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Research Article

Sexual Functioning and Quality of Life of Women with Opioid Dependence Maintained on Buprenorphine/Naloxone vs Community Norms

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Abstract

Long term use of opioids has been linked to sexual dysfunction. Problems with sexual functioning have been reported in males maintained on buprenorphine/naloxone (bup/nlx), though the results are variable. Bup/nlx is becoming a popular maintenance option for women given its advantages over methadone. Sexual functioning of females maintained on bup/nlx has not been studied so far.

Objectives: Examine the sexual functioning and quality of life of opioid dependent females maintained on bup/nlx.

Methods: Twenty one non pregnant females maintained on bup/nlx in an office based setting were interviewed using a pre-designed data sheet for socio-demographic and clinical histories. Subjects completed 3 self-administered questionnaires- Female sexual function index (FSFI), Depression, Anxiety and Stress Scale (DASS) and the Quality of life Enjoyment and Satisfaction Questionnaire- Short Form (Q-LES-Q-SF).Results were compared to existing community norms.

Results: 21 subjects with mean age 35.6±8.4 (19-50) years, mean body mass index (BMI) 32.3 kg/m2± 8.9 (19.0-52.1) and mean daily dose of bup/nlx was 17.7±6.0 mg/day participated. Subjects were more likely to have sexual dysfunction (19.1±12.8) $p<0.0001$ on FSFI. Quality of life was rated significantly poorer on Q-LES-Q-SF (47.6±7.9; $p<0.0001$). Results on DASS were not significant. Significant correlation was found between BMI and sexual functioning and sexual functioning and quality of life, while other factors were not significant.

Conclusions: Maintenance with Bup/nlx in women may be associated with significant sexual dysfunction and quality of life impairment. This may impact compliance. Further research is warranted as bup/nlx becomes a popular treatment among females with opioid dependence.

INTRODUCTION

Opioid dependence is a growing public health problem in the United States. The total estimated annual cost of prescription opioid abuse in the US was 55.7 billion in 2007 (Birnbaum HG et al. 2011). This includes costs to workplace, healthcare and the criminal justice system. Among patients with opioid dependence, approximately one third are women of child bearing age (Unger A et al. 2010).

Long term opioid use is known to cause sexual dysfunction

Males with opioid dependence disorder are known to have testosterone deficiency and sexual dysfunction (Bliesener et al. 2005). A potential mechanism is the inhibition of hypothalamic GnRH production, suppression of the normal pituitary secretion of FSH and LH as well as direct reduction of the testicular testosterone secretion by opioids (Danielle HW. , 2002). Sexual dysfunction may manifest as hypoactive sexual desire, erectile and orgasmic dysfunction associated with long term use of opioids/opiates. Most of the studies evaluating sexual dysfunction have been done in methadone maintained and/ or heroin dependent males.

Buprenorphine is a relatively new drug for maintenance treatment of opioid dependence. Its unique receptor profile, being a partial μ agonist and kappa antagonist, suppresses withdrawal and targets cravings. Buprenorphine has a favorable safety profile and low abuse potential. Being a partial agonist with strong adherence, it also blocks the simultaneous binding

of other opioids, preventing relapse (Ling W & Wesson DR. , 2003). To our knowledge, there are only a few studies that have evaluated the impact of buprenorphine on sexual functioning and testosterone levels in men maintained on this medication. Bliesener et al. 2005 used a two question self rating scale along with hormonal assays and found that in contrast to methadone, buprenorphine at a dose of 8-20mg/day did not suppress plasma testosterone in heroin addicted men when compared to normal healthy controls. In a British study Al- Gommer et al. 2007 compared sexual dysfunction across 3 groups (heroin, methadone and buprenorphine) using a self-rated questionnaire and found that sexual dysfunction associated with buprenorphine was significantly less than methadone or heroin. Hallinan et al. 2007 measured sexual function in methadone and buprenorphine maintained men in comparison to a community reference group, and also evaluated the role of several other possible confounds in association with sexual function measures. Buprenorphine maintenance treatment was associated with lower prevalence of erectile dysfunction in comparison to methadone maintenance treatment (MMT). Total testosterone accounted for 16% of the International Index of Erectile Function (IIEF) and 15% of Erectile Function (EF) variance. On multiple regression, depression, older age and lower total testosterone were associated with lower IIEF and EF domains. On multivariate analysis, there was no significant association between IIEF or EF and free testosterone, opioid dose, cannabis or other substance use, viral hepatitis or BMI. This suggests that hormonal suppression may not be the only mechanism through which opioid agonists exert their effects on sexual functioning.

