The Effect of Opioid Therapy on Endocrine Function

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ABSTRACT

Opioids are an established option in the analgesic armamentarium for managing moderate-to-severe chronic pain. Long-term opioid use, however, is associated with several potential adverse effects and toxicities, such as peripheral edema, immune suppression, hyperalgesia, sleep apnea, and changes in endocrine function, many of which are not fully appreciated. Opioid endocrinopathy can greatly affect patients, causing reduced sexual function, decreased libido, infertility, mood disorders, osteoporosis, and osteopenia. Furthermore, although opioid endocrinopathy appears to be common, many patients do not report their symptoms, thus causing this adverse effect to go unnoticed and without clinical monitoring, particularly in patients chronically taking the equivalent of \( \frac{21}{4} \text{mg} \) of morphine daily. Indeed, diagnosing hypogonadism as opioid-related can be challenged by other influences on endocrine function, such as pain pathophysiology, comorbidities, other drug therapies, and patient age. Management options for opioid endocrinopathy include discontinuing opioid therapy, reducing the opioid dose, switching to a different opioid, and hormone supplementation.

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KEYWORDS: Adverse effects; Endocrinopathy; Hormone supplementation; Hypogonadism; Opioid; Opioid rotation

Opioid-induced changes in endocrine function are common and have been recognized for more than a century, yet the phenomenon remains underappreciated. Such changes represent one of several described side effects and possible toxicities associated with the chronic use of opioids. Other issues that also may be associated with chronic opioid use include peripheral edema and immune suppression. Methadone treatment specifically has been associated with certain cardiac arrhythmias. Controversial case reports and small studies in the literature suggest that patients taking opioids for chronic noncancer pain can develop hyperalgesia and have exacerbated central sleep apnea, particularly when methadone and benzodiazepines are coadministered. Sedation, nausea, vomiting, and constipation are commonly recognized as classic opioid side effects, with constipation often regarded as the most frequent complication of opioids. In actuality, hypogonadism may be the most common toxicity associated with long-term opioid treatment.

The symptoms of opioid endocrinopathy are insidious and tend to overlap the symptoms of pain disorders; therefore, routine screening is required to identify and treat affected patients. Eliminating opioids from the treatment plan is one option discussed herein for managing this adverse effect. Because some evidence suggests that opioid effects on the endocrine system may be dose- or dose frequency–related, management options for patients who develop opioid endocrinopathy also include reducing the dose. Although no evidence supports the value of opioid rotation as a treatment option for opioid endocrinopathy, the observed patterns of idiosyncratic effects of different opioids suggest that rotation could possibly be beneficial. For instance, a study by Hallinan et al noted a reduced effect on testosterone levels in patients maintained on buprenorphine compared with those maintained on methadone. Alternatively, opioid endocrinopathy can be addressed by hormone supplementation.

COMORBIDITIES ASSOCIATED WITH HYPOGONADISM

Pain typically does not occur absent underlying illness, injury, or other comorbidities. Indeed, pain pathophysiology, pain comorbidities, opioid dosage, and patient age, and several other factors can be direct causes of or contributors to hypogonadism. The Hypogonadism in Males (HIM) study demonstrated a relation between hypogonadism and
several comorbid conditions. Ninety-five primary care practices assessed hypogonadism within a population of 2162 men aged ≥45 years regardless of the reason they were seeking medical care. Overall, the prevalence of hypogonadism was 38.7%, with higher prevalences in subgroups who were not receiving testosterone replacement therapy (TRT) and in those who presented with obesity (52.4%), diabetes mellitus (50.0%), hypertension (42.4%), rheumatoid arthritis (47.3%), osteoporosis (44.4%), hyperlipidemia (40.4%), asthma/chronic obstructive pulmonary disease (43.5%), or prostatic disease (41.3%). Moreover, it has long been recognized chronic illness is associated with reduced testosterone levels. Thus, it is reasonable to expect that as many as one-third of male patients visiting a medical office will have low testosterone levels. Additionally, other studies have found a hypogonadism prevalence of 50% in patients with acquired immunodeficiency syndrome (AIDS) and of 30% in patients with human immunodeficiency virus (HIV), which may reflect lymphocyte depletion and weight loss, concurrent medications, and age-related decline in these patients. A recent study of men with erectile dysfunction found a hypogonadism prevalence of 36%. A statistically significant association was found between hypogonadism and hypertension (P = .025), tobacco abuse (P = .0059), sleep apnea (P = .0001), and work-related stress (P = .0041). The incidence of hypogonadism was highest in men with sleep apnea (64.3%). The emerging recognition of a relation between hypogonadism and sleep apnea may be particularly important for pain physicians, especially in the context of the recent research describing the frequency of sleep-disordered breathing in patients using long-term opioid therapy.

