Archives of Psychiatry and Psychotherapy, 2020; 1: 63–69

DOI: 10.12740/APP/109265

Opioid withdrawal and its stabilization on sublingual buprenorphine in intravenous drug users: A South Gujarat Perspective

Saumitra Shankar Nemlekar, Ritambhara Yeshwant Mehta, Kamlesh Rushikray Dave, Falguni Patel

Summary

Opioid substitution therapy involves replacing the client's primary drug of use (opioid) with a medically safe drug or the same opioid in a safer mode of administration under medical supervision.

Objectives and methodology: It is a prospective follow up study observing opioid withdrawal and its stabilization on buprenorphine sublingual tablets. Patients who fulfilled the criteria for Opioid substitution therapy by NACO guidelines were enrolled and given buprenorphine sublingual tablets; (0.2 mg and 2 mg). They were followed up on 1st to 3rd, 7th, 14th and 28th day for assessment of withdrawal and its resolution on buprenorphine. The withdrawal was assessed using Clinical Opioid Withdrawal Scale (COWS). Duration of study was 2 years.

Results and conclusions: Total 44 patients were enrolled. 37 IDU users completed the period of observation. They belonged to 19 to 52 years age group, the duration of use ranged from 2 to 32 years. Patients had mild to moderate range of withdrawal. The mean score of COWS was 11.2 with a range of 5 to 24. Mean buprenorphine dose requirement on 1st day was 6.19 mg with range from 1.2 mg to 14 mg. Dose requirement at day 28 was in the range from 0.6 to 16mg. This study is empirical information on the issue of a reference dosage for buprenorphine regimen in an Indian population. We found that dosages required in our study population were lesser that dosage guidelines in western countries. However further research on such lines is required to suggest guidelines for Indian population.

IV Users, opioid stabilization, buprenorphine, India

INTRODUCTION

The problem of drug abuse has existed for centuries. However, the problem has become more complex and alarming in the recent years [1]. There were 15.5 million opioid-dependent people globally in 2010 [2]. Opioid dependence has a worldwide prevalence that ranges from 0.6 to 0.8%, and opioid consumption and the demand for treatment for dependence are highest in Europe and Asia [3-5]. In India, nearly 3 million are opioid users [6].

Management of opioid – dependent patient requires effective pharmacotherapy as the withdrawals are severe. Treatment modalities include use of medications such levo-α-acetyl

[1]Saumitra Shankar Nemlekar, [2]Ritambhara Yeshwant Mehta, [3]Kamlesh Rushikray Dave, [4]Falguni Patel: [1]Consultant Psychiatrist, NMHP, Directorate of Health Services, Goa, India; [2]Department of Psychiatry, Government Medical College and New Civil Hospital, Surat – 395001, India; [3]Department of Psychiatry, Government Medical College and New Civil Hospital, Surat, India; [4]Department of Psychiatry, SMIMER, Surat, India

Correspondence address: saumitra121@yahoo.co.in

methadol (LAAM), methadone, buprenorphine which have opioid receptor actions. Clonidine is also used for management of opioid-dependent patients. Methadone and buprenorphine are available as maintenance therapy in patients who have been using opioids for period of 1 year [3]. Buprenorphine, a μ-opioid partial agonist is a relatively newer treatment modality that became available for office-based opioid treatment in 2000 [4].

Under the National Aids Control Programme (NACP) the drug has been provided as oral substitution therapy. The tablets contain 2mg and 0.2mg of buprenorphine administered sublingually as a crushed powder. Oral substitution therapy with buprenorphine was introduced under the third phase of NACP. Injecting drug users were found to be a high risk group with high prevalence of HIV infection; hence OST was added as a service for better care. The NACP harm reduction package includes a pack of needle and syringe apart from the oral substitution therapy services. The medication is administered as observed dosages and not ambulatory treatment; to reduce chances of diversion. There are many guidelines [7-14] regarding the dosage regimen of buprenorphine for management of injecting drug users. Here we present the opioid withdrawal stabilizing doses in the outpatient population of patients from the South Gujarat area.

AIMS

To study the opioid withdrawal symptoms in the intravenous opioid users attending de-addiction and opioid Substitution Therapy (DOST) centre and the stabilization of buprenorphine dose.