An Italian study (Quaglio et al. 2008) recruited 201 males with a mean age of 31, maintained on buprenorphine (58%) and methadone (42%). Of these, 58% reported no erectile dysfunction (ED), 24% reported mild to moderate ED and 18% severe ED. Men on buprenorphine reported less erectile dysfunction as compared to methadone maintained patients on univariate analysis but not confirmed on multivariate analysis. Additionally, this study highlighted the importance of psychological and social factors associated with ED especially in patients in methadone or buprenorphine treatment.

In addition, buprenorphine induced symptomatic hypogonadism has been reported in 10 cases in patients recruited from a pain clinic who had a history of prescription opioid abuse or dependence (Colameco et al. 2008). In an Indian study that used the Brief Male Sexual Functioning Inventory (BMSFI), 83% of the men maintained on buprenorphine reported at least one sexual dysfunction symptom. Similar results were also found in patients maintained on naltrexone therapy (Ramdurg S et al. 2012).

Opioid endocrinopathy has been reported in women consuming prescribed, sustained-action oral or transdermal opioids for control of nonmalignant pain. The investigators recorded menstrual histories and measured gonadotrophin, androgen and estradiol levels in 47 women ages 30-75. Profound inhibition of ovarian sex hormone and adrenal androgen production was observed (Daniell HW. , 2008).

Only one European study (Giacomuzzi SM et al. 2009) comparing sexual behavior and dysfunction in buprenorphine maintenance treatment had an equal sex distribution of men and women in both buprenorphine and methadone groups (30 men and 30 women). Significant differences between both groups could be observed regarding sexual excitation disturbances (33% in methadone group vs 3.3% in buprenorphine group) and ability to orgasm (40% in methadone group vs 10% in buprenorphine group). Sexual life satisfaction scores were noted to be significantly higher by the buprenorphine maintained group (90%) compared to the methadone maintained group (63.3%) (p=0.030).

Overall, the current literature suggests that the impact of buprenorphine maintenance treatment on sexual functioning of men may be variable and somewhat controversial, at best. Most of the above mentioned studies have been conducted on male heroin users and in countries outside of the United States. Hence the present study sought to assess the sexual functioning and quality of life in prescription opioid dependent females maintained on bup/nlx treatment, and also to assess the impact of factors such as age, depression, BMI, dose and duration of bup/nlx treatment, and history of sexual trauma with sexual function measures.

MATERIALS AND METHODS

Design

This was a cross sectional study in non pregnant women aged 18-55 maintained on buprenorphine/naloxone for opioid dependence in an office based setting.

Participants

Subjects were recruited from the psychiatry outpatient clinic of the principal investigator at a tertiary level teaching health care facility. All potential subjects meeting study inclusion and exclusion criteria were given verbal and written information about the study. A total of 27 subjects were provided information regarding the study; the first 21 candidates who met study criteria and gave signed informed consent were enrolled for the study. Inclusion criteria were non- pregnant females, age range of 18-50years, meeting DSM-IV criteria for opioid dependence, who were actively being treated with buprenorphine/naloxone for over three months in an outpatient setting. Subjects who were currently using alcohol, opiates, or other illicit drugs for the last one month (verified from urine drug screen results), on any hormonal therapy, actively suicidal/homicidal or psychotic were excluded from the study.

The study was approved by the Carilion Clinic Institutional Review Board.

Materials

All enrolled subjects were interviewed by one psychiatry resident under the supervision of a board certified psychiatrist in a private setting for 45 minutes. A predesigned data sheet was used to collect relevant socio-demographic information and clinical/ drug use histories.

