

Opioid-Induced Sexual Dysfunction: Causes, Diagnosis, & Treatment



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A Common But Undiagnosed Problem

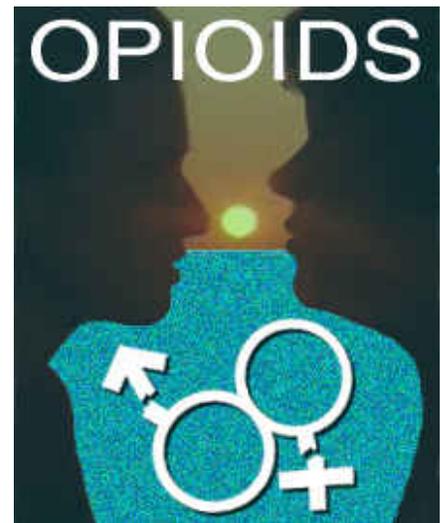
Sexual dysfunction is a common problem among patients with chronic pain. Yet, many of these patients suffer in silence, healthcare providers rarely ask about patients' sexual concerns, and guidance literature on the subject is relatively scarce. Ironically, in many of these cases the long-acting opioid medications prescribed to relieve patients' pains may be causing or contributing to their sexual problems.

Since the 1990s, prescriptions written for opioid medications have significantly and steadily increased [Olsen et al. 2006]. Along with that, there have been increasing concerns about adverse consequences of opioid treatment, and opioid-induced endocrine deficiency leading to sexual dysfunction is one the most common yet most frequently undiagnosed problems with opioids.

Considerable evidence through the years has suggested that long-acting opioids used on a daily basis for more than a month can have a number of adverse effects on human endocrine function. The most common and clinically significant effects are androgen deficiencies and menstrual cycle abnormalities [Abs et al. 2000; Adams et al. 1993; Allolio et al. 1986; Blank et al. 1986; Christo 2003; Finch et al. 2000; Kalyani et al. 2007; Lee et al. 2002; Rajagopal et al. 2004; Taylor et al. 2003].

These hypogonadal and androgen-inhibiting effects, which are a "class effect" of all opioids to some extent, can lead to sexual dysfunctions in both men and women. Therefore, potential endocrine deficiencies should be considered in all patients taking daily opioids equivalent to or greater than 100 mg morphine. If present, opioid-induced sexual dysfunction can be treated, but approaches are quite different for men versus women.

This paper examines the causes and diagnosis of endocrine dysfunction related to opioid therapy. Recommended clinical approaches for treatment of this disorder are discussed, and it is hoped that through a better understanding of these issues opioid therapy can be more effectively used in the treatment of pain.



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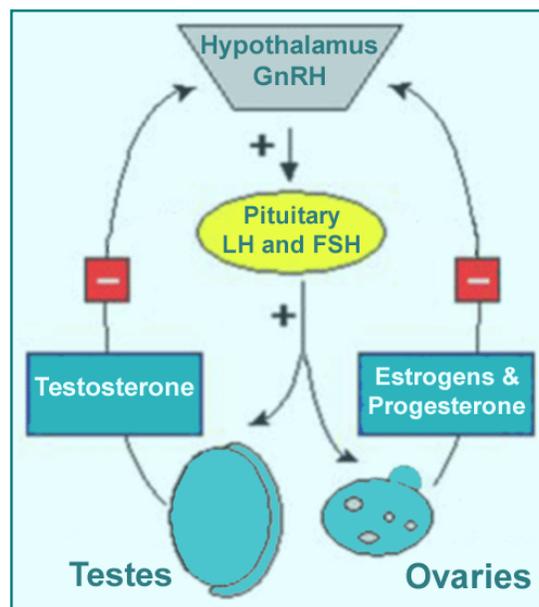
Disrupting HPG Processes

Opioid medications can exert a number of effects that alter the normal functioning of hormones found in hypothalamic-pituitary-gonadal (HPG) pathways, which are depicted in the **Figure**. HPG processes controlling the production of sex hormones begin with secretion by the hypothalamus of gonadotropin-releasing hormone (GnRH). In turn, GnRH stimulates the pituitary gland to secrete the gonadotropins LH and FSH. These stimulate production in the testes and ovaries of gonadal hormones – testosterone, estrogens, and progesterone.

As gonadal hormone levels rise, they signal back to the hypothalamus to decrease production of GnRH which, in turn, decreases pituitary gonadotropin secretion. Thus a feedback control loop is formed.

