINALYSIS FINDING	OST MEDICATION		MH STATISTICS
	Buprenorphine	Buprenorphine/ Naloxone	
Buprenorphine absent	32.80%	13.90%	MH 16.13 *df*=1 $p<0.005$
	(67/204)	(22/158)	
Buprenorphine present	67.20%	86.10%	
	(137/204)	(136/158)	

MH: Mantel-Haenszel statistics

in the study. All the consecutive samples received over a one-year period were included.

The collection of urine samples (50mL) from patients at the de-addiction center was supervised by a member of the laboratory staff. The samples were collected randomly during indication, stabilization, and maintenance phases. It was immediately sent to the laboratory for analysis. All urine samples were screened for common drugs of abuse in the region as well as for medications prescribed for OST at the center. Adherence to OST was assessed by detection of buprenorphine in the urine samples on urinalysis. Possible misuse of buprenorphine/naloxone combination through injecting route was indicated by presence of both buprenorphine and naloxone in the urine samples. A modified hydrolysis method followed by thin layer chromatography (TLC) was used for the detection of abused drugs in urine.[15,16] The detection limit for urinalysis in the laboratory was 1.0µ/mL for buprenorphine and 0.5µ/mL for naloxone. Additionally, detection limits for heroin (tested as morphine) was 0.5µ/mL. Despite its relatively lower sensitivity and specificity as compared to gas chromatography and mass spectroscopy, TLC offers a cost-effective strategy in developing countries with limited resources.[17]

The reports of the urine testing were made available to the respective clinicians as part of the clinical service delivery. Each clinician would then make individualized decisions in accordance with the urinalysis reports. This involved a re-evaluation of the case. The reasons for use of the illicit drug were explored and appropriate interventions were made. These included adjusting the dose of medication, adjusting the dosing schedule, use of motivation enhancement therapy, and relapse prevention sessions depending on the requirement of the individual case.

Data were analyzed using SPSS version 17.0. In between group difference for treatment adherence with buprenorphine and buprenorphine/naloxone combination was done using the Mantel-Haenszel test. These statistics took into account the possible prescription differences between the two groups during the induction and maintenance stages. Level of statistical significance was kept at $p<0.05$.

Conditions of confidentiality, as specified in the institutional ethical guidelines, were ensured through the course of study and reporting of findings.

RESULTS

A total of 362 urine samples were analyzed. The analysis included 204 samples from patients prescribed buprenorphine as OST and 158 samples from patients prescribed buprenorphine/naloxone combination as OST.

Of the total 204 samples from patients on buprenorphine, 137 (67.2%) tested positive for buprenorphine. One-hundred and thirty-six out of 158 (86.1%) samples from patients on buprenorphine/naloxone combination tested positive for buprenorphine. Mantel-Haenszel statistics revealed that a higher proportion of samples from patients on buprenorphine/naloxone tested positive for buprenorphine as compared to patients on buprenorphine (MH 16.13, df=1, $p<0.005$) (Table 1). This suggests that adherence was significantly higher for buprenorphine/naloxone combination compared to buprenorphine.

Twelve (7.6%) of the urine samples from patients on buprenorphine/naloxone tested positive for naloxone. Five percent of urine samples testing positive for buprenorphine among individuals prescribed buprenorphine also tested positive for unprescribed opioids. Twenty-three percent of urine samples tested positive for unprescribed opioids along with prescription buprenorphine. In the buprenorphine/naloxone group, 10 percent of the samples tested positive for unprescribed opioid as well as buprenorphine. Around 45 percent of the samples that tested positive for unprescribed opioids tested negative for buprenorphine.

DISCUSSION

The current study aimed at comparing the difference in adherence rates between buprenorphine and buprenorphine/naloxone combination used for OST. We used a urinalysis to check adherence. The study also aimed at exploring the possible misuse of buprenorphine/naloxone combination through injecting route.

Although buprenorphine has been established as an effective OST, concerns have been expressed about its misuse through injection due to

the ease in which the sublingual tablets of buprenorphine can be dissolved and injected. Many such reports have come from Italy where buprenorphine has been used extensively with minimal restrictions. These studies have reported up to 20 percent of the patients using their prescription buprenorphine intravenously.[6] Misuse of prescription buprenorphine through injection has been reported from treatment settings in other countries as well, including Australia, England, Finland, Ireland, Malaysia, New Zealand, and Scotland.[18–23] Another alarming observation is that of some users mixing the prescription sublingual buprenorphine tablets with heroin or benzodiazepine in order to obtain greater euphoria.[24] Even supervised buprenorphine administration has been associated with misuse.[25]

Buprenorphine/naloxone combination was introduced with an aim to prevent this misuse of buprenorphine through injection. The buprenorphine/naloxone combination was expected to have a lower risk of misuse.[26] Lower misuse liability is expected to ease the restrictions associated with use of buprenorphine. Guidelines in India recommend directly supervised administration of buprenorphine to opioid dependents.[27] This recommendation is aimed at reducing the chances of misuse, including injection. However, stringent guidelines on buprenorphine dispensing are likely to limit the availability and accessibility of treatment. This consequently reduces the effectiveness of the treatment for heroin dependence and intravenous drug use.[24,28]

