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Research Article

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Sexual Dysfunction in Males Receiving Buprenorphine-Naloxone Based Opioid Substitution Therapy

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Introduction

Abuse of opioids and related substances have exerted a tremendous economic, social, legal impact apart from its dire consequences on the individual user's health. Heroin is a quite common illicit opioid that is covertly made available by illegal traders and has a wide client base. The abuser self-administers heroin by two common methods, namely chasing and intravenous injection. Intravenous administration is associated with high risks of contracting parenterally transmitted infections like hepatitis B, hepatitis C, HIV, as well as infective endocarditis, thrombophlebitis etc. The unsafe injecting practices include sharing of needles, syringes, and other paraphernalia. The National Aids Control Programme, currently in its fourth phase (NACP-IV), makes provisions for strategies known as 'harm reduction' to prevent transmission of HIV among intravenous drug users. The harm reduction strategies include needle syringe exchange programme (NSEP), behaviour change communication (BCC), outreach, condom promotion, and substitution therapy (1).

In opioid substitution therapy (OST) the drug user's primary drug of abuse (opioid) is replaced with a medically safer alternative drug or the same opioid in a safer mode of administration under medical supervision (2). The replacement drug is a medication which is long acting and safer, and administered through oral/sublingual route. Buprenorphine is a commonly used opioid medication for OST. It is often used in combination with Naloxone. Buprenorphine-naloxone is a 4:1 combination of buprenorphine, a partial mu receptor agonist, and naloxone, an opioid antagonist. It has been found that opioid maintenance treatment is effective in reducing mortality, criminal activities as well as in improving psychosocial functions (3). Buprenorphine-naloxone maintenance treatment was showed to be associated with good treatment retention and significantly reduced opioid use (4, 5).

Buprenorphine is a semi-synthetic opioid derivative of thebaine which is a derivative of opium. Buprenorphine is a partial μ receptor agonist with potent antagonistic action at ƙ-receptor. Buprenorphine being a partial agonist, decreases the side effects of opioid substitution like risk of respiratory depression with overdose. Naloxone is added in the combination so as to prevent the intravenous abuse potential of buprenorphine given alone. As an opioid antagonist, it nullifies the effects of buprenorphine if any user attempts to use the combination drug intravenously, thereby precluding the abuse potential of the drug.

Despite their great utility, such substitution drugs come with their own side effect profile which includes sexual dysfunction. Sexual dysfunction is a complex phenomenon where various hormonal, neurobiological, and psychosocial factors are at play. It is a condition which may manifest as reduced sexual interest, problems with sexual arousal and ejaculation, and orgasmic dysfunction (6). Drugs used in opioid substitution therapy influence the hormonal axes involved in sexual functioning. They may act via (1) acting on hypothalamic-pituitary-gonadal axis (affecting LH, FSH, GnRH), (2) elevation of serum prolactin, (3) suppressing testosterone production with direct action on the testes (7). Such side effects associated with long-term use of opioid antagonists or agonists could result in abandoning the substitution therapy (8, 9).

Under Assam State AIDS Control Society, opioid substitution therapy(OST) centres have been opened in the state. One such centre was functionalized within the premises of Silchar Medical College & Hospital, Silchar in June 2019. There has been a satisfactory level of utilization of its services by clients from different parts of the Barak valley. However, possible sexual dysfunction reduces quality of life in patients on OST, which may contribute to treatment non-adherence. Therefore, it is necessary to assess the quality of sexual experience in patients on opioid substitution therapy.

Materials and Methods

Participants and Data Collection

It was a hospital based observational study. Participants for our study were recruited from patients attending the OST centre at Silchar Medical College & Hospital. Fifty consecutive patients undergoing OST were selected as per the following inclusion and

exclusion criteria:

Inclusion criteria:

1. Male married/sexually active patients attending OST centre who are on buprenorphine-based OST for a period of six months or longer.
2. Patients in the age group 18-60 years.
3. Patients providing informed consent.