Both endogenous (eg, endorphins) and exogenous opioids (eg, analgesics) exert an inhibitory effect on GnRH, thus decreasing LH [Mendelson et al. 1980]. In women, blunting of the normal pulsatile release of LH interferes with the menstrual cycle, often causing irregular or absent menses that also may result in decreased ovarian testosterone secretion. In men, decreased LH causes the testes to produce less testosterone [Adams et al. 1993].

Testosterone deficiency in both men and women results in adverse effects such as weight gain, fatigue, depression, and sexual dysfunction. This effect of opioids in reducing production of sex hormones from the gonads – testes in men, ovaries in women – is referred to as *hypogonadism*.



Opioid Interference with Adrenal Androgen Production

Opioids also exert a negative influence on adrenal androgen production. In women, both the ovaries and adrenal glands play important roles in overall androgen production. The adrenal hormones dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenedione are weakly androgenic in and of themselves, and they are precursors of testosterone. Serum DHEAS levels are used to determine adrenal function in general and, more specifically, adrenal androgen production. Daily use of opioids decreases adrenal androgen production as measured by DHEAS levels.

Daniel [2006] assessed DHEAS levels in patients treated with sustained-action oxycodone, sustained-action morphine, continuous transdermal fentanyl, or methadone and found decreased DHEAS levels in over half of those studied. The exact mechanism by which opioids reduce DHEAS and, consequently, interfere with adrenal androgen production is not known; however, the resultant deficiency is of clinical importance in women (discussed below).

The daily use of opioids may decrease adrenal androgen production in more than half of patients, as measured by lowered DHEAS levels.

Opioid-Induced Endocrine Deficiency in the Clinical Setting

It appears that all opioids cause endocrine deficiencies at least to some degree, which may influence sexual problems. A significant proportion of men treated with sustained action opioids, estimated at 5 million in the US and Canada, are testosterone deficient [Daniel 2006c; Mazer et al. 2004].

Deleterious opioid effects on endocrine function and sexual health were first noticed decades ago in sexual dysfunction associated with intravenous heroin use [Azizi et al. 1973; Daniell 2006a, Goldsmith et al. 1984]. Decreased libido is common among addicts in general, but erectile dysfunction in men and menstrual cycle disturbances in women are especially common in those with opioid dependence.

For example, studies have shown that about two-thirds of patients entering methadone maintenance treatment for opioid addiction complain of some form of sexual dysfunction, and about one-third continue to have symptoms while receiving treatment. Researchers recognized that both heroin and methadone were associated with decreased serum testosterone levels in men [Brown and Zuedorf 2007; Cicero et al. 1975; Hanbury et al. 1977; Mendelson et al. 1975a, 1975b]. This results predominately in decreased libido and erectile dysfunction, and men may also commonly complain of fatigue, hot flashes, weight gain, or increased sweating. In addition to those effects, women in methadone maintenance treatment often have menstrual cycle abnormalities.

Despite the fact that hypogonadism has been a well-known adverse effect of methadone treatment for many years, it never became common practice to screen for this disorder; perhaps because methadone treatment takes place in single purpose clinics that do not routinely diagnose or treat conditions other than opioid dependence. Inadequate clinic staff education regarding the adverse endocrine effects of methadone treatment may be another factor. Therefore, thousands of individuals receiving methadone for addiction have not been treated for symptomatic endocrine deficiencies.

Of even greater importance, methadone’s ability to disrupt normal endocrine function is a “class effect” shared with other opioids. With the dramatic increase in the use of sustained-release oxycodone, morphine, and oxymorphone for chronic noncancer pain, these drugs are the most common cause of opioid-induced endocrine deficiency.

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Screening and Diagnostic Testing

Causes and symptoms associated with hormonal deficiencies are summarized in the **Table**. There are no validated questionnaires for screening women for opioid-induced endocrine deficiencies, but structured interview instruments have been proposed to screen men for hypogonadism.

These questionnaires, however, have clinical limitations. The Androgen Deficiency in Aging Men (ADAM) questionnaire was validated for men over the age of 40 [Morley et al. 2000]. Another one – the Androtest[®] – is a 12-item structured interview designed to screen for male hypogonadism [Corona et al. 2003]. Laboratory assessments of male testosterone levels were used to determine the predictive values of both ADAM and the Androtest. These levels are mandatory for confirming the diagnosis of hypogonadism and as a clinical basis for deciding whether or not to initiate testosterone replacement therapy.

