

## **Opioid Substitution with Methadone and Buprenorphine: Sexual Dysfunction as a Side Effect of Therapy**

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### *Summary*

Opioid substitution is the most widespread and well-researched treatment modality for opioid dependence. Methadone and buprenorphine are currently the most commonly used pharmacotherapeutic agents. Sexual dysfunction has been reported as an adverse effect of opioids including methadone and buprenorphine. The current article describes proposed mechanisms for sexual dysfunction as an adverse effect of methadone and buprenorphine, summarizes research conducted on subjects on these agents, and explores appropriate evaluation and intervention in the management of the types of sexual dysfunction most commonly encountered during opioid substitution treatment (libido, erectile, and orgasm dysfunction).

Key Words: Opioid Replacement Therapy - Methadone -  
Buprenorphine - Sexual Dysfunction

Opioid substitution treatment (OST) is the most common and most effective modality for the treatment of opioid dependence. Currently, in Europe, over 460,000 individuals<sup>(18)</sup> and, in the U.S., over 241,000(32) receive opioid substitution in the form of methadone or buprenorphine. Of individuals receiving methadone or buprenorphine for opioid dependence, 99% in the U.S.<sup>(31)</sup> and 91% in Europe<sup>(18)</sup> receive methadone.

Sexual dysfunction is a commonly reported side effect of opioid medications, and has been investigated in samples receiving OST, primarily methadone maintained males. Common complaints related to sexual function, and potentially to sex hormone levels,

among those on OST include decline in libido, orgasm dysfunction (delayed orgasm or inability to achieve orgasm), and menstrual irregularity (primarily oligomenorrhea and amenorrhea)<sup>(16,17)</sup>. Disorders of detumescence, or resolution, have not been associated with opioids or OST.

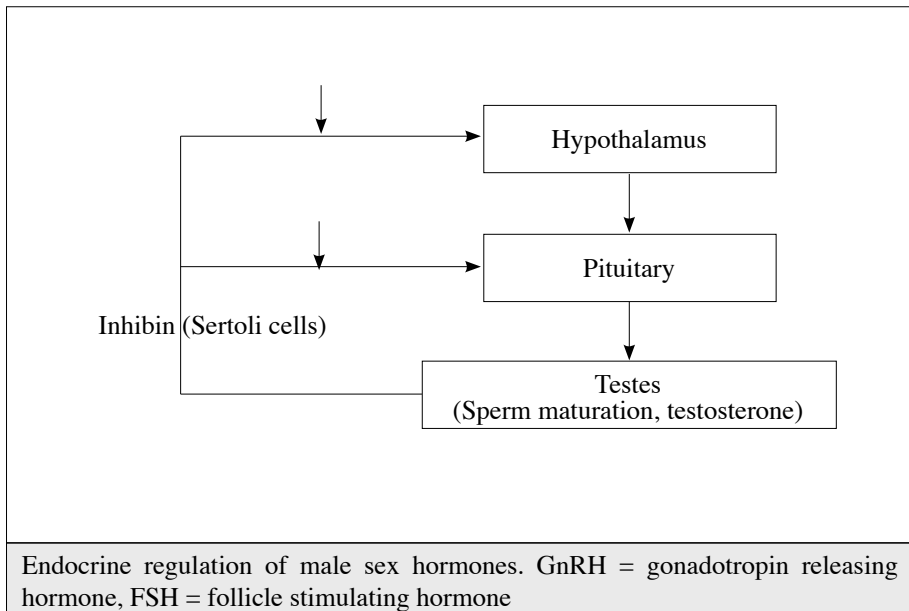
Consideration of sexual dysfunction as a medication side effect is important, because, besides creating difficulty in intimate relationships, it has the potential to lead to decreased compliance with therapy and to interfere with the known benefits of OST. While the impact of sexual dysfunction upon treatment compliance has not been studied in OST-receiving samples, sexual dysfunction has been shown to interfere with therapeutic compliance among subjects with depression,<sup>(22)</sup> HIV,<sup>(37)</sup> and hypertension<sup>(31)</sup>.

## Reproductive physiology

### Male

The normal secretion of male sex hormones (i.e. androgens) is mediated by pituitary hormones, primarily FSH, which is regulated by inputs from the hypothalamus (gonadotropin releasing hormone = GnRH) and gonadal tissue (inhibin). This feedback pathway is illustrated diagrammatically in Figure 1.