Sexual function was evaluated using the Female sexual function index (FSFI) (Rosen R et al. 2000), which is a 19 item brief self report instrument for assessing sexual functioning in

females. It uses a 5 point likert scale and questions are related to six major domains: desire (2 items: assessed as frequency and desire level), sexual arousal (4 items: assessed as frequency, level, confidence and satisfaction), lubrication (4 items: assessed as frequency, difficulty, frequency of maintaining and difficulty in maintaining), orgasm (3 items: assessed as frequency, difficulty, and satisfaction), satisfaction (3 items: assessed as the amount of closeness with partner, sexual relationship and overall sex life) and pain (3 items: assessed as pain frequency during vaginal penetration and pain frequency following vaginal penetration) over the previous four weeks. The FSFI provides scores for each domain as well as a total score, with higher scores indicating better sexual function. The FSFI is shown to have psychometric and clinical validity as well as high test-retest reliability for each of the individual domains. We used the validated FSFI-total cut-off score of 26.55 to classify women with and without Female Sexual Dysfunction (FSD) (Wiegel M et al. 2005). The control population by Rosen et al. was used as the normative population for analysis on FSFI scores.

The 42 item DASS (Depression, anxiety and stress scale) (Lovibond &Lovibond 1995, Antony M et al. 1998) was used for assessment of negative emotional states of depression, anxiety and stress. It is a self-report questionnaire with three scales, each containing 14 items, divided into subscales of 2-5 items with similar content. Respondents are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. Scores for each scale are calculated by summing the scores for the relevant items. The subject scores in each category- depression, anxiety and stress are then evaluated as per a severity rating index ranging from normal to extremely severe. Scores above 20, 14, and 25 on the depression, anxiety, and stress subscales respectively are indicative of severe levels. The DASS has demonstrated good validity, high internal consistency and reliability, with Cronbach's alpha reported at 0.94 for Depression, 0.87 for Anxiety and 0.91 for Stress. Normative data used in our study was obtained by averaging the normative data from an Australian study cited with the scale and the British study by Crawford and Henry 2003. In the Australian sample of 2914 adults the means (and standard deviations) were 6.34 (6.97), 4.7 (4.91), and 10.11 (7.91) for the depression, anxiety, and stress scales, respectively. For the British sample of 1771 adults, the means and (standard deviation) were 5.55 (7.48), 3.56 (5.39) and 9.27 (8.04) for the depression, anxiety and stress scales respectively.

Quality of life was assessed using the short form version of Quality of Life Enjoyment and Satisfaction Questionnaire Q-LES-Q (SF) which is a 16- item scale that is the same as the general activities domain of the long-form Q-LES-Q. Responses from the first 14 items of the short form, each scored on a response scale ranging from 1 (very poor) to 5 (very good), are summed to create a total score, which can range from 14-70. This total score is then converted to a percentage of the maximum (% maximum) score ranging from 0 to 100 for ease of interpretation, with a high score indicating greater enjoyment or satisfaction. The 15th item queries respondents' satisfaction with the medication and the last item is a global rating of overall life satisfaction and contentment; however, neither is used in the scoring process (Endicott J et al. 1993). The Q-LES-Q (SF) has been shown to be a reliable, sensitive and responsive scale for assessment of quality of life in both patient and non-patient populations (Wyrwich KW et al. 2011).Two methods for identifying responders have been described in the literature: the community norm method and the clinical global impression method. Though some researchers prefer the mean change scores associated with patient's CGI-I or CGI-S improvement ratings, the community norm method was used in our study as longitudinal assessments for change or improvement were not made. Rapaport et al. 2005 established a responder definition using the community norm of the Q-LES-Q-SF to be 58.1 on the total score scale, which was reported as an 83% maximum score on the 0-100 scale. The norm value responder threshold of 83% was obtained from a community sample (N=67) with an average age of 32.4 years who were mostly females (65.8%), white (approximately 75%), and college- educated (approximately 75%).

Data analysis

The data were analyzed using the 2-sided Fisher's Exact Test for categorical data and 2-sided one- and two-sample t-tests for scale data. Bonferroni correction was applied to account for multiple testing. Regression analysis was performed with FSFI Total Score as the dependent variable and others as independent variables.