Exclusion criteria:

1. Patients who reported sexual dysfunction prior to initiation of buprenorphine-based OST.
2. Patients having medical or surgical conditions known to contribute to sexual dysfunction (e.g. diabetes mellitus, lower spinal cord injury).
3. Patients with significant psychiatric comorbidities These patients were on sublingual buprenorphine therapy with maintenance doses of buprenorphine ranging from 2mg to 6mg sublingually per day after at least 6 months of therapy.

Semi-Structured Questionnaire:

A semi-structured questionnaire was designed to gather sociodemographic data such as the age, gender, religion, residence, educational status, occupation, income etc. It also included questions pertaining to presence of symptoms of sexual dysfunction like decreased sexual desire, erectile dysfunction, premature ejaculation, lack of satisfaction with sexual life prior to initiation of OST.

Asex and Iief-15

After getting informed consent the patients were interviewed with a semi-structured proforma to gather data regarding sociodemographic profile, duration of opioid use, medical history, pre-existing sexual issues. They were then administered two scales for assessment of sexual functioning: Arizona Sexual Experience Scale (ASEX) and International Index of Erectile Function (IIEF-15).

ASEX is a questionnaire with five questions the responses to which are scored in a Likert type style with scores ranging from 1 to 6 for each, a minimum total score of 5 and maximum total score of 30.10 The questions address issues of sex drive, arousal, penile tumescence and vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. A total score of 19 or more, or a score of 5 in one or more question, or scores of 4 in three or more questions is indicate presence of sexual dysfunction. It is a widely used reliable and validated instrument for assessment of sexual functioning (10).

IIEF-15 is a fifteen-question self-reporting instrument with Likert type scoring (11). It is a validated diagnostic tool for identifying and grading the degrees of erectile dysfunction in males (12). The scale is subdivided into five domains to assess various aspect of sexual functioning: erectile function (questions 1, 2, 3, 4, 5, and 15), orgasmic function (questions 9 and 10), sexual desire (questions 11 and 12), intercourse satisfaction (questions 6, 7, and 8), and overall satisfaction (questions 13 and 14). A higher score indicates better sexual functioning. In the erectile function domain, a score of 26-30 is considered as normal functioning. While scores less than 26 are taken to be indicative of various degrees of erectile dysfunction: mild dysfunction (22-25), mild to moderate dysfunction (17-21), moderate dysfunction (11-16), severe dysfunction (6-10) (12). There is no consensus regarding the interpretation of the scores in the other domains (13).

Statistical Analysis

Collected data were analysed using the IBM Statistical Package for the Social Sciences (SPSS), version 21. Chi-square or Fisher's exact test was used to compare categorical variables between groups. ANOVA was employed to compare means between groups, while Pearson's correlation was used to find linear relationship between different quantitative variables.

Results

Sociodemographic Characteristics

The participants ranged in age from 23 to 56 years with a mean age of 35.70±7.305 years. As shown in table 1, most (58%) were in the third decade of their lives, were Muslims by religion (60%), from a rural or semi-urban background (94%). Maximum were educated up to middle (50%) or primary (26%) level of schooling. By occupation, a major (42%) proportion were drivers of private transport vehicles or trucks, 18% were small vendors, while 14% were daily wage labourers, and another 14% unemployed. Maximum (66%) participants belonged to upper lower socioeconomic class.

Table 1. Sociodemographic characteristics of the study participants

Variable		Frequency	Percentage
Age group	20-29 years	8	16%
	30-39 years	29	58%
	40-49 years	11	22%
	50-59 years	2	4%
Religion	Islam	30	60%
	Hinduism	20	40%
Residence	Rural	21	42%
	Semi-urban	26	52%
	Urban	3	6%
Type of family	Nuclear	23	46%
	Joint	6	12%
	Extended	21	42%
Educational status	Illiterate	2	4%
	Primary schooling	13	26%
	Middle schooling	25	50%
	High school	8	16%
	Higher secondary	2	4%
	Graduate or above	Nil	0%
Occupation	Unemployed	7	14%
	Farmer	4	8%
	Daily wage earner	7	14%
	Vendor	9	18%
	Driver	21	42%
	Salaried person	2	4%
Socioeconomic status	Lower	9	18%
	Upper lower	33	66%
	Middle	5	10%
	Upper middle	2	4%
	Upper	1	2%