GnRH exhibits wide diurnal fluctuations in serum concentration. GnRH, in turn, regulates the secretion by the pituitary of FSH in men, which, in turn, stimulates the production of sperm and testosterone (by Leydig cells) in the testes. Only the portion of testosterone which is free in serum (as opposed to that portion which is protein-



bound) is physiologically active. Inhibin, secreted by Sertoli cells in the testes, provides negative feedback to both the pituitary and the hypothalamus to further regulate this feedback system in the male.

Achievement of normal arousal, erection, and ejaculation also depends upon intact neurological and vascular function. Parasympathetic stimulation of nitric oxide (endothelial-derived relaxation factor) secretion results in relaxation of corporeal smooth muscle and erection. Ejaculation is controlled via sympathetic input. Sympathetic input then results in stimulation of alpha-1 and alpha-2 adrenergic receptors in the corpora cavernosum and, hence, detumescence.

Testosterone plays an important role in sexual functioning for males. Lower-than-normal serum testosterone may manifest as reduced libido and erectile dysfunction. With prolonged depression of serum testosterone, seminal emission may be inhibited, as well. Hypogonadal men who undergo testosterone replacement demonstrate increases in sexual interest and erectile function<sup>(4)</sup>.

Sexual dysfunction among men on OST appears to be related to lower-than-normal serum levels of testosterone<sup>(10, 13, 24, 25)</sup>. The association between opioids and low serum testosterone levels may occur through a variety of mechanisms. Opioids have been shown to suppress normal pituitary secretion of FSH and LH, which, in turn, would interfere with normal testosterone and sperm production by the testes. More proximal interruption of normal endocrine function may occur through alteration of the normal pulsatile secretion of GnRH by opioids, which would also interfere with normal activity of LH and FSH. Interference with the usual dopaminergic mediation of prolactin secretion, leading to elevated prolactin levels, and, in turn, decreased testosterone production may also cause sexual dysfunction in men on OST. Opioids may also act directly upon testicular tissue to suppress normal testosterone production<sup>(14)</sup>.

### ***Female***

Research regarding sexual dysfunction among females on OST is more scant. Sexual dysfunction among women on OST 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). Interference with these sex hormones is thought to lead to the common signs and symptoms of sexual dysfunction and hormonal dysregulation among women on OST: depressed libido and oligomenorrhea or amenorrhea.

While it is clear that impaired androgen production is closely and directly associated with sexual dysfunction in males, the relationship within females is more complicated and less clear. The normal mid-cycle rise in serum androgens in women has not been strongly related to sex drive<sup>(4)</sup>. Transdermal replacement of lower-than-normal serum androgens in female subjects, however, has been shown to result in improvements in mood and libido<sup>(3, 7)</sup>. Additionally, women with normal levels of serum testosterone, when given testosterone supplementation, have demonstrated an increased sexual response<sup>(38)</sup>.

### **Methadone: Specific study findings**

Studies have demonstrated higher rates of sexual dysfunction in methadone-maintained populations than in the general population<sup>(9, 20, 23, 27, 28, 35, 36)</sup>. Estimates of prevalence, however, vary significantly: 30-100%<sup>(14, 17, 20)</sup>. Additionally, the prevalence of specific types of sexual dysfunction (libido, erectile, and orgasm dysfunction) has not been examined in detail.

Early studies did not consistently demonstrate a dose-response relationship between methadone and sexual dysfunction or between methadone dose and serum hormone levels. In 1974, Cushman and colleagues failed to find a main relationship between a one-time methadone dose and serum levels of LH, FSH, prolactin, or testosterone in 8 male volunteers. Stable long-term doses of methadone were likewise not found to have an effect on serum LH, FSH, prolactin, or testosterone in these subjects<sup>(12)</sup>. Early work also indicated that, if LH and FSH levels were affected by methadone, that the effect was likely mild and transient<sup>(6, 12)</sup>. In an interview study of 50 men enrolled in a methadone maintenance program, sexual dysfunction was highly prevalent in the group (33%), but no relationship was found between sexual dysfunction and demographics, methadone dose, or substance use history<sup>(20)</sup>.