RESULTS

Demographic characteristics

A total of 21 females in the age range of 18-55 participated and completed the study. Sixteen (76.2%) were married or living with a sexual partner and were currently sexually active in the last month. Work/ Employment were the current source of income for 10 (47.6%) while the rest were unemployed, disabled or supported by partners. All 21participants (100%) reported having adequate social support (Table 1).

All participants (100%) had been addicted to prescription opioid drugs as their primary drug of choice prior to starting treatment with bup/nlx. Three (14.3%) had "ever used" heroin in their lifetime and one had been through a methadone maintenance treatment program before. Eighteen of the participants (85.7%) were maintained on the bup/nlx film while 3 subjects (14.3%) were maintained on the tablet formulation of bup/nlx. Eighteen of the participants had been maintained on bup/nlx longer than one year and 3 had been maintained on bup/nlx for more than three months but less than one year. Mean dose of bup/nlx was 17.7mg/day (range 8-28mg/day).

Table 1: Demographics.

Variable	range	mean± Std. Dev	median
Age (yrs)	19-50	35.6±8.4	36
Weight (lb)	110.0-313.0	195.5±59.8	180.0
Height (in)	59.0-72.0	65.0±3.3	65.0
BMI	19.0-52.1	32.3±8.9	30.1
Education(yrs)	10-16.0	12.7±1.5	12.0
Duration of opioid use(yrs)	1.3-15.0	6.6±3.5	6.0
Amount of daily use (in oxycodone equivalents mg/day)	60.0-1200.0	200.8±249.2	120
Bup/nlx dose in mg/day	8.0-28.0	17.7±6.0	16.0

Substance use profile

Table 2 shows the substance use profile prior to start of bup/nlx treatment. Nineteen participants (90.5%) endorsed using other illicit drugs and alcohol in addition to opioids prior to starting treatment with bup/nlx. Eighty percent of the patients were currently smoking and 36% had reported an increase in their smoking following the start of bup/nlx treatment. At the time of participation in this study all subjects denied current use (one month prior) of illicit drugs or ongoing alcohol use in compliance with the clinic rules. Subjects (52.4%) were noted to have urine drug screens positive for various drugs including opioids, benzodiazepines, amphetamines, cannabis and PCP during the one year prior to testing as noted in medical records. However, these were less than 3 in number for each subject and had been addressed by the treating provider.

Comorbidities and medications

Psychiatric and medical comorbidities reported on interview were also confirmed by the medical record. Four (19%) participants reported no co morbid psychiatric diagnosis. Fifteen (71%) reported problems with depression and or anxiety, while one patient had an established diagnosis of schizophrenia and one participant had bipolar I disorder. Eight participants (38%) were on antidepressant therapy with an SSRI/SNRI while 2 were on Bupropion (9.5%). Quetiapine was being used for 4 subjects as a sleep aid at doses less than 100mg /day (not antipsychotic doses) (Table 3).

Medical comorbidities included hypertension in 6 subjects (28.6%), DM in two subjects, and Hepatitis C in one subject. Two subjects had preexisting gynecological conditions (Polycystic ovarian disease and pelvic pain) that existed prior to starting treatment with bup/nlx and could potentially be contributing to problems with sexual functioning. Two subjects were maintained on antihypertensive medications.

Six (28.6%) had a history of prior sexual trauma while 8 (38.1%) had a history of physical or emotional abuse.

Side effects: Participants were asked questions related to side effects using the predesigned data sheet. On spontaneous reporting, constipation was the most frequently (19%) reported adverse effect of bup/nlx, while 3 subjects reported sexual dysfunction spontaneously (14.3%) (Table 5).

On questions related to sexual functioning on the data sheet, subjects were asked if they had noted a change after initiation of bup/nlx. On a subsequent question, they were asked how current sexual functioning compared to their sexual functioning while they were actively using opiates. Over half of the group (52.4%) noted no change in sexual functioning on bup/nlx as compared to actively using opiates. For those who did report a change 29% noted an improvement and 19% felt their sexual functioning had worsened on bup/nlx treatment.