Drug use and treatment related variables

It was found that the duration of opioid use ranged from 1 year to 25 years, with 34% having 5 years or less, 36% having 6-10 years and 30% having more than 10 years of usage. Most of the participants were interviewed after completion of 6 months (52%) and 7 months (40%). The dose of sublingual buprenorphine ranged from 2mg/day (30%) through 4mg/day (46%) to 6mg/day (24%). (Table 2)

Table2: Drug use and Treatment variables

Variable		Frequency	Percentage
Duration of opioid use	5 years or less	17	34%
	6-10 years	18	36%
	More than 10 years	15	30%
Duration of OST (in completed months)	6 months	26	52%
	7 months	20	40%
	8 months	4	8%
Current dose of buprenorphine (per day)	2mg	15	30%
	4mg	23	46%
	6mg	12	24

Sexual functioning

As assessed by ASEX scale, 52% of the participants were found to be having sexual dysfunction, with individual mean scores for each component as shown in table 3. IIEF-15 scorings showed a total mean score of 41.12±8.969 (range 15-61). In the erectile function domain, the scores ranged from 7 to 24 with a mean of 16.22±3.840. As shown in table 3, a major proportion of the participants had mild to moderate erectile dysfunction (44%) followed by moderate dysfunction (40%), while 4% had mild and 12% had severe erectile dysfunction.

On further analysis, statistically significant negative correlations were seen between analogous components of the two scales. For example, as can be seen in table 4, significant negative correlations were seen between ASEX question 1 (sexual drive) score and IIEF-15 sexual desire domain score; between ASEX question 3 (erection) score and IIEF-15 erection function score. Hence, despite the two scales measuring different prevalence of sexual dysfunctions, the levels of dysfunction as assessed by the two scales had significant linear relationships, i.e. the findings elicited by the two different scales were consistent with each other.

Table 3: Mean scores of ASEX and IIEF domains, and prevalence of sexual dysfunction and severity of erectile dysfunction

	Variables	Mean scores	
ASEX component	**Sexual drive**	3.48±0.735	
	Psychological arousal	3.58±0.673	
	Erection	3.62±0.805	
	Ease of orgasm	3.54±0.788	
	Orgasm satisfaction	3.56±0.705	
	ASEX total	17.58±2.865	
IIEF domains	**Erection function**	16.22±3.840	
	Orgasmic function	6.10±1.403	
	Sexual desire	5.38±1.227	
	Intercourse satisfaction	7.38±2.329	
	Overall satisfaction	6.04±1.399	
	IIEF total	41.12±8.969	
		Frequency	**Percentage**
ASEX	**Sexual dysfunction**	26	52%
IIEF-15	**Mild ED**	2	4%
	Mild to moderate ED	22	44%
	Moderate ED	20	40%
	Severe ED	6	12%

Table 4: Correlation between ASEX item scores and IIEF-15 domain scores

			IIEF-15 domains				
			Erection function	**Orgasmic function**	**Sexual desire**	**Intercourse satisfaction**	**Overall satisfaction**
ASEX Items	**Sexual Drive**	**PC**	-.523	-.542	-.568	-.419	-.634
		p	.000	.000	.000	.002	.000
	Psychological arousal	**PC**	-.595	-.538	-.421	-.365	-.567
		p	.000	.000	.002	.009	.000
	Erection	**PC**	-.533	-.489	-.636	-.444	-.620
		p	.000	.000	.000	.001	.000
	Ease of orgasm	**PC**	-.546	-.622	-.449	-.392	-.409
		P	.000	.000	.001	.005	.003
	Orgasm satisfaction	**PC**	-.424	-.409	-.605	-.456	-.603
		p	.002	.003	.000	.001	.000
PC= Pearson Correlation coefficient, p= p-value (2-tailed)							

As for the possible determinant effect of age on sexual functioning, weakly statistically significant differences in mean scores were seen among the age groups for the first two items (sexual drive and psychological arousal)in ASEX scale, with the youngest age group (20-29 years) scoring lesser than the rest of the groups. However, no such differences could be seen for the rest of the items as well as for the total ASEX score. (Table 5.1)

On the other hand, as seen in table 5.2, no statistically significant differences in the mean scores for individual IIEF-15 domains and mean total IIEF-15 scores were seen among the different age groups. Similarly, the degree of erectile dysfunction had no statistically significant difference in their occurrence among different age groups.

