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'Too little dose – too early discontinuation?'—Effect of buprenorphine dose on short term treatment adherence in opioid dependence

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ABSTRACT

Background: Opioid substitution therapy is an evidence-based treatment for opioid dependence syndrome. Retention in treatment is a crucial mediator of treatment success. Our study aims to examine factors associated with early treatment non-compliance among patients who are initiated on office-based Buprenorphine Maintenance Treatment (BMT).

Method: This is a prospective observational study conducted among 89 subjects who were initiated on BMT and were followed up to 6 weeks. At baseline, we evaluated subjects using: Mini International Neuropsychiatric Interview Plus, Addiction Severity Index-Lite, Multi-Dimensional Scale of Perceived Social Support, Heroin Craving Questionnaire, and urine toxicological analysis. Treatment adherence for six weeks was noted.

Results: Among Eighty-nine subjects, 57 per cent of the sample reported addiction to pharmaceutical opioids. The mean dose of Buprenorphine was 6.7 mg (SD = 4.1). During follow up 67 per cent (n = 62) patients were adherent to treatment while 33 per cent (n = 27) non-adherent to treatment. The mean dose of buprenorphine in the non-adherent group was significantly lower than the adherent group (4.3 mg and 7.7 mg, respectively, t [87] = 3.8, $p < 0.001$). A comparison of groups based on the dose of Buprenorphine (6 mg or higher vs lower than 6 mg) revealed that odds of treatment non-adherence were three times higher in patients receiving 6 mg or lesser dose (Odds Ratio = 3.15 [95% CI = 2.0–8.6], χ^2 [1] = 4.75, p = 0.035).

Conclusion: Dose of Buprenorphine prescribed by the treating clinician influences early treatment compliance significantly.

1. Introduction

The Global Burden of Disease (GBD) study, 2010 reported that opioid dependence syndrome (ODS) accounts for 9.2 million Disability-adjusted life years and 2 million years of life lost prematurely. Importantly, it reflects a 73 per cent increase in opioid use over two decades (1990–2010) (Degenhardt et al., 2014). Notwithstanding the fact that ODS has effective treatment in the form of Opioid substitution therapy (OST) (Mattick et al., 2009, 2014). Buprenorphine and Methadone are two commonly used medications in OST. Treatment seeking for ODS has increased in India as reflected by data from the Drug Abuse Monitoring System (Ray and Chopra, 2012). A recent study of magnitude of substance use in India has reported that approximately 22.6 million individuals use opioids in India (Ambekar et al., 2019). Earlier studies from National Institute of Mental Health and Neurosciences (NIMHANS) have demonstrated the utility of take-home buprenorphine (Chand and Murthy, 2013) and its superiority in ensuring short term treatment retention (Bandawar et al., 2015).

Treatment adherence is a complex concept reflecting the degree to which a patient's behaviour concurs with therapeutic advice (Aronson, 2007). It includes adherence to prescribed medication and regular follow up with the clinician. Socio-demographic characteristics, cost-effectiveness, adverse effects, motivation to change, social support and stigma influence treatment adherence in OST (Egan et al., 2011). An

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important determinant of treatment effectiveness is the dose of Buprenorphine used during the initial period of treatment. A multi-centre study found that aggressive dosing is three times superior to low doses in promoting treatment adherence (Jacobs et al., 2015). Characteristically, Buprenorphine doses used in India are much smaller than international guidelines. Ambekar et al. summarise empirical studies that have guided optimal buprenorphine dose (4–8 mg) recommended in India, which is about one-third of that recommended in international guidelines (Ambekar et al., 2018). Considering these facts, it is essential to evaluate the relationship between Buprenorphine dose and short-term treatment adherence. This study aimed to evaluate this relationship prospectively controlling for other factors that might act as confounders.