Table 2: Substance use profile prior to starting bup/nlx treatment.

Preferred route of opioid use	oral	52.38%
	Snorting	28.57%
	i/v	19.05%
Source of introduction to opioids	physician	61.9%
	friends	23.81%
	family	14.29%
Illicit drug/Alcohol use while using opioids	yes	90.48%
	no	9.52%
Family history of drug use	yes	66.67%
	no	33.33%
Family history of alcohol use	yes	80.95%
	no	19.05%

Table 3: Concurrent psychotropic medications.

Medication category	Number of Subjects
SSRI/SNRI	8 (38%)
Bupropion	2
Sleep aids (trazodone/hydroxyzine)	2
Mood stabilizer (topiramate)	1
Quetiapine (less than 100mg /day)	4 (19%)

Table 4: Spontaneously reported side effects with bup/nlx.

Side effect	# spontaneously reported
Constipation	4
Dry mouth	2
Sexual dysfunction	3
Sedation	2
Insomnia	3
Fatigue	2
Headache	2
Menstrual irregularity	1

Table 5: Response of subjects on questions related to sexual dysfunction on predesigned data sheet.

Noted a change in sexual functioning after starting bup/nlxt	yes	47.61%(10)
	no	52.38%(11)
How sexual functioning now(on bup/nlx) compares to when actively using opiates in the past	Better now	28.57%(6)
	Worse now	19.0%(4)
	unchanged	52.38%(11)

Comparison with community norms on self rated scales

Data from the subjects were compared with community norms established in prior studies for the three primary outcome variables. On the FSFI, a validated cut off score of 26.55 is used to classify women as with or without Female Sexual Dysfunction (FSD). In comparison with community norms on full scale mean scores (30.5±5.29) (Rosen et al. 2000), there was a statistically significant difference in the women maintained on bup/nlx (19.1±12.8) ($p<0.0001$). Further analysis of domain characteristics also showed significant results indicating presence of female sexual dysfunction in the study population. Results for the subscales evaluating satisfaction, lubrication, pain, desire, orgasm, and arousal were also highly significant with $p<0.0001$ (Table 6).

Among the subjects 47.5 % were on an antidepressant of which 38% were on an SSRI/SNRI as compared to the norms used from the study by Rosen et al. 2000 where only 7% had been taking some form of medication for depression/anxiety. These authors did not exclude the 3 subjects in the control group-(2.33%) who had not been sexually active in the one month prior

Table 6: FSFI Domain characteristics.

Domains	Subjects		Community norms		P value
	N	mean±SD	N	mean±SD	
Satisfaction	21	3.2±1.79	130	12.8±3.03	<0.0001
Lubrication	21	3.3±2.52	130	18.6±3.17	<0.0001
Pain	21	3.8±2.66	130	13.9±2.79	<0.0001
Desire	21	2.7±1.42	131	6.9±1.89	<0.0001
Orgasm	21	2.9±2.51	129	12.7±3.16	<0.0001
Arousal	21	2.7±1.99	130	16.8±3.62	<0.0001
Full scale	21	19.1±12.8	129	30.5±5.29	<0.0001

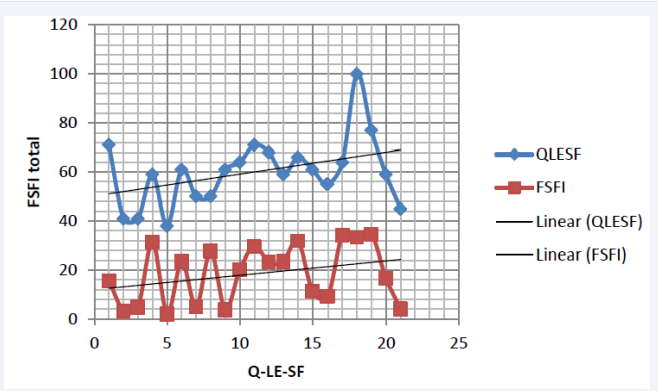

Figure 1 Significant association between quality of life and sexual functioning.

to the study to ensure uniformity. Data was not further analyzed excluding the 5 subjects (23.8%) in our population who had reported no sexual activity in the last one month.