Table 5.1 Mean ASEX scores and interpretation across age groups

Age group (in years)	Percentage of sexual dysfunction as per ASEX	Mean scores for ASEX domains					
		Sexual drive	Psychological arousal	Erection	Ease of orgasm	Orgasm satisfaction	Total score
20-29	25.0	2.88	3.00	3.13	3.38	3.13	15.50
30-39	51.7	3.52	3.66	3.66	3.52	3.59	17.59
40-49	72.7	3.82	3.82	3.91	3.73	3.73	19.00
50-59	50.0	3.50	3.50	3.50	3.50	4.00	18.00
P -value	0.215	0.044	0.047	0.211	0.811	0.215	0.068

Table 5.2. Mean IIEF scores and interpretation across age groups

	Age group (in years)					
		20-29	**30-39**	**40-49**	**50-59**	**P-value**
Mean scores for IIEF domains	**Erection function**	16.50	16.90	14.45	15.00	0.332
	Orgasmic function	6.50	6.28	5.45	5.50	0.290
	Sexual desire	5.63	5.59	4.91	4.00	0.151
	Intercourse satisfaction	7.88	7.79	6.45	4.50	0.105
	Overall satisfaction	6.50	6.10	5.64	5.50	0.557
	Total score	43.00	42.66	36.91	34.50	0.195
Erectile dysfunction (percentage)	**Mild**	0%	6.9%	0%	0%	0.779
	Mild to moderate	50.0%	48.3%	27.3%	50.0%	
	Moderate	50.0%	34.5%	45.5%	50.0%	
	Severe	0%	10.3%	27.3%	0%	

We wanted to examine whether there was any correlation between the current dose of buprenorphine with levels of sexual functioning. No statistically significant differences were seen in the prevalence of sexual dysfunction or erectile dysfunction across different dosages of buprenorphine. Again, when individual scores for the items in ASEX and the individual domains in IIEF-15 were compared for different current dosages of buprenorphine, no significant difference was found. Similarly, no statistically significant differences were seen among participants undergoing different durations of OST as regards the mean scores across all the items in both the scales. (Table 6.1, 6.2, 6.3)

Table 6.1: Prevalence of sexual dysfunction and erectile dysfunction across different buprenorphine doses

Dose of buprenorphine (per day)	Presence of sexual dysfunction (as per ASEX)	Erectile dysfunction as per (IIEF-15)			
		Mild	Mild to moderate	Moderate	Severe
2mg	53.3%	0.0	53.3%	33.3%	13.3%
4mg	52.2%	4.3%	39.1%	43.5%	13.0%
6mg	50.0%	8.3%	41.7%	41.7%	8.3%
Level of significance	Pearson Chi-Square value=0.030 P=1.000	Fisher's exact value=2.404 P=0.956			

Table 6.2: Mean ASEX and IIEF scores across different buprenorphine doses

Variables		2mg/day	4mg/day	6mg/day	Significance level (p value)
ASEX domains	Sexual drive	3.60	3.48	3.33	0.654
	Psychological arousal	3.60	3.48	3.75	0.530
	Erection	3.60	3.74	3.42	0.538
	Ease of orgasm	3.53	3.48	3.67	0.804
	Orgasm satisfaction	3.60	3.65	3.33	0.440
	ASEX total	17.60	17.74	17.25	0.895
IIEF-15 domains	Erection function	16.27	16.09	16.42	0.971
	Orgasmic function	6.33	5.96	6.08	0.728
	Sexual desire	5.00	5.48	5.67	0.333
	Intercourse satisfaction	7.20	7.35	7.67	0.876
	Overall satisfaction	5.80	6.13	6.17	0.736
	IIEF total	40.60	41.00	42.00	0.922

