

Opioid-Induced Endocrinopathy

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Debilitating chronic nonmalignant pain is often managed using opioid medications. However, with increased use of this drug class comes concern about adverse effects on patients' endocrine function. In the present review, the authors discuss opioid-induced interference with the hypothalamic-pituitary-gonadal axis, effects on adrenal androgen production, and endocrine deficiency. In addition, the authors describe symptomology for opioid-induced endocrinopathy as well as diagnostic testing options. Treatment modalities for those afflicted with this condition are also described.

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In the 1990s, patient advocacy groups and professional health-related organizations in the United States commanded national attention to the problem of chronic, non-malignant pain.¹ With increased public awareness came renewed interest in the use of opioid medications.^{1,2} As a result, opioid prescribing guidelines and pharmaceutical marketing became more prevalent, and the number of prescriptions written for opioid medications increased substantially.^{3,4}

In 2003, the US Department of Veterans Affairs and the Department of Defense recommended the use of long-acting opioid medications to manage chronic pain.¹ This recommendation was based on data that suggested short-acting opioids (eg, oxycodone, acetaminophen) pose an increased risk of addiction or opioid-induced hyperalgesia and on the assumption that chronic pain requires continuous analgesia.¹ Healthcare providers seemed to agree. As suggested by pharmaceutical sales, opioid therapy is far more common today than it was 10 years ago. One review³ analyzed sales data and determined that opioid sales increased 127% from 1997 to 2006.

However, as opioid use increased, so did the incidence of associated adverse effects. In the present review, we discuss the various symptoms associated with opioid-induced endocrinopathy and outline screening tools physicians can use to diagnose this condition. Treatment options are also described.

Adverse Effects

Concern has grown regarding the adverse consequences of opioid treatment, which range from fatigue and depression to sexual dysfunction (*Figure 1*).⁵

Opioid-induced endocrinopathy is one of the most common yet least often diagnosed consequences of prolonged opioid therapy. Sustained-action opioids used on a daily basis for more than a month have a number of adverse effects on human endocrine function.⁵⁻¹⁴ For example, opioids decrease levels of the gonadal sex hormones, growth hormone, cortisol, and dehydroepiandrosterone sulfate (DHEAS).^{6,9} Opioids also blunt the cortisol response to corticotropin.^{8,13}

While the clinical significance of decreased growth hormone and cortisol levels remain speculative, decreased gonadal and adrenal androgen production contribute to the now well-documented symptoms of opioid-induced endocrinopathy.^{15,16}

Hypothalamic-Pituitary-Gonadal Axis

The primary mechanism for opiate-induced sex hormone deficiency is suppression of the hypothalamic-pituitary-gonadal axis. Sex hormones are produced by the gonads—testes in men, ovaries in women. The principal sex hormones are testosterone in men and estradiol in women. The luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are referred to as gonadotropins because they stimulate production of gonadal hormones.

The hypothalamic-pituitary-gonadal process of controlling the production and secretion of sex hormones begins with secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus (*Figure 2*). This hormone stimulates the pituitary gland to secrete LH and FSH. Once released into systemic circulation, these two hormones interact with the testes or ovaries to secrete testosterone or estrogen, respectively. As sex hormone levels rise, they signal the hypothalamus to decrease production of GnRH, thus forming a feedback control loop.

Levels of testosterone and estradiol are just two of the influences on GnRH production and release. Many neuro-

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■ Sex Hormone Deficiency

- Anemia
- Decreased libido
- Decreased muscle mass
- Depression
- Erectile dysfunction
- Fatigue
- Menstrual irregularities
- Osteoporosis
- Vasomotor instability
- Weight gain

■ Cortisol Deficiency

- Decreased response to stress

Figure 1. Adverse effects of sustained-action opioids. Sex hormone deficiency is identified by hypogonadotropic hypogonadism (ie, decreased levels of gonadotropin-releasing hormone, luteinizing hormone, testosterone, or estradiol) or decreased adrenal androgen production (ie, decreased levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate). Cortisol deficiency is identified by decreased levels of cortisol and decreased cortisol response to corticotropin.

transmitters may influence the GnRH secretory pattern, and endogenous and exogenous opioids exert an inhibitory effect on GnRH. Opioids decrease LH while opiate antagonists (eg, naloxone hydrochloride) increase these hormone levels.¹⁷ Although opioids' affect on LH and subsequent sex hormone release is not completely understood, opioids may alter the sex hormone–hypothalamic feedback process.