On the QLES-Q-SF there was a statistically significant difference between the study subjects (47.6±7.90; p<0.0001) and community norms (58.1). For the 42 item DASS, on subscales for depression, anxiety and stress no significant difference was found when compared to community norms. For the DASS subscales, the depression mean was (9.8±11.5; p=0.0166), anxiety mean (7.5±5.9; p=0.0036) and stress mean (13.5 ±9.7; p=0.0344). The mean values for depression and stress were within normal range and anxiety was noted to be in the mild range.

Subjects were divided into two groups based on total FSFI score in to less than (LT) and greater than or equal to (GE) the median score to evaluate for the impact of quantitative variables such as age, BMI and daily dose of bup/nlx. On t- test for pooled data, association with age was not found to be significant. However, a significant correlation was found with BMI, indicating worse sexual functioning with higher BMI (P=0.0499). Relationship of variables like FSFI score and QLESF scores to the bup/nlx Dose was examined. When a regression analysis was performed with FSFI Total Score as the dependent variable and Bup Dose and Quality of Life as the independent variables, the bup/nlx Dose is not significantly associated with Sexual Functioning. However, Quality of Life is statistically associated with Sexual Functioning (p=0.0004). This suggests worse sexual functioning could have a negative impact on overall quality of life.

Even though the DASS scores were not statistically different from the normative controls the impact of the DASS scores on sexual functioning were independently evaluated and found not to be significantly different. The thirteen subjects who were not on an SSRI/SNRI were compared to the 8 subjects maintained on an SSRI/SNRI and the difference was not found to be statistically significant.

Similarly, duration of bup/nlx treatment and smoking status did not have a statistically significant impact on sexual functioning. Possible contribution of medical comorbidities such as HTN, DM, hepatitis C status and use of antihypertensive medication on sexual functioning could not be evaluated due to small number of subjects with these conditions but cannot be completely ruled out. The differences between subjects with a history of sexual trauma when compared to those without history of sexual trauma were not statistically different for sexual functioning.

DISCUSSION

According to current literature, bup/nlx is a safe and effective treatment option for women with opioid dependence even during pregnancy (Jones HE et al. 2010). However, little is known about the sexual functioning, quality of life, levels of depression, anxiety, and stress in women with history of prescription opioid use, maintained on bup/nlx. To our knowledge this is the first such study on this patient population looking at these aspects of treatment with bup/nlx.

We recruited 21 subjects who were relatively young (age 35.6±8.4) and had been on maintenance treatment with bup/nlx. All subjects had previously used prescription opioids as their drug of choice which possibly places this group favorably in terms of lower health risk and social burden as compared to heroin users (Fischer B et al. 2008). Since 52% of the subjects had violated and clinic rules and tested positive in the year prior to this particular month, subjects' self-reported sobriety is not completely reliable. It is interesting to note that only 3 subjects spontaneously reported sexual dysfunction with the medication but on assessment using a standardized rating scale, the FSFI, subjects displayed higher levels of sexual dysfunction as compared to community norms. Consistent with data from previous studies carried out in male subjects, the results strongly support the presence of sexual dysfunction in women maintained on bup/nlx for the treatment of opioid dependence. The results provide qualified evidence of poor sexual functioning in all domains (satisfaction, lubrication, pain, desire, orgasm, and arousal) and quality of life in women maintained on bup/nlx in the absence of significant depression, stress or anxiety as noted on the DASS. Role of depression, anxiety, and stress and their treatment (SSRI/SNRI) in association with sexual dysfunction has previously been studied and reported but was not found to be significant in our study.

Another important finding is that 52% of the subjects reported no change in their sexual functioning after starting treatment as compared with active use of opiates in the past. Of the 47.61% who did report a change, 28.57% felt that their sexual functioning had improved from when they had been actively using opiates. This finding may have important implications for treatment of opioid dependence as bup/nlx treatment may help improve sexual functioning in some people, though some impairment may persist. Additionally, the validity of the reports of 19% of subjects who reported decline in their sexual functioning after

initiation of bup/nlx treatment are somewhat questionable given the intoxication/withdrawal cycles with ongoing use of illicit substances.