2. Materials and methods

This is a prospective cohort study with convenient sampling and follow-up duration of 6 weeks. The study was carried out at Centre for Addiction Medicine (CAM), NIMHANS Bangalore. Eighty-nine subjects diagnosed with Opioid Dependence syndrome (F 11.2) as per ICD – 10 criteria (W.H.O, 1992) who enrolled for office-based BMT were recruited after obtaining informed consent. The first author (MP) evaluated all subjects at baseline (before initiation of BMT) and six weeks follow-up. Subjects were evaluated using a semi-structured work-up pro forma that provided addiction-related information (type of opioid used, frequency, duration), Mini International Neuropsychiatric Interview Plus (MINI-PLUS), (Sheehan et al., 1998) Addiction Severity Index-Lite (ASI) (McLellan et al., 1980), Multi-Dimensional Scale of Perceived Social Support (MSPSS) (Zimet et al., 1988) and Heroin Craving Questionnaire – short Form (HCQ-SF) (Tiffany and Wray, 2012). At baseline, urine testing was done to detect the presence of opioids (Point of Care test confirmed by Gas chromatography-Mass spectrometry). Patients who reported for follow-up were tested at six weeks for the presence of opioids as well as Buprenorphine. Treatment outcome measured at six weeks was operationalised as a dichotomous variable:

Treatment Adherence (TA): Defined as consumption of not less than 90% of the prescribed dose of Buprenorphine and follow-up at six weeks.

Treatment Non-Adherence (TNA): Defined as consumption of less than 90% of the prescribed dose of Buprenorphine or absence of follow-up at six weeks.

We have chosen a higher threshold of 90 percent for two reasons. First, population based studies have shown that more than 80 percent adherence is predictive of better outcomes (Tkacz et al., 2014). Second, buprenorphine treatment is conventionaly studied as an office-based (directly observed treatment) wherein a 100 percent adherence is expected (Fareed et al., 2014).

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) 16. Data were summarised using appropriate measures of central tendency and dispersion. Comparison between TA and TNA groups was made using independent sample *t*-test and chi-square test to identify potential differences. Further, to study the effect of dose on the probability of treatment non-adherence sample was split at a median dose (6 mg), and the two groups were compared using the chi-square test of independence.

The study was approved by the institute ethics committee, and patients have been recruited after informed consent.

3. Results

Eighty-nine subjects completed the study (N = 89), with a mean age of 33.3 years (SD = 10.4), 5.6 per cent of the sample was female (n = 5), 60 per cent (n = 53) had an education of fewer than 12 years, and 22 per cent (n = 20) were unemployed. Importantly, fifty-seven per cent of the sample reported addiction to pharmaceutical opioids, and thirty-five per cent (n = 31) reported injection drug use in their lifetime. Thirty-two per cent (n = 29) had a co-morbid psychiatric disorder as evaluated by MINI-plus, most common diagnosis (n = 14) was Attention deficit hyperactivity syndrome (ADHD). Mean dose of Buprenorphine was 6.7 mg (SD = 4.1), median dose =6 mg (IQR = 4).

Table 1
Comparison of treatment adherent and non-adherent patients receiving buprenorphine maintenance treatment.

	Treatment non-adherent (n = 27)	Treatment Adherent (n = 62)	Test Statistic (df)	P value
Mean Age in years (SD)	31 (8.68)	34.4 (11)	t = −1.43 (87)	0.16
Type of opioid abused, n (%)				
Illicit	6 (22.2)	28 (45.2)	χ^2 = 4.81 (2)	0.09
Pharmaceutical	17 (63)	30 (48.4)		
Both	4 (14.8)	4 (6.5)		
Route of opioid intake, n (%)				
Injection Drug use	8 (29.6)	23 (37.1)	χ^2 = 0.462 (1)	0.50
Others	19 (70.4)	39 (62.9)		
Mean Duration of drug dependence in months (SD)	73.22 (70.81)	90.27 (74.11)	t = −1.01 (87)	0.32
Presence of other SUD (except nicotine), n (%)				
Absent	16 (59.3)	36 (58.1)	χ^2 = 0.11 (1)	0.97
Present	11 (40.7)	26 (41.9)		
Presence of psychiatric co morbidity, n (%)				
Absent	16 (59.3)	45 (72.6)	χ^2 = 1.54 (1)	0.21
Present	11 (40.7)	17 (27.4)		

Using the study definition of treatment adherence at six weeks, 67 per cent patients were classified as treatment-adherent (n = 62) (TA) and 33 per cent (n = 27) as treatment non-adherent (TNA). These two groups were compared concerning age, ASI Composite scores, HCQ scores, MSPSS scores, gender, type of opioid used, route of opioid used, duration of opioid use, comorbid psychiatric or substance use disorder diagnosis, and the dose of Buprenorphine received. Table 1 reports some key comparisons between the two groups. The only variable found to be unequally distributed between the two groups was the Dose of Buprenorphine. TA group received a significantly higher total dose (mean = 7.7, SD = 4.0) as compared to TNA group (mean = 4.3, SD = 3.5) (t = 3.8, df = 87, p two-tailed < .001). All patients received standard non-pharmacological treatment consisting of psychoeducation, motivation enhancement and relapse prevention counselling.