Opioids may also interfere with the pituitary release of LH and FSH. In women, blunting of the normal pulsatile release of LH interferes with the menstrual cycle.¹⁸ Also, opioids may have direct negative effects on the testes resulting in decreased testosterone secretion and decreased testicular interstitial fluid.⁷

Decreased Adrenal Androgen Production

The major androgens secreted by the adrenals are dehydroepiandrosterone (DHEA), DHEAS, and androstenedione. Adrenal androgens are secreted synchronously with cortisol in response to corticotropin. However, other factors may influence adrenal androgen production and secretion. As previously noted, opioids have been shown to decrease cortisol.⁹ Although DHEAS is a relatively weak androgen, it attains much higher serum concentrations than adrenal DHEA or androstenedione, making it an excellent marker for adrenal androgen production.

Many actions of adrenal androgens are exerted through their conversion to active androgens or estrogens such as

testosterone, dihydrotestosterone, estrone, and estradiol. In men, less than 2% of the biologically important androgens are derived from adrenal production. In women, approximately 50% of androgens are of adrenal origin.¹⁹

Daily use of opioids for the treatment of chronic pain has been demonstrated to cause a dose-related decrease in adrenal androgen production measured by DHEAS levels.²⁰ Daniell²⁰ studied patients treated with sustained-action oxycodone, sustained-action morphine, continuous transdermal fentanyl, or methadone for at least 1 month and found DHEAS levels that were below normal in 67% of study participants. For 24.8% of men and 31.6% of women, DHEAS values were within the normal range of age-related values.²⁰

Values of DHEAS are likely to be a clinical marker for overall adrenal function, including cortisol production, but the clinical significance of this association requires further investigation.

Endocrine Deficiency and Sexual Dysfunction

The inadequate production of sex hormones is referred to as *hypogonadism*. Despite the fact that this condition was well established as an adverse effect of methadone therapy in the 1970s and 1980s, screening for hypogonadism was not common. One reason may be that methadone therapy typically occurs in single-purpose clinics that do not routinely diag-

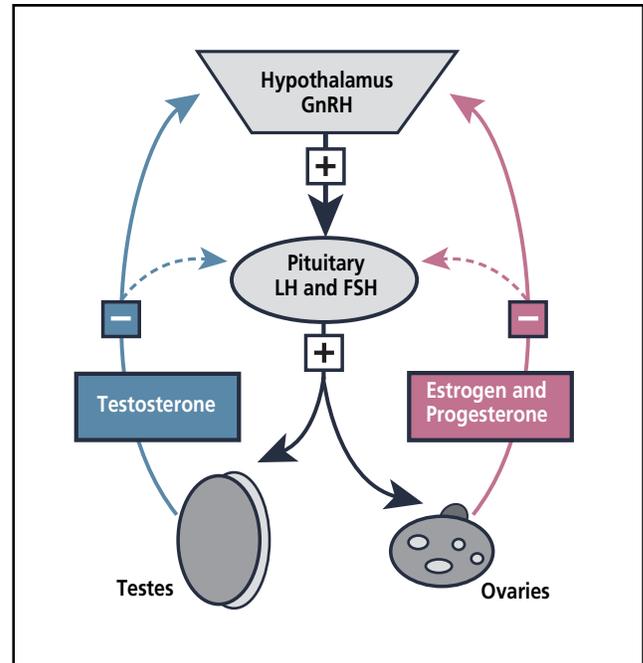


Figure 2. The hypothalamic-pituitary-gonadal axis controls the production and secretion of sex hormones. Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus and stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones cause the testes to secrete testosterone and the ovaries to release estrogen. As testosterone and estrogen levels rise, the hypothalamus produces less GnRH.

nose or treat conditions other than opiate dependence. Inadequate clinical awareness regarding the adverse endocrine effects of methadone may be another factor. For whatever reason, countless individuals receiving methadone for addiction have not been diagnosed or treated for symptomatic endocrine deficiencies.