Opioid-Induced Deficiencies	
<p>Hypogonadism Decreased GNRH Decreases LH Decreased Testosterone</p>	<p>Symptoms Anemia Decreased Libido Decreased Muscle Mass Depression Erectile Dysfunction Fatigue Hot Flashes Menstrual Irregularities Osteoporosis Sweating Weight Gain</p>
<p>Adrenal Androgen Deficiency Decreased DHEA Decreased DHEAS Decreased androstenedione</p>	

A diagnosis of endocrine deficiency should be considered in all patients receiving daily opioid treatment in an amount equivalent to or greater than 100 mg morphine [Daniell 2002]. Patients should routinely be asked about symptoms suggestive of sex-hormone deficiency prior to treatment and at regularly scheduled follow-up medical visits. Questions to ask might include the following:

- Have you experienced a decrease in sex drive?
- Are you having difficulty with erections (men)?
- Have you noticed a lack of energy, strength, or endurance?
- Have your menstrual periods become abnormal (premenopausal women)?
- Have you noticed a decreased enjoyment in life or have you become depressed?
- Have you gained weight?
- Have you noticed increased sweating?
- Are you experiencing hot flashes (both men and women)?

In men, diagnostic laboratory testing begins with assessing serum testosterone concentrations, which are the principal measure for diagnosing hypogonadism. Blood samples for analysis should be obtained in the early morning as concentrations do vary throughout the day.

Clinical laboratories report a wide range of normal serum testosterone concentrations (eg, 275-800 ng/dL) without specifying age-range-specific values. The normal range for free testosterone – that is testosterone not bound to protein – is also very wide (eg, 5-21 ng/dL). Typically, young men have much higher levels of total or free testosterone than older men, so young men with clinical hypogonadism may still have testosterone levels within the normal range.

Whenever testosterone levels are low, men also should be screened via serum prolactin levels for pituitary tumors. As a further test, decreased LH levels in men support a diagnosis of opioid-induced hypogonadism, but LH may be within the normal range. Also, testosterone maintains red blood cell production, so men with reduced testosterone associated with hypogonadism may exhibit mild anemia due to decreases in those cells.

In women, LH and FSH levels change with the menstrual cycle, so these are of limited value in diagnosing androgen deficiency. Premenopausal women with absent menses should be screened for abnormal pituitary function (via assessing prolactin levels) and referred for a gynecologic evaluation. While some specialists recommend testing for testosterone deficiency in women, most laboratories do not set a lower limit to the normal range for females. When clinical findings suggest androgen deficiency in a woman, DHEAS levels may be the best indicator of androgen production.

Diagnostic laboratory testing begins with assessing serum testosterone concentrations, which are the principal measure for diagnosing hypogonadism in men.

Treatment for Overcoming Opioid-Related Sexual Dysfunction

In men, the primary treatment for opioid-induced endocrine deficiency resulting in hypogonadism is testosterone supplementation [Daniell 2006b; Daniell et al. 2006; Endocrine Society 2006b, 2006c]. Testosterone is available in gel, cream, buccal, transdermal patch, and intramuscular injectable formulations. Topical and buccal medications are preferred over injections because they provide relatively stable testosterone concentrations not easily attainable with intramuscular injections.

Also, these medications are supplied in “unit doses”; eg, the contents of one gel pack are applied once daily at approximately the same time to clean dry skin of the shoulders and/or upper arms. Testosterone supplementation should be administered in amounts needed to manage symptoms of hypogonadism. Amounts higher than needed may increase the risk of prostatic hypertrophy and prostate cancer growth rates.

Symptoms of hypogonadism would be expected to improve with testosterone replacement therapy, but erectile dysfunction may persist to some degree because of psychological factors or co-occurring medical conditions. In such cases, prescribing FDA-approved erectile dysfunction medications could be appropriate (eg, sildenafil, tadalafil, vardenafil).

There has been far less research regarding opiate-induced endocrine deficiencies in women than in men. Hypothetically, androgen treatment would relieve clinical symptoms and reduce risks of osteoporosis in affected women. In younger women, oral contraceptive pills (OCPs) might have benefit; particularly an OCP with a relatively androgenic progestin component. However, OCPs are also known to suppress free testosterone.