METHODS

The study was conducted at the De-addiction and Opioid Substitution Therapy (DOST) centre, Department of Psychiatry, New Civil Hospital, Surat. According to available data there were 627 opioid users in Surat. Opioid drug users that were attending DOST centre were eligible for oral substitution therapy, according to guidelines [9] by National AIDS Control Organisation were enrolled in the study.

Tools

Data obtained included the identifying information and the socio – demographic profile, viz. occupational status, religion, educational status, marital status and type of family. Opioid use parameters included the dependence criteria as per the DSM IV TR. Details of financial spending on acquiring the substance and the total amount of substance use were also obtained.

Clinical opiate withdrawal scale (COWS) [15]

The opioid withdrawal in patients was assessed by COWS. It is an 11 – item clinician rated scale for observing opioid withdrawal. It indicates the physical dependency to chronic opioid use. A score of less than 5 is diagnosed as "no withdrawal" 5–12 as "mild withdrawal" and 25-36 as "moderately severe" and more than 36 as "severe withdrawal."

After scoring patients were administered sublingual tab. buprenorphine dosages. They were observed over the next hour. Patients were assessed for withdrawal resolution every hour. In case of withdrawal features another dose of buprenorphine 0.2 mg or 2 mg was delivered. The dose was decided on clinical evaluation and all changes were made on the basis of COWS.

Patients enrolled in the study were assessed at the beginning of sublingual buprenorphine therapy day (if different from the day of consultation), at 24 or 48 hours and then evaluation was done 1 week, 2 week and 4 weeks after initiation. After stabilization of the titration of the dose (increase/decrease), an attempt was made to obtain the minimum optimal dose for each patient. The total number was 44, 37 patients completed the study, 7 did not continue treatment. They did not complete the follow up over 4 weeks.

Statistical Analysis

The data was analysed using Microsoft Excel 2007 and openepi,com website. Mean, standard deviation, and percentages were used to describe the sample.

RESULTS

Demographic Parameters

All participants were males. Patients under 20 years of age comprised of (n=23) 63% of the total population. Most patients had not received formal education. Majority of patients 81.08% (n=30) belonged to Muslim religion while the rest were Hindus. This difference may be caused by the place of targeted intervention in an area inhabited by Muslims. showed that 40.54 % of patients were not married / never married, 35.13 % (n = 13) were currently married, 24.32 % (n=9) were separated, while one patient was a divorcee. The patients reported that the separation had been due to substance – related financial problems, interpersonal problems during intoxication or inability to provide for the family. 32.38% (n=12) were unemployed. The unemployment may be attributed to a longer period required for complete recovery, associated social stigma hampering job opportunities, lack of motivation and widespread unemployment. Other patient who were regularly on treatment were able been able to consider and pursue new employment opportunities.

Opioid and other substance use profile

Our patient told that they had acquired opioids illegally from suppliers or drug peddlers. The opioid used was heroin or "brown sugar". These were available in 5 grams quantity to the users. The users reported that the heroin was often mixed some impurities which decided the cost. The exact constituents of these bags apart from the heroin is not known. The cost ranged from Rs.30-40 to Rs.100, on basis of purity of this powder. Mean use of substance was around 6 such packets per day. Our patients have reported seizures on stopping withdrawal. Seizures are unlikely in opioid withdrawal and probably could be due to other impurities in the powder.

The mean age of onset was 20.48 years. Our patients reported to that they started using opioids as early as at the age of 10 years. Patients were introduced to the substance use by peers and all had been using tobacco prior to opioids. Only 3 patients had a positive family history for substance use. Patients mean time spent was 12.51 hours of a day. This was for searching, recovering and intoxicated state of opioid use. Amongst other substance use all patients used nicotine with opiates. Use of cannabis was prevalent – 56.75% (n=21). Patients reported using cannabis when opioids were not available.

Opioid withdrawal at presentation (Day 1)

In our study, no patients had severe withdrawal features at presentation. 24 had mild withdrawal and 13 had moderate withdrawal. The clinical symptoms contributing to withdrawal were high pulse rate, sweating, restlessness, pupillary dilatation, runny nose and bone pain. The average score of withdrawal symptoms contributed by bone or joint pains was the highest. The cold turkey effect, commonly associated with opioid users, was not seen.