Methadone-induced disruption of normal endocrine function is a “class effect” shared with other opioids. Before the 1990s, methadone was the only sustained-action opioid medication available in the United States. Physicians now commonly prescribe sustained-action formulations of oxycodone, oxymorphone, morphine, and fentanyl for the treatment of chronic nonmalignant pain. When used in equianalgesic doses, all opioids cause some degree of endocrine dysfunction.²¹

The association of intravenous heroin use with sexual dysfunction has been recognized for decades.^{22,23} Decreased libido is common among individuals with substance addictions, but other symptoms are especially common among opiate-dependent individuals—specifically, erectile dysfunction among men^{21,24-27} and menstrual cycle abnormalities in women.²¹

Heroin and methadone are also associated with decreased serum testosterone levels in men,^{22,23,28} potentially causing depression, fatigue, hot flashes, sweating, weight gain, and other symptoms.²⁹⁻³² In fact, a substantial proportion of men treated with sustained-action opioids—previously estimated at 5 million in the United States and Canada—are testosterone deficient.^{33,34}

Screening and Diagnostic Testing

Opioid-induced endocrinopathy should be considered in any patient receiving daily opioid treatment in an amount equivalent to 100 mg of morphine or more.³⁵ In addition, patients should be asked routinely about symptoms suggestive of sex hormone deficiency (*Figure 1*) before treatment and at regularly scheduled follow-up medical visits.³⁶

Serum testosterone concentration is the principal laboratory test used to diagnose hypogonadism in men. There is no consensus as to when laboratory tests should be ordered, but it is reasonable to do so when patients report one or more symptoms suggestive of endocrinopathy. Testosterone specimens should always be obtained in the morning because concentrations will vary throughout the day.³⁶

Most clinical laboratories consider the normal serum total testosterone range for men to be 300 to 1200 ng/dL and free testosterone to be 9 to 30 ng/dL (2.0- 4.8%).³⁷ However, there is no absolute threshold testosterone level below which symptoms of androgen deficiency may occur. For example, a young man whose serum testosterone level decreases by half from 600 ng/dL to 300 ng/dL as a result of opioid treatment may have clinically significant symptoms of hypogonadism despite the fact that 300 ng/dL may be above the laboratory’s lower limit of normal.

The Endocrine Society³⁶ recommends measuring morning total testosterone as an initial screening test, with the subsequent measure of morning total or free testosterone for confirmation. Men with clinical symptoms of hypogonadism and testosterone values below normal or in the low normal range should be considered for additional testing and testosterone replacement therapy. In such cases, routine testing should also include serum prolactin and gonadotropin levels.³⁸ Measurement of hemoglobin and hematocrit may also be helpful as red blood cell production decreases in men with hypogonadism.³⁹

Compared with the number of clinical studies on opioid-induced hypogonadism in men, few studies have investigated similar effects in women. As noted previously, menstrual abnormalities and decreased DHEAS levels are observed in women receiving sustained-action opioids,^{20,21} but there are no established diagnostic criteria.^{40,41} Many women with low androgen levels complain of weight gain, fatigue, abnormal menses, and decreased libido.⁴² In women with clinical symptoms suggestive of opioid-induced endocrinopathy, routine testing should include serum prolactin, estradiol, testosterone, gonadotropin, and DHEAS levels.¹⁶ Measurements of bone density, estradiol, and free testosterone may also help guide therapy.¹⁶

Because estradiol and gonadotropin concentrations vary during the menstrual cycle, clinical interpretation is difficult in women with irregular menses.¹⁶ Furthermore, diagnosing androgen deficiency in women is problematic because it is difficult to accurately measure low testosterone levels and because normal testosterone values for women are not well established.⁴⁰ When opioid-induced endocrinopathy is suspected in a woman, DHEAS may be the preferred indicator of endocrine function in women.¹⁶ However, more research—particularly controlled trials—is needed.

Treatment

The primary treatment for men with opioid-induced endocrinopathy is testosterone supplementation.^{36,40,43,44} Testosterone is available in gel, cream, buccal, transdermal patch, and injectable formulations. However, intramuscular treatments may result in fluctuating serum testosterone levels.^{39,45} Topical and buccal medications, which provide relatively stable testosterone concentrations, may be preferred.^{36,39}

Patients receiving testosterone should be monitored for both clinical and laboratory response to treatment. The Endocrine Society³⁶ recommends following up with patients 2 or 3 months after testosterone therapy is initiated and adjusting dosages as necessary.

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.⁴⁶ Therefore, prostate-specific antigen levels should be monitored in accordance with current screening guidelines.⁴⁶

While most research has focused on hypogonadism, decreased adrenal androgen production also contributes to endocrinopathy, especially in women. However, the clinical literature provides little guidance on treating hypogonadism or adrenal androgen deficiency in women.

Younger women receiving long-term opioid treatment may also be consuming oral contraceptive pills. These pills—particularly “third generation” oral contraceptive pills—suppress total and free testosterone. This suppression is the basis for their efficacy in reducing acne. However, in women receiving opioid treatment, oral contraceptive pills may contribute to hormone deficiency.⁴⁰ For this reason, clinicians should consider the relative androgenicity of progestin in the contraceptive management for female patients receiving opioid pain treatment.