Table 6.3: ASEX and IIEF scores across duration of buprenorphine based OST

		6 months	7 months	8 months	Significance level (p value)
ASEX domains	Sexual drive	3.58	3.40	3.25	0.592
	Psychological arousal	3.62	3.60	3.25	0.601
	Erection	3.69	3.55	3.50	0.805
	Ease of orgasm	3.69	3.40	3.25	0.349
	Orgasm satisfaction	3.54	3.55	3.75	0.858
	ASEX total	17.81	17.40	17.00	0.822
IIEF-15 domains	Erection function	16.00	16.05	18.50	0.473
	Orgasmic function	6.04	6.00	7.00	0.416
	Sexual desire	5.19	5.65	5.25	0.453
	Intercourse satisfaction	7.04	7.85	7.25	0.509
	Overall satisfaction	6.15	5.95	5.75	0.814
	IIEF total	40.42	41.50	43.75	0.772

DISCUSSION

The combination of buprenorphine and naloxone is a commonly used drug in opioid substitution therapy. Buprenorphine has a safer side effect profile than a number of other drugs used for this purpose. However, it is not without its own side effect profile, which includes sexual dysfunction. As sexual dysfunction as a consequence of medication use may lead to treatment non-adherence, it is essential to assess the prevalence and degrees of sexual dysfunction among the clients receiving such opioid substitution drugs.

The current study employed two widely used and validated instruments, namely ASEX and IIEF-15, in an attempt to assess the prevalence and extent of sexual dysfunction, if any, among individuals receiving buprenorphine based opioid substitution therapy for a duration longer than 6 months.

The rate of prevalence of a complex problem like sexual dysfunction depends on the methodological aspects including the quantitative assessment tools used in a study. Ramdurg et al. (2012), in a study conducted in the Delhi NCR region, using the Brief Male Sexual Functioning Inventory (BMSFI) reported experience of at least one sexual dysfunction symptom in 83% of the opioid using subjects treated with buprenorphine therapy. 14 On the other hand, Mattoo et al., in a study recruiting forty male patients on buprenorphine-naloxone based substitution therapy, found the prevalence of sexual dysfunction to be 40% using the ASEX scale. 15 The current study, while employing the ASEX scale, found sexual dysfunction in 52% of the subjects.

Khreadmand et al. conducted a study comparing sexual dysfunc-

tion among patients undergoing opioid substitution therapy by different maintenance drug regimens (buprenorphine, methadone, opium tincture).16 At the end of 3 months of therapy, the mean scores for the ASEX items (sexual drive, psychological arousal, erection, ease of orgasm, orgasm satisfaction) in the 28 patients on buprenorphine were 3.6±0.7, 4.2±1.1, 3.5±1.2, 4.2±1.1, 3.3±0.9 respectively, with a mean total score of 18.6±4.1. Baykara and Alban conducted a similar study on subjects on buprenorphine-naloxone maintenance therapy for 4 months.7 The mean scores for the individual components, and mean the total score in their study, respectively, were 3.01±1.56, 3.11±1.44, 3.03±1.44, 2.93±1.39, 2.95±1.59, and 15.03±6.61. These scores were more or less comparable to the findings in our study: 3.48±0.735, 3.58±0.673, 3.62±0.805, 3.54±0.788, 3.56±0.705, and 17.58±2.865 respectively. Hence, a comparable level of dysfunction in sexual desire, arousal, erection, orgasm, and orgasmic satisfaction were found in our study participants.

When we assessed sexual functioning using the IIEF-15, some degree of erectile dysfunction was found in all the participants. In the study by Baykaraa and Alban (2019) the same rate was found to be 64.2%.7 In the study by Quaglio and Lugoboni among 201 male patients on maintenance therapy (42% on methadone; 58% on buprenorphine), only 36.3% subjects on buprenorphine-based therapy were found to be having erectile dysfunction as assessed by IIEF-15. Among the participants, 12.9% had mild ED, 3.5% mild to moderate ED, 1.8% moderate ED, and 18.1% severe ED.17 In contrast, the current study found some degree of erectile dysfunction in every participant, with 4% having mild, 44% mild to moderate, 40% moderate, and 12% severe erectile dysfunction. Response bias cannot be ruled out to be accounting for such a higher prevalence. This bias might be rooted in prevalent cultural beliefs regarding virility, perceived 'penile strength' etc. It is worth mentioning that many of the participants as well as a considerable section of other male patients attending psychiatric outpatient department present with complaints of having not enough tumescent penile length or 'strength', while history and clinical evaluation most often rules out true erectile dysfunction. However, this possible cultural artefact needs further systematic investigation. Notwithstanding such possible cultural confounding factors, the distress due to perceived erectile problems was high among the participants. This necessitates the role of proper psychosexual counselling to all the patients undergoing opioid substitution therapy. Those participants (nine in number) who scored significantly low (<14) were suggested a trial course of sildenafil for taking into consideration.