Several studies provided conflicting results, however, indicating that methadone influenced sex hormone levels. Willenbring et al demonstrated a maximally stimulated level of prolactin in 15 men (average daily dose of 52.7 mg of methadone, average duration of maintenance 18 months), providing evidence for interference by prolactin as a potential pathway leading to depressed testosterone and, hence, to sexual dysfunction in men on methadone maintenance<sup>(39)</sup>. Cicero et al in their 1975 study found multiple sexual effects in 29 methadone-maintained male subjects. Ejaculate volume and seminal and prostatic secretions were found to be 50% of those in 43 narcotic-free controls. Serum testosterone levels were, on average, 43% of control subjects'. The mean daily methadone dose in this study population was 67 mg.<sup>(9)</sup> Cicero replicated similar findings in a male rat model. Serum levels of LH were undetectable in rats receiving methadone or morphine. This led to the hypothesis that methadone may act to reduce serum testosterone levels via interference with pituitary or hypothalamic regulatory hormones.

In one of the first studies to examine particular types of sexual dysfunction in a methadone maintained sample, Teusch et al found men maintained on methadone to report reduced libido and orgasm dysfunction more frequently than controls<sup>(36)</sup>. Similar to earlier studies, however, the severity of dysfunction and methadone dose were unrelated. In more recent work, Brown et al also demonstrated a link between methadone dose and orgasm dysfunction among 92 men maintained on an average of 100 mg methadone daily<sup>(8)</sup>. Surprisingly, serum testosterone and prolactin levels were not found to be, on average, outside the normal range in spite of the relatively high daily methadone dose compared to previous study samples. Elevated prolactin was, however, the most common endocrinologic abnormality in the sample.

Spring et al provided some of the earliest evidence demonstrating a relationship

between sexual dysfunction and methadone dose<sup>(35)</sup>. Their study used a validated instrument to examine sexual dysfunction in 25 men maintained on methadone for an average of 2 months. They found that men experiencing significant sexual dysfunction were more likely to be on higher doses of methadone. However, this was a cross-sectional study, and men with sexual dysfunction also endorsed a greater number of psychological symptoms, an important potential confounder for an effect by higher methadone dose.

Mendelson et al conducted a prospective study of the effect of acetylmethadol administration on serum testosterone levels in 13 men with opioid dependence which yielded significant results. A statistically and biologically significant decrease in serum testosterone was found 7-9 hours after acetylmethadol administration. Testosterone levels attained normal levels 48 hours after drug administration<sup>(24)</sup>. Mendelson also conducted some of the earliest work demonstrating a relationship between methadone dose and serum testosterone concentration<sup>(25)</sup>. When the sample (n =38) was dichotomized into groups receiving lower dose (10-60 mg) and higher dose (80-150 mg) methadone, the men receiving higher daily doses of methadone were found to be more likely to have abnormally low serum testosterone. As further evidence of an inverse relationship between methadone dose and serum testosterone levels in this study, reductions in methadone dose were associated with recovery of testosterone levels. Mendelson et al found similar results in a sample of 10 men administered heroin in a controlled setting for 7 days and then detoxified using methadone at a starting dose of 35 mg.<sup>(26)</sup> Again, abnormally low serum testosterone levels found during and after the period of heroin administration were found to recover to baseline after methadone detoxification.

Literature regarding sexual dysfunction in female subjects on OST is scant. One study indicated that 50% of women switching from heroin to methadone experienced improvement in sexual function<sup>(1)</sup>. Methadone was shown to depress serum testosterone levels in female subjects in one study<sup>(11)</sup>. This depression of testosterone in women was also associated with increases in serum prolactin<sup>(34)</sup>.

Nearly 50% of women experience menstrual irregularity while on methadone maintenance. The effect appears to be dose-related, and appears to decline over time, with the potential for resumption of normal menses without alteration of methadone dosing<sup>(33)</sup>.

### **Buprenorphine: Specific study findings**

Buprenorphine is a partial mu agonist with a high receptor affinity and, like full mu agonists, has been shown to be efficacious in the treatment of opioid dependence. Studies comparing buprenorphine to the more commonly used methadone have found that rates of success in treatment are similar and that buprenorphine may result in fewer adverse effects. However, only one study to date has examined the prevalence of sexual dysfunction in particular among patients treated with buprenorphine.

In 2005, Bliesener and colleagues examined 17 male patients maintained on

buprenorphine and 37 male patients maintained on methadone<sup>(5)</sup>. Patients self-reported effects on libido and potency, and total and free testosterone, LH, FSH, estradiol, and prolactin were assayed. Blood samples from 51 male volunteers were used as a control group for the hormone analyses.

Twenty-three percent of patients in the buprenorphine group reported a decrease in libido, as compared to 83% in the methadone group. Twelve percent reported reduced potency, as compared to 72% in the methadone group. Other forms of sexual dysfunction, such as orgasm dysfunction, were not examined in this study.