Few clinical trials⁴⁷ have examined the efficacy or safety of testosterone therapy in women. The theoretical goal of such treatment is to raise free testosterone levels while monitoring for adverse androgenic effects such as acne, hirsutism, or deepening voice. Although testosterone therapy has been supported in treating patients with postmenopausal sexual dysfunction, most studies^{47,48} have had small sample sizes and were of limited duration. Therefore, little clinical support exists for the use of testosterone as a replacement for or addition to estrogen in postmenopausal hormone replacement therapy.^{49,50} In addition, researchers⁵¹ have raised concerns that testosterone treatment might increase women’s breast cancer risks.

Testosterone in the form of estrogen-methyltestosterone oral medication is approved for use in the United States for the treatment of vasomotor symptoms associated with menopause.⁵² However, given the lack of long-term studies of efficacy and safety, testosterone use in women for indications other than vasomotor symptoms associated with menopause is generally not recommended.^{40,53}

In the United States, DHEA is available as a dietary supplement and is marketed with claims that daily treatment will decrease postmenopausal bone loss and improve muscle strength, sexual performance, and memory.⁵⁴ Unfortunately, clinical research^{55,56} that claims to support these benefits is limited by the studies’ methodology and duration of treatment.⁵⁷

As previously noted, sustained-action opioids decrease adrenal androgen and cortisol production, creating moderate adrenal insufficiency.⁹ In our experience, female patients with suspected androgen deficiency who are receiving long-term opioid treatment have reported increased energy, increased libido, and weight loss with DHEA supplementation.

One randomized controlled trial⁵⁸ evaluated DHEA treatment and supported its use in women with adrenal insufficiency, which is a potential consequence of opioid use. Another study⁵⁹ indicated that 50 to 100 mg/day of DHEA supplementation has the potential to raise androgen levels to normal or near-normal levels. Despite the potential value of DHEA

therapy for women, it remains controversial and is not considered standard treatment.

Opioid rotation—the switch from one opioid to provide pain relief and minimize adverse effects—is primarily used in palliative care. However, it may have benefits in the management of opioid-induced endocrine dysfunction.⁶⁰

For example, a patient receiving morphine may experience inadequate analgesia as a result of sedation, but he or she may respond favorably to fentanyl. Some patients with nonmalignant pain may achieve improved analgesia from opioid rotation, but there is far less clinical support for this practice, which is based on the assumption that some opioids at equianalgesic doses will cause less endocrine dysfunction than others because of differential binding to opioid receptors (eg, μ_1 , μ_2 , μ_3 , δ , κ).

Although data to support this assumption is lacking, general observations have suggested that opioids are unique. In clinical practice, it is generally recognized that some opioids tend to be more sedating than others. As noted on various Internet forums,⁶¹⁻⁶³ individuals who abuse oxycodone often report stimulation or “energy” as the basis of their preference for one opioid medication over another (eg, morphine).

Differences in patient response to opioids—mood, analgesia, side effects—may be explained by genetics, pharmacokinetics, opioid receptor-binding properties, or other mechanisms.⁶⁴ Patients experiencing opioid-induced endocrinopathy may benefit from opioid rotation as an alternative to treatment with testosterone or DHEA supplementation. In our experience, patients who gained weight when receiving long-term treatment with morphine or methadone subsequently lost substantial weight when rotated to oxycodone or buprenorphine.

Given the inadequacy of clinical evidence for testosterone or DHEA supplementation, rotation may also be particularly appealing for women with opioid-induced endocrine dysfunction.

Conclusion

Opioids are increasingly used to treat chronic nonmalignant pain. However, long-term opioid treatment can cause endocrinopathy. Therefore, physicians must be aware of the various challenges associated with opioids.

Before initiating daily opioid treatment, physicians should inform patients in writing of all the risks and benefits associated with treatment—as specified in the *Model Policy for the Use of Controlled Substances for the Treatment of Pain*.⁶⁵ Based on the prevalence of opioid-induced endocrinopathy, physicians should include specific mention of depression, fatigue, hormone deficiency, osteoporosis, sexual dysfunction, vasomotor instability, weight gain, and, in women, menstrual cycle irregularities as possible adverse effects.

After opioid treatment is initiated, patients should be routinely evaluated for signs and symptoms of endocrinopathy.

Testosterone supplementation is the primary treatment option for men, while DHEA supplementation may be preferred in women. Because some opioids may result in less endocrine dysfunction than others, rotation to a different opioid may also be an appropriate treatment option, particularly for women.

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