The current study identified some important sociodemographic pattern to opioid use. In our study sample, a typical opioid abuser tended to be of lower socioeconomic strata with lower level of education and engaged in a poorly renumerated occupation. A certain demographic section among the participants was engaged in driving (private goods carrying vehicles or autorickshaw). This finding points toward the need of targeted intervention in curbing opioid abuse in the population.

As for the ASEX domains, our study found the youngest age group (20-29 years) to have significantly lesser dysfunction as regards sexual drive and psychological arousal than the rest of the groups. However, no such differences in extent of dysfunction could be observed among the different age groups in regard to the rest of the domains of ASEX as well as all the domains in IIEF-15. On the other hand, when linear regression was applied to assess the strength of association of age of the individuals with the domain scores in both the scales, it was found that no domain score in ASEX scale had any significant association with age. Except the sexual desire domain in IIEF-15, which had a minimally significant negative correlation (p=0.040) with age, all other domains failed to exhibit any significant correlation with age. Therefore, it can be concluded that age had a minimal role in determining the extent of sexual dysfunction among our study participants. Similarly, the current dose of buprenorphine also did not determine the extent of sexual dysfunction among the participants.

The duration of buprenorphine therapy as well did not have any such significantly determinant role in sexual dysfunction. However, the range of duration of therapy among our participants was very narrow (6-8 months). Therefore, further longitudinal study needs to be carried out to find out such duration related effects of buprenorphine-naloxone based OST.

Limitations:

Several limitations need mention in the current study. First, the study was a cross-sectional one, collecting data at a point of time. Therefore, a longitudinal comparison of pre-treatment and post-treatment sexual dysfunction status could not be done. The pre-OST sexual dysfunction was assessed only by means of retrospective data obtained with the help of a semi-structured interview, which is prone to recall bias. Second, there was no control group in our study. Again, response bias might be in play which might possibly be rooted in cultural beliefs as we have mentioned earlier. Thirdly, number of participants was a relatively small one (fifty only). Further, due to a resource limited setting, we could not do hormonal measurements to complement our study findings.

The strength of our study lies in its being one of the first to assess sexual dysfunction in long term buprenorphine-naloxone based OST in this particular population.

Conclusion:

Opioid substitution therapy has become an established harm reduction method in preventing illicit opioid use and subsequent adverse events. Opioid substitution therapy centres has been functionalized under government agencies like State AIDS Control Society which have seen a satisfactory level of utilization by the population. The possible adverse effects of the buprenorphine-based therapy provided in these centres however can potentially mar the benefits. As sexual dysfunction is one of such adverse effects it becomes imperative to assess the prevalence and degrees of sexual dysfunction among the clients, particularly after long duration of therapy. The current study employed two widely used and validated instruments namely Arizona Sexual Experience Scale (ASEX) and International Index of Erectile Function (IIEF-15). ASEX scorings showed 52% prevalence of sexual dysfunction among the participants. Further, IIEF-15 scorings showed some degrees of erectile dysfunction among all the participants. 84% of the erectile dysfunction were of mild to moderate and moderate severity. Such a high prevalence of erectile dysfunction may be attributed among

other factors to response bias rooted in cultural beliefs regarding virility and sexual performance. On further analysis, no significant effects of age, current dose of buprenorphine, and duration of therapy on the prevalence and degree of sexual dysfunction were found. The study also revealed important sociodemographic correlates of opioid use. These findings suggest the need for evaluation of sexual functioning in all the clients of OST, the need of psychosexual counselling and timely medical or psychological interventions.

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