Introduction of buprenorphine/naloxone combination has provided the option of home-based induction among opioid-dependent individuals. It has been found to be a safe and effective approach.[29–31] Home-based induction has been associated with less use of resources compared to office-based induction. An adherence rate of 88 percent was reported in a study on home-based induction using the buprenorphine/naloxone combination.[32]

However, there are no reported head-to-head comparisons of adherence to buprenorphine and buprenorphine/naloxone combination. The current study found a significantly higher adherence to buprenorphine/naloxone compared to buprenorphine alone among opioid-dependent subjects from the same center. It is likely that the provision of being able to take home the OST of buprenorphine/naloxone contributed to the higher adherence rate. Patients receiving buprenorphine are expected to visit the treatment center daily or at least twice weekly. However, buprenorphine/naloxone is dispensed as take home medication for up to two weeks. The findings of current study support use of buprenorphine/naloxone combination over buprenorphine for OST to improve treatment adherence. Requirement of less frequent visits to treatment center has been reported to be a desirable attribute of an OST center by service users. Studies have reported that frequent visits to the treatment center for "supervised administration" are a key limitation of buprenorphine treatment.[7]

Retrospective surveys have documented lower misuse rates after buprenorphine/naloxone was introduced in areas known to have high rates of buprenorphine injection.[33] Drug abuse liability studies have found a lower likelihood of self-administration of injection of buprenorphine/naloxone combination compared to buprenorphine among individuals maintained on sublingual buprenorphine alone. Similarly, these subjects reported a comparatively lower likelihood for injecting buprenorphine/naloxone.[34]

However, recent post-marketing surveys suggest otherwise. Abuse of the combination through injection has steadily increased in United States.[35] This has been revealed in a recent series of surveys conducted in different settings, including applicant surveys, physician surveys, forensic data, emergency department visits, and calls to Poison Control Centers in the country. These findings are not in keeping with some of the earlier studies from United States that reported little evidence of abuse of the combination.[26] Our study reports a rate of 7.6 percent of buprenorphine/naloxone combination misuse based on urinalysis findings. It is possible that some of the urinalysis findings can be attributed to the patients experimenting, via injection, with a new medication. Similar explanation has been given for such observations in other countries as well.[36] These individuals, however, are unlikely to have experienced the euphoric effects of buprenorphine due to its combination with naloxone and hence are not likely to continue with the practice of injecting the combination. However, this practice exposes the users to possible complications of injecting drug use.

It is worth mentioning that there are reports of users avoiding the effects of the naloxone when injecting buprenorphine/naloxone in some settings. This is achieved by dividing the tablets into small pieces.[24] The possibility of misuse of buprenorphine/naloxone combination through injection should be considered along with our finding of improved treatment adherence through its administration.

Our study presents a head-to-head comparison of the adherence to buprenorphine alone to the adherence to buprenorphine/naloxone combination in a real-life, clinic-based setting. Our findings have important implications across different settings. Methadone continues to remain the most

commonly used OST for opioid dependence globally. However buprenorphine and buprenorphine/naloxone are increasingly being introduced in various countries. A better safety profile makes buprenorphine suitable for office-based dispensing. Additionally, the availability of buprenorphine/naloxone combination has introduced the possibility of home-based dispensing. Both of these medications have been approved for office-based dispensing in the United States.[37] Such approaches are likely to reduce cost of treatment and improve treatment adherence. On the other hand, in light of high diversion rates, there is a need to examine the policy of dispensing take-home buprenorphine in some countries. Substituting buprenorphine/naloxone for buprenorphine in some settings is likely to address the issue of high diversion rates in these settings. Finally, our findings also highlight the importance of adequate psychoeducation for those being prescribed buprenorphine/naloxone regarding the lack of its effect through injecting route. This would help prevent the experimental injection of the combination and associated complications.

The current study has certain limitations. The study design was based on a retrospective chart review. Hence we only could analyze already recorded information. Many variables (e.g., client perspective) could not be included in the analysis for this reason. Because of the naturalistic nature of the study, we could not control for any of the possible confounders. Future studies with a component of the client perspective regarding the two dispensing regimens could help provide further insights in OST issues. Also, the findings need to be replicated in other settings as well. There is a need to carry out follow-up studies to observe time trends in misuse of buprenorphine/naloxone combination vis-a-vis buprenorphine. This would help evaluate the pros and cons of buprenorphine/naloxone combination. Such data would help decide the future course of OST with regard to the choice of medication for treatment and dispensing practices.

CONCLUSION

The findings of our current study suggest that buprenorphine/naloxone combination has a higher adherence rate among our OST patients compared to buprenorphine treatment alone. However, buprenorphine/naloxone combination is not entirely free of the possibility of misuse through injection. The limitations of our study must be kept in mind while drawing conclusions. Additionally, the issue needs to be studied further in order to have more definitive answers.

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