Sexual dysfunction among women on opioid substitution therapy appears to be primarily related to interference with the normal cyclic production of LH and FSH, possibly due to elevated production of prolactin. This process interferes both with hormones necessary for maintenance of a normal menstrual cycle (estrogen, progesterone) and for normal libido (androgens). Interface with these sex hormones is thought to lead to the common signs and symptoms of sexual dysfunction and hormonal deregulation among women maintained on opioid substitution therapy: depressed libido and oligomenorrhea or amenorrhea (Brown &Zueldorff 2007). However, the impact of bup/nlx may not be as robust when compared to a pure agonist. It has been proposed that stimulation of k-opioid receptors causes a suppression of the gonadal axis. The antagonism of buprenorphine at the k-opioid receptor may possibly counteract the mu- opioid receptor- mediated depression of gonadal axis. This a possible explanation for men maintained on bup/nlx who performed better on sexual functioning scores as compared to men maintained on methadone, a pure agonist (Hallinan et al. 2008,Quaglio et al. 2008). The kappa antagonism is also proposed to have an antidepressant effect which may have contributed to a lack of significant difference between the study and community norms on the DASS.

Similar to studies in men (Hallinan et al. 2008) a dose correlation was not found with sexual functioning scores. Even though no dose relationship was found with the sexual functioning scores, this may become apparent in a larger sample size. The 5 subjects who had not been sexually active in the last one month were not excluded from the analysis as has been done in some other studies assessing sexual functioning in men (Ramdurg et al. 2012). This subgroup may be representing the subjects who are most severely affected by sexual dysfunction and have thus been sexually inactive. However, the converse may also be true, and these women may represent a subgroup that is 'satisfied' with their sexual function and hence less likely to sexually engage as often. In the normative data used for the study this number was small (2.3%).

It is notable that the BMI of our study population was significantly higher (32.3 kg/m2± 8.9) than the recommended normal of <25 kg/m. The Literature supports the connection between opiate use and development of preference for sweet tastes and further association with dental pathology, weight gain and loss of glycemic control (Mysels & Sullivan,2010). A study of the nutritional status of opiate dependent persons after 4 years of methadone maintenance treatment showed variable results with body weight loss among women but an increase in body weight and BMI among men (Kolarzyk E et al. 2005). Since baseline weights prior to starting treatment with bup/nlx were not part of this investigation, it is difficult to comment on the role of maintenance treatment. In our literature review, we did not find any human studies regarding the same either. However, maintenance treatment is known to bring significant behavioral and health changes in the lives of opioid addicts as they free themselves from cycles of intoxication and withdrawal. The noted BMI could be a cumulative effect of prolonged opioid use with poor lifestyle choices, relative life stability, and intake of excessive sugar in the maintenance phase. A significant correlation was found between sexual functioning and BMI in our sample. This is in contrast to a recent population based study of sexually active men and women that reported no significant associations between BMI and sexual difficulties other than noting an association between higher BMI and a lack of sexual interest among women (Smith AM et al. 2012). Literature regarding relationship of obesity and sexual function is scant in general and very limited in the female population. A Swedish population study by Adolfsson et al. 2004 found no difference in satisfaction of sexual life between the obese and the normal weight women. However, there was a tendency towards lower sexual satisfaction and sexual desire associated with higher weights in the youngest age groups. Esposito et al. 2004 used the FSFI to examine if the metabolic syndrome could act as a cause for sexual dysfunction in premenopausal women. The results indicated that women with the metabolic syndrome had an increased prevalence of sexual dysfunction compared to the controls ($p<0.001$). Our findings imply that high BMI and metabolic syndrome may be just as big a problem in the bup/nlx treatment seeking population as in the general population. Strong and complex interrrelationship of psychological factors and the occurrence of sexual dysfunction, obesity and opioid dependence is not completely understood but cannot be undermined.