The Bliesener study also found that patients treated with buprenorphine had significantly higher mean levels of total ( $5.1 \pm 1.2$  ng/mL) and free ( $17.1 \pm 4.8$  pg/mL) testosterone than did patients treated with methadone ( $2.8 \pm 1.2$  ng/mL and  $7.8 \pm 2.9$  pg/mL, respectively), and that in fact mean total testosterone levels of those patients being treated with buprenorphine did not significantly differ from levels in the healthy control group sample ( $4.9 \pm 1.3$  ng/mL). Mean levels of prolactin were significantly higher in the methadone group ( $8.7 \pm 8.3$  ng/mL) than in the buprenorphine group ( $5.0 \pm 2.0$  ng/mL), though all groups were in the normal range. There were no other significant differences found in the hormonal analysis.

In an examination of BDI scores collected in the same study, mean scores of the opioid therapy groups were not found to differ significantly from one another. This lack of difference, as well as a lack of significant difference in age, medical status, length of addiction concurrent medications, or frequency of illicit opioid use led the authors to conclude that it was most likely the treatment drug rather than other variables that contributed to the differences between therapy groups in hormone levels and reports of sexual dysfunction.

## **Implications for evaluation and treatment**

### ***Libido dysfunction***

Low serum testosterone due to opioid effects on the hypothalamic-pituitary-gonadal axis may explain libidinal depression. However, because psychological factors are common causes of depression of sex drive, and because psychiatric comorbidity is so prevalent in the substance dependent population, mental and emotional health should be investigated in addition to hormonal assays. Conditions of potential importance include mood disorders, psychosis, situational stressors, gender identity issues, and age-related psychological issues.

Medications other than OST should also be reviewed, as these are also common causes of a depressed sex drive. Common offenders include antihypertensives and psychotropic agents.

Should other etiologies be ruled out, given the associations in the literature between methadone dose and serum testosterone level, reasonable therapeutic approaches may include replacement (parenteral or transdermal) of abnormally low testosterone or a reduction in daily methadone dose. In an open-label study, methadone-maintained men

with depressed testosterone levels responded to transdermal testosterone in terms of serum testosterone levels, sexual function, and measures of well-being<sup>(15)</sup>. Bromocryptine may be a therapeutic alternative, as well. Bromocryptine may act via reestablishment of CNS levels of dopamine and normalization of dopaminergic regulation of prolactin production<sup>(34)</sup>.

### **Erectile dysfunction**

Erectile dysfunction (ED) more commonly has an organic or iatrogenic etiology. A variety of systemic illnesses are associated with ED. These include chronic liver disease, renal failure, arteriosclerotic cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and malignancy. Spinal trauma and genitourinary surgery are of potential etiologic importance in ED, as well<sup>(21)</sup>. Though more rare, congenital and other anatomic genitourinary anomalies (e.g. Peyronie's Disease, phimosis, post-traumatic aneurysm) should be considered.

Medications commonly associated with ED include antihypertensives, psychotropic agents, and medications with anticholinergic effects. Smoking<sup>(19)</sup> is strongly associated with ED. The relative risk for ED increases by 1.31 for every 10 pack-years of smoking<sup>(29)</sup>.

Though organic factors commonly cause ED, mental and emotional health issues may be significant contributors, as well. Depressive symptoms have been most strongly associated with ED, with 90% of men with severe depression reporting ED in one study<sup>(2)</sup>. Association with anxiety disorders has also been reported<sup>(32)</sup>.

### **Summary**

OST, primarily methadone, appears to be associated with alteration of serum levels of hormones related to normal sexual function. In males, opioids may act via: (1) interference with the normal production of hypothalamic and pituitary regulatory hormones (LH, FSH, GnRH), (2) elevation of serum prolactin, (3) direct action on the testes to suppress testosterone production. While elimination of other common medical and psychiatric etiologies for sexual dysfunction is warranted, replacement of abnormally low serum testosterone may effectively treat libido or erectile dysfunction, and potentially delayed orgasm or anorgasmia. Replacement of abnormally low androgens in women on OST may also improve libido as well as mood. Abnormalities in the menstrual cycle are thought to be transient and may not require alteration of OST dosing. Patients with refractory sexual dysfunction and a stable course in terms of their opioid use disorder may respond to reduction in the dose of their OST agent, with methadone likely being of greater significance here than buprenorphine.

In light of the paucity of studies in the area of sexual dysfunction as an adverse effect of buprenorphine, more research is needed, utilizing larger patient populations and examining more thoroughly specific types of dysfunction in both male and female populations.

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