Comparing withdrawal with opioid dependence

We compared the substance use profile with the severity of withdrawal at presentation prior to any treatment with buprenorphine (Table 1).

Table 1. Withdrawal severity at presentation (COWS Score), compared with opioid use parameters

No.	Clinical parameter	Withdrawal severity (COWS Score)		T test
		Mild (5 – 12)	Moderate (12 – 24)	p value
1	Duration of use of opioids (in years)	12.60 years SD 6.93	15.92 years SD 5.79	>0.05

2	Onset of tolerance (in months)	3.35 months SD 4.98	6.76 months SD 8.255	0.03
3	Onset of withdrawal (in months)	9.06 months SD 9.07	14.53 months SD 17.83	0.005

The parameters compared were total duration of use (in years), the onset of tolerance (in months) and onset of withdrawal (in months). For the above three parameters, the t test was used, to compare the differences on the basis of severity of their withdrawals (COWS score categorised as mild and moderate) Patients with mean use of 12.60 years had mild withdrawal, while in patients with moderate withdrawal mean use of 15.92 years had moderate withdrawal. This difference was not statistically significant (p>0.05, t test). Those with mild withdrawal features had the onset of tolerance within 3.35 months, while in patients having moderate withdrawal score tolerance had the onset wthin 6.76 months (p=0.03, t test). Patient with mild withdrawal features had the onset of tolerance within of 9.06 months, while patients with moderate withdrawal score had a mean use of 14.53 months (p=0.005, t test). These difference were significant. The duration of use of opioids was not associated with severity of withdrawal. Later onset of tolerance, withdrawal, longer period abstinence and a greater amount use of substance use, were associated with more severe withdrawal in the study population.

Table 2. Number of patients stabilized on buprenorphine

	COWS Score	Number of patients stabilized			
		Day 3	Day 7	Day 14	Day 28
1	< 5	1	15	28	36
2	5 – 12	35	20	9	1
3	>12	1	2	0	0

Stabilization with buprenorphine

Patients were given buprenorphine on day of presentation. Stabilization was achieved if patient had a score less than 5 as per COWS, on the day subsequent to the induction of buprenorphine treatment. The following table shows the stabilization (complete resolution of withdrawal). At the end of 1 week of sublingual buprenorphine treatment, 15 patients had a complete resolution. At two weeks the number increased to 28. Only 1 patient did not achieve stabilization on buprenorphine.

Profile of resolution of withdrawal on buprenorphine

We observed the changes and resolution of the opioid withdrawal symptoms on buprenorphine regimen. The mean score is tabulated below (Table 3).

Table 3. Resolution of withdrawals on buprenorphine

No.	COWS Component (Mean score)	Day 1	Day 3	Day 7	Day 14	Day 28
1	Resting Pulse Rate	1.43	1.32 (-7.6%)	1.32 (-7.6%)	0.94 (-34%)	0.45 (-68%)
2	Sweat	1.16	0.64 (-45%)	0.4 (-65%)	0.16 (-86%)	0.05 (-95%)

3	Restlessness	1.13	0.62 (-45%)	0.48 (-57%)	0.29 (-74%)	0.10 (-91%)
4	Pupils	1.08	0.97 (-10%)	0.97 (-10%)	0.73 (-32%)	0.75 (-30%)
5	Bone or joint aches	1.7	1.1 (-35%)	1.1 (-35%)	0.83 (-51%)	0.54 (-68%)
6	Runny nose or tears	1	0.78 (-22%)	0.59 (-41%)	0.27 (-73%)	0.18 (-82%)
7	GI upset	0.81	0.43 (-47%)	0.35 (-57%)	No Score	No Score
8	Tremor	0.67	0.29 (-57%)	0.18 (-73%)	No Score	No Score
9	Yawning	0.62	0.43 (-30%)	0.27 (-56%)	0.13 (-79%)	0.08 (-87%)
10	Anxiety	0.97	0.81 (-16%)	0.78 (-19.5)	0.62 (-36%)	0.32 (-67%)
11	Gooseflesh	0.45	0.08 (82%)	0.05 (-88%)	No Score	No Score
12	Mean COWS Score	11.08	7.51 (-32.2)	6.51 (-41.2)	4.11 (-63%)	2.51 (-77%)

We observed that mean scores of resting pulse rate did not show drop till by 7th day of assessment. After two weeks, symptoms of tremor, GI upset and gooseflesh completely subsided. The parameter contributing to withdrawals were increased pulse, pupillary dilatation and bone or joint aches.