Few clinical trials have examined the efficacy or safety of testosterone therapy in women. The theoretical goal of such treatment would be to raise free testosterone levels while monitoring for adverse androgenic effects such as acne, hirsutism or deepening voice. Medications containing testosterone are approved in the US for the treatment of vasomotor symptoms associated with menopause; however, studies on testosterone treatment in women have involved relatively small sample sizes and short-durations [Bolour and Braunstein 2005; Kingsberg et al. 2007]. Additionally, researchers have raised concerns that testosterone treatment might increase women’s breast cancer risks [Schover 2007]. Given the lack of long-term efficacy and safety studies, testosterone use in women is generally not recommended for the treatment of androgen deficiency, other than to treat menopausal symptoms [Endocrine Society 2006a; NAMP 2005].

Another approach might be the administration of DHEAS, which is available as a dietary supplement in the US. It is marketed with claims that daily treatment will decrease postmenopausal bone loss and improve muscle strength, sexual performance, and memory. Although the potential value of DHEAS therapy in women remains controversial, it may be the most appropriate treatment option for those with opioid-induced endocrine deficiency. The highest quality studies evaluating DHEAS treatment support its use in women with adrenal insufficiency [Gurnell et al. 2007, Morales et al. 1998; Panjari and Davis 2007]. Usually, DHEAS supplementation of 50 to 100 mg/day will sufficiently raise androgen levels to normal or near normal levels.

Anecdotally, it has been observed that patients experiencing weight gain with long-term methadone treatment may lose weight when rotated to fentanyl or oxycodone. Therefore, opioid-induced endocrine deficiency syndrome also may respond to opioid rotation. This is based on an assumption that some opioids at equianalgesic doses will cause less endocrine dysfunction than others because of differential binding to opioid receptors (eg, mu-1, mu-2, mu-3, delta, kappa).

It is presently unknown if equianalgesic doses of opioids cause comparable endocrine dysfunction, but rotation may be a treatment option for female patients with opioid-induced endocrine dysfunction. This author has “rotated” a number of female patients from high dose methadone analgesia (eg, 100 mg/day) to



Symptoms of hypogonadism would expectedly improve with testosterone replacement therapy; however, approved medications for erectile dysfunction may be appropriate for some patients.

Opioid rotation may be an a good option in female patients with opioid-induced endocrine dysfunction.

equianalgesic doses of oxycodone or buprenorphine with subsequent weight loss of 15 to 20 pounds and reported increases in energy.

Conclusion

Endocrine deficiency and subsequent hypogonadism influencing sexual dysfunction is a relatively common but often unrecognized adverse consequence of long-term opioid therapy. The syndrome is caused by suppression of gonadal hormones and adrenal androgens; its symptoms include weight gain, fatigue, depression, osteoporosis, vasomotor instability, sexual dysfunction, and menstrual cycle irregularities.

Several recommendations for addressing these issues are proposed:

- ◆ Prior to the initiation of daily opioid treatment, providers should inform patients (eg, with an opioid-treatment “contract”) that endocrine disturbances are common with higher dose, long-term opioid treatment.
- ◆ After treatment is initiated, patients should be routinely evaluated for signs and symptoms of endocrine deficiency, including sexual dysfunction.
- ◆ When endocrine deficiency is suspected, appropriate laboratory testing should be ordered.
- ◆ The primary treatment of hypogonadism in men is testosterone supplementation. Topical, buccal, or transdermal formulations are preferred over intramuscular injections.
- ◆ In women, adrenal gland suppression is a greater contributor to androgen deficiency than in men. Testosterone treatment in women is controversial. Supplementation with DHEA/DHEAS may be a preferred treatment in women due to its ability to raise androgen levels without significant side effects. Anecdotally, rotation from one opioid medication to another may also be effective.

In summary, opioid treatment is intended to reduce patients' pain, and to improve physical and social functioning. The opioid-induced endocrine syndrome with its associated sexual dysfunction – which are common and often overlooked consequences of opioid treatment – may negate the potential benefits of this analgesic therapy. Healthcare providers who prescribe sustained-release opioids should inform patients of potential adverse consequence, screen patients for this syndrome, and initiate treatment when clinically indicated.

Opioid analgesics are intended to reduce patients' pain, and to improve physical and social functioning. The opioid-induced endocrine syndrome with its associated sexual dysfunction are common and often overlooked consequences of opioid therapy and need to be addressed.

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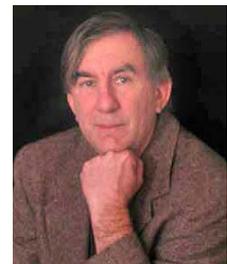
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