A number of studies have demonstrated that history of sexual abuse among individuals seeking treatment for substance abuse is related to a range of psychiatric and medical problems and overall poorer outcome. In our sample, history of sexual trauma did not appear to impact sexual functioning.

The lack of relationship for age, duration of treatment, DASS scores, and history of sexual trauma, when seen in relation to sexual functioning supports the possibility that the long term use of opioids and treatment medication may have a causal relationship.

This study has several limitations to consider. Firstly, the small sample size is likely a major reason for not seeing additional significant differences; it also makes drawing conclusions difficult, especially when combined with the lack of a comparison group. Furthermore, participants in the study represent a relatively financially stable subgroup that either had insurance or could afford bup/nlx and were thus seeking this relatively novel and expensive medication for maintenance treatment of opioid dependence. To offset this limitation, community norms established in previous studies were used for comparison on the three self rating scales. The absence of baseline sexual functioning data before initiation of bup/nlx treatment is another limitation. Lack of this information makes it difficult to differentiate the impact on sexual functioning due to long term illicit opioid use and that of substitution therapy. Even though questions on the predesigned data sheet addressed a subjective comparison of sexual functioning before (on opioids) and after being maintained on bup/nlx, 52.38% indicated noting no change in sexual functioning; such questions are albeit subject to recall bias. Personal memories of sexual enjoyment before and after treatment are less likely to be reliable and difficult to interpret

in a quantitative study. Lack of hormonal assays to support and confirm the finding is another limitation. However, if hormonal assays were to be done, they would ideally need to be coordinated with menstrual cycles. Potential impact of medical comorbidities and their treatments could not be assessed due to small numbers.

Despite the limitations the study has several strengths. Most importantly, this is the first study evaluating the sexual functioning and quality of life in females maintained on bup/nlx. The study analyzed a large number of possible factors for association with the primary outcome measure.

With the emergence of the opioid abuse/ dependence epidemic, an increasing number of youth and young females seek treatment with bup/nlx , and highlight the importance of clinical integration of the results of this and other investigations. The effects of active addiction are likely to persist beyond abstinence, and may require years of healthy living in order to return to baseline, if addicts ever do. Increased awareness among clinicians of possible sexual side effects related to bup/nlx may help with early identification and treatment. Patients, especially females with sexual dysfunction may fail to mention the problem to clinicians due to embarrassment and many clinicians in turn may also feel uncomfortable addressing the issues of sexual problems. Increased awareness among clinicians regarding this significant issue hopefully would result in open and direct discussions about sexual dysfunction and opioid use with their patients. These discussions should include possible confounding factors such as confirming sobriety, psychiatric and medical comorbidities and medications that may be causal agents (SSRIs, antihypertensives) being reviewed, followed by a complete hormonal assay including LH, FSH, prolactin, estrogen, progesterone ad serum androgens as needed. Lack of dose relationship in our study should not deter bup/nlx providers from attempting to lower treatment dose in response to reports of sexual dysfunction. The need for hormonal replacement may be assessed on a case by case basis upon consultation with endocrinologists. Additionally a need to monitor weight of females maintained on this treatment is also highlighted. High BMI may negatively impact sexual functioning and quality of life in turn.

Future research could build on the current findings by focusing on, larger sample size, opioid using control population, longitudinal studies and use of more specific assessment of sexual functioning such as frequency and recency of dysfunction while simultaneously obtaining hormonal assays that are coordinated with menstrual cycles. It is hoped that this study will lead to additional studies that are able to assess women maintained on bup/nlx in comparison to current illicit opioid users, women maintained on methadone maintenance treatment, and normal healthy controls in the community.

Summary and clinical implications*:* We have demonstrated for the first time that females maintained on bup/nlx for the treatment of opioid dependence suffer from sexual dysfunction and impaired quality of life independent of ongoing depression, anxiety and stress. This may very well be the cumulative impact of years of active addiction. However, sexual dysfunction associated with medication may be a motivating factor for patients to take the lowest therapeutic dose. This may have clinical implications for compliance, evaluation and management of side effects. Future research in this area is warranted as bup/nlx quickly becomes a popular treatment among young females with opioid dependence.

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