Dose requirement in the study population

The doses of buprenorphine were given according to the symptoms. We found that the dosage requirement in our population was in the range of 1.2 mg – 14 mg on first assessment day of the study, while at the end of the study was 0.6 mg – 16 mg. The need for doses were higher on day 7 (Table 4).

Table 4. Mean buprenorphine dose across the period of observation

	In mg	Day 1	Day 3	Day 7	Day 14	Day 28
1	Mean	6.191	6.74	6.92	6.47	6.42
2	Range	1.2-14	1.2 – 18	1.2-20	1.2-16	0.6-16
3	Minimum	1.2	1.2	1.2	1.2	1.2
4	Maximum	14	18	20	16	16

We tried to compare the variations against the opioid use parameters and COWS score. The results were not statistically significant.

DISCUSSION

Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a partial opioid agonist at the mu (μ) opioid receptors in the nervous system [16]. Due to this partial action, it has a ceiling effect [17]. Buprenorphine is newer agent used in detoxification of opioid withdrawals, as compared to methadone has been preferred due to absence of pure agonist action, unlike methadone, and therefore has less addictive potential [18]. Also regular tobacco use was noted in all of our study population. Nicotine is

well documented for it's "gateway effects" [19]; all our patients were initially introduced to nicotine and later went on to use opioid. Dosage parameters for buprenorphine were first introduced in 1980 [20-23]. Similar modules as mentioned in Table 5 are being followed and advocated dosage in range of 2mg onwards.

Table 5. Buprenorphine dosing guidelines

No.	Study	Dose Used
1.	The NIDA Clinical Trials Network Field Experience [14]	8 mg buprenorphine-2 mg naloxone on the first day and a target dose of 16mg buprenorphine-4 mg naloxone in three days.
2.	Buprenorphine Tapering Schedule [24]	Buprenorphine dosages were fixed with two taper regimens. The starting dose was 8mg in either group. Doses fixed at 8mg,16 and 24mg. Taper schedules were over 7 day versus one over 28 days.
3.	American Society of Addiction Medicine (ASAM) National Practice Guideline. [25]	Induction of buprenorphine should start with a dose of 2–4mg. Incremental dosages of 2mg to 4mg. Maximum dose of 24 mg.
4.	National Guidelines for Medication-Assisted Treatment of Opioid Dependence, Australia.	Induction of buprenorphine should start with a dose of 2–4mg. Prescribers should try to achieve a dose of 12-16mg by day 3.

In guidelines for opioid substitution the dosages are fixed, we did not find a study wherein, the withdrawals formed the basis of dosage administration. We monitored the withdrawals; the buprenorphine dosages were from 1.2 mg to 16 mg/day. The cumulative dose of buprenorphine received over the observation period was less. Our study contributes to the observation in the recently published National AIDS Control Organization [11] guidelines regarding the dose of buprenorphine, being lower in Indian population.

CONCLUSION

We studied the opioid withdrawals in the population, and the buprenorphine dosages were titrated according to the symptoms and not based on fixed dose. We tried to understand the importance of monitoring buprenorphine induction and stabilization. Clinical guidelines are formulated on data that is specific for a population. Since there is no such data regarding these lines we propose that further research could be planned to obtain a buprenorphine dose requirement on the basis of the opioid use profile and withdrawals, in the Indian setting.

LIMITATIONS

This is a hospital-based study evaluating patient attending outpatient department, therefore the results cannot be generalised. We did not obtain the data regarding the abstinence from opioid use. The sample size was small, and therefore extrapolating the data to Indian population is not possible. Therefore, further studies are needed, with a proportionate sample size.

REFERENCES

1. Avasthi A, Basu D, Subodh BN, Gupta PK, Sidhu BS, Gargi PD, Sharma A, Ghosh A, Rani P. Epidemiology of substance use and dependence in the state of Punjab, India: Results of a household survey on a state wide representative sample. Asian J Psychiatr. 2018; 33:18-29.
2. Degenhardt L, Charlson F, Mathers B, Hall WD, Flaxman AD, Johns N. and Vos T. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. Addiction. 109: 1320–1333.
3. Practice guideline for the treatment of patients with substance use disorders: alcohol, cocaine, opioids. American Psychiatric Association. Am J Psychiatry. 1995; 152(11 Suppl):1-59.
4. Reckitt Benckiser Pharmaceuticals, Inc. Suboxone (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets) prescribing information. [Internet]. c2006. [Updated September 2006; Cited January 26, 2017.] Available from www.suboxone.com/hcp/pi/.