A comparison of groups based on the dose of Buprenorphine (6 mg or higher vs lower than 6 mg) revealed that odds of treatment non-adherence were three times higher in patients receiving 6 mg or lesser dose as compared to those receiving higher than 6 mg dose. This is summarised along with test statistics in Table 2.

4. Discussion

This is a prospective study of 89 subjects enrolled for office-based BMT and followed up for six weeks to study factors affecting early treatment non-adherence. At baseline, variables related to differences in socio-demographic profile, addiction severity, craving measures, type of opioid used, comorbidity and social support were equally distributed and thus are not considered as confounders. The study found that the dose of Buprenorphine prescribed by the treating clinician influenced subsequent treatment non-adherence significantly. These

Table 2
Effect of buprenorphine dose on early treatment non-adherence in opioid dependence syndrome.*

Dose of buprenorphine in mg/day	Treatment non-adherence (N)	Treatment adherence (N)	Odds of treatment non-adherence
Group1- dose ≤6	21	33	.63
Group2- dose > 6	6	29	.20

* Odds ratio = 3.15, χ^2 = 4.75, df = 1, 2 sided exact sig (p) = .035, Mantel-Hanszel common odds ratio 95% CI = . 2.0–8.6.

findings need discussion in the light of other studies and its implications for treatment.

Firstly, treatment non-adherence during the early part of treatment needs attention as it jeopardises opportunities of long-term psychosocial intervention. The relationship between retention and outcome is a smooth curve with no sharp threshold. Thus, it is also useful to study short-term retention (Zhang et al., 2003). The relationship of Buprenorphine dose and long-term retention (3 months and more) is reported in a meta-analysis (Fareed et al., 2012). A recent study comparing different induction regimens of Buprenorphine reported favourable trajectories with higher doses (Jacobs et al., 2015). Hence, our study is in agreement with these findings. It also highlights that dose of Buprenorphine may exert a disproportionate influence in short-term retention.

Buprenorphine has different dose thresholds for withdrawal management, craving reduction and reinforcement blocking effects. Relief of withdrawal symptoms is achieved at a low dose of 4 mg while craving reduction requires eighty per cent mu-opioid receptor occupancy, which can only be achieved at higher doses (Greenwald et al., 2014). This reflects the fact that control of withdrawal symptom may not be a sufficient end-point for deciding the doses of Buprenorphine.

Lastly, we should discuss the factors leading to the prescription of low doses of Buprenorphine to our patients. An important reason could be that our sample had a predominance of non-injection drug users, pharmaceutical opioid cases. This leads to a dilemma on the part of the clinician as available guidelines are mostly for heroin injection drug users. An ongoing Cochrane review will likely fill this gap and provide evidence for the optimal use of BMT in pharmaceutical opioid addiction (Nielsen et al., 2014). Another important factor leading to the choice of low doses of Buprenorphine in this group is that many of the pharmaceutical Opioids like Propoxyphene, Tramadol and Pentazocine are considered less potent than Buprenorphine. For example, an equianalgesic dose of 1.6 mg, sublingual Buprenorphine is approximately 130 mg of Propoxyphene. These considerations, however, should not apply in BMT as patients surmount the barriers of potency by increasing the dose of abused opioid (Pereira et al., 2001). Nevertheless, the average prescribed dose of buprenorphine in the current study (6.7 mg) is higher than the 4.4 mg dose reported by Chand et al. in 2011 (Chand and Murthy, 2013). Thus, assessment of craving for Opioids and tolerance for Buprenorphine should guide the titration of sublingual as well as transdermal buprenorphine (Dhawan et al., 2019).

Significant limitations of this study are: it was underpowered to evaluate individual effects of various factors on treatment adherence, it was a flexible dosing study, and thus division of groups based on median dose was used as a posthoc comparison. Also, it was not designed to evaluate factors determining the choice of Buprenorphine dose by the clinician. The findings, however, calls for more considerable attention to optimal dosing of Buprenorphine in clinical practice. The study also highlights the need for prospective studies in Indian population to determine optimal guidelines for BMT induction and maintenance.

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Declaration of Competing Interest

None of the authors have any conflict of interest to declare.

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