5. World Health Organization. Guidelines for the psychosocially assisted pharmacological management of opioid dependence. WHO Press, Geneva. [Internet]. c2009. [Updated 2009; Cited January 29, 2017.] Available from www.who.int/ substance_abuse/ publications/ opioid _dependence _ guidelines.pdf.
6. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville MD: Substance Abuse and Mental Health Services Administration, 2004.
7. Nicholls L, Bragaw L and Ruetsch C. Opioid dependence treatment and guidelines. J Manag Care Pharm. 2010; 16(1 Suppl B):S14-21.
8. Clinical guidelines for withdrawal management and treatment of drug dependence in closed settings. [Internet] WHO Library Cataloguing in Publication Data World Health Organization. c 2009. [Updated 2009; Cited 26 March 2017.] Available from http://www.wpro.who.int/publications/docs/ClinicalGuidelines_forweb.pdf
9. National AIDS Control Organization, Substitution Therapy with Buprenorphine for Opioid Injecting Drug Users. [Internet] c2008. [Updated 2008 ; Cited 21 April 2014]. Available from www.nacoonline.org/
10. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clinical Pharmacology and Therapeutic. 1994; 55(5):569-580.
11. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. Psychopharmacology (Berl). 1995;119(3):268-76.
12. O'Connor PG, Oliveto AH, Shi JM et al. A randomized trial of buprenorphine maintenance for heroin dependence, in a primary care clinic for substance users versus a methadone clinic. Am J Med. 1998; 105(2):100-5.
13. Amass, L., Ling, W., Freese et al. Bringing Buprenorphine-Naloxone Detoxification to Community Treatment Providers: The NIDA Clinical Trials Network Field Experience. The American Journal on Addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2004. 13(Suppl 1), S42–S66.
14. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. Cochrane Database of Systematic Reviews Cochrane Database Syst Rev. 2009 Jul 8;(3):CD002025. doi: 10.1002/14651858.CD002025.pub4.
15. Wesson, D. R., & Ling, W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003; 35(2): 253–9.
16. Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaeli P. Opioid detoxification using high doses of buprenorphine in 24 hours: a randomised, double-blind, controlled clinical trial. Journal Substance Abuse Treatment. 2004; 27:75–82.
17. Rao R, Agrawal A, Ambekar A. Opioid Substitution Therapy under National AIDS Control Programme: Clinical Practice Guidelines for treatment with Buprenorphine. Department of AIDS Control, Ministry of Health and Family Welfare, Government of India, New Delhi. 2014.
18. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine–naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction (Abingdon, England) 2005; 100(8):1090-1100.
19. Phillips CV. Gateway Effects: Why the Cited Evidence Does Not Support Their Existence for Low-Risk Tobacco Products (and What Evidence Would). Burstyn I, Luta G,eds. International Journal of Environmental Research and Public Health. 2015; 12(5): 5439-5464.
20. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use: An International Review. Current drug abuse reviews. 2011; 4(1):28-41.
21. Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. Am J Addict. 2004;13 (Suppl 1):S17–28.
22. Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. Science. 1980; 207 (4431):657–659.
23. Schuman-Olivier Z, Albanese M, Nelson SE, et al. Self-treatment: illicit buprenorphine use by opioid-dependent treatment seekers. J Subst Abuse Treat. 2010; 39(1):41–50.
24. Ling W, Hillhouse M, Domier C, et al. Buprenorphine tapering schedule and illicit opioid use. Addiction (Abingdon, England). 2009; 104(2):256-265.
25. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Journal of Addiction Medicine. 2015; 9(5):358-367.
26. Lintzeris N, Clark N, Winstock A, Dunlop A, Muhleisen P, Gowing L, Ali R et al. National clinical guidelines and procedures for the use of buprenorphine. [Internet] Commonwealth of Australia. October 2006. Available from www.ag.gov.au/cca