**OPioid Effects on the Hypothalamic-Pituitary-Gonadal Axis**

Opioids have a well-documented effect on 2 endocrine systems. The first is the hypothalamic-pituitary-gonadal axis. In the normally functioning system, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus and targets the pituitary gland, which is then stimulated to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones enter the systemic circulation and stimulate the end organs of the axis—the testes or ovaries—to respectively produce primarily testosterone or estrogen. Extensive preclinical and clinical data demonstrate that opioids inhibit the functioning of the entire hypothalamic-pituitary-gonadal axis in large part by binding to opioid receptors in the hypothalamus, thereby decreasing the secretion of GnRH. This inhibitory effect of opioids on the catalyzing members of the endocrine pathway is then realized throughout the cascade, but opioids also directly bind and inhibit other members of the axis. For example, opioids bind receptors in the pituitary gland, limiting the production of LH in women, thereby interfering with the menstrual cycle. The direct effects of opioids on the ovaries are to reduce sex hormone production, consequently leading to a risk of altered menstrual flow and probable reduced fertility. Direct effects of opioids on the testes include decreased production of sperm, testicular interstitial fluid, and intratesticular testosterone.

Numerous studies in settings ranging from tissue culture to animal studies, from healthy human volunteers to patients, have demonstrated the effects of opioids on the hypothalamic-pituitary-gonadal axis, with consistent results: opioids lower sex hormone levels. These effects have been observed in heroin addicts, in patients taking methadone for maintenance, in patients taking opioids intrathecally, in patients with chronic pain taking systemic (oral or transdermal) opioids, as well as in patients with cancer. Opioid effects on the endocrine system begin as soon as an opioid is taken. Although many studies in this area are small, some evidence indicates that the prevalence of opioid-induced hypogonadism in patients taking chronic opioid therapy is as high as 90%. Moreover, this adverse effect is typically seen in most patients taking chronic opioid therapy.

The more well-described symptoms of hypogonadism include reduced sexual function, decreased libido, and infertility. A number of constitutional and musculoskeletal complaints also have been described. Mood disorders such as depression, anxiety, or apathy have been clearly demonstrated to be potential consequences of hypogonadism. Fatigue as well as loss of muscle mass and strength are seen, particularly in older men (average age 49.9 years, range 30–78). Hot flashes, night sweats, and mild anemia also are reported adverse effects of opioids. In men, erectile dysfunction resulting from anticholinergic effects also is a potential opioid adverse effect on endocrine function, while women can be prone to developing amenorrhea, hypomenorrhea, or galactorrhea. Furthermore, recent evidence suggests that hypogonadism may enhance pain and interfere with the therapeutic effect of opioids.

Definitive evidence has linked opioid use with osteoporosis and increased risk of fractures. A small study has indicated that the incidence of osteoporosis in hypogonadal men taking opioids for chronic pain is 50%. Indeed, several large epidemiologic and clinical studies have shown an association between opioid use for pain or that associated with addiction and low bone marrow density or fractures. Although low bone mineral density (BMD) and fractures can be a cause of chronic pain for which people take opioids over an extended period, covariant analyses demonstrated that these conditions also are adverse effects of opioids, unexplained by comorbid pain. Patients aged ≥60 years taking opioids equivalent to ≥50 mg/day morphine for pain have a 10% rate of fracture per year (relative risk, 2; 95% confidence interval, 1.24 to 3.24). These patients, when controlled for other confounding variables, have a 2-fold higher risk of fracture than if they did not take opioids. When considering prescribing opioids, the presence of other risk factors for osteoporosis—alcohol, tobacco, and HIV—can influence the treatment choice.
The mechanisms that cause opioids to induce osteopenia have not been completely characterized. While hypogonadism itself has been associated with reduced BMD, this opioid-induced endocrine effect can only partially explain the observed increased fracture rate. Both preclinical and clinical studies have suggested a second mechanism by which opioids affect fracture risk: that is, opioids directly inhibit osteoblast activity by binding opioid receptors located on those cells, thereby reducing bone formation. Osteocalcin, a marker of osteoblast activity, is reduced in those who abuse heroin. Furthermore, other opioid effects—such as dizziness, weakness, sedation, and cognitive dysfunction—can predispose a person to fracture.

The link between hypogonadism and heightened pain is becoming established in both preclinical and clinical arenas. Several preclinical studies have demonstrated that castrating male or female rats increases pain sensitivity. In addition, 2 studies have shown that castration diminishes the beneficial effects of opioids for ameliorating pain in rats. Meanwhile, an open-label study by Daniell and colleagues showed that testosterone supplementation in opioid-induced androgen-deficient men resulted in improved quality of life and pain control from opioid therapy, without a concomitant increase in use. Compared with baseline measurements of pain severity and interference with quality of life as measured on the Brief Pain Inventory—Short Form (BPI-SF), pain scores following 6 months of testosterone patch therapy were reduced, while the reduction in interference scores reached statistical significance (P < .05). Further support was provided unintentionally by a randomized, placebo-controlled trial of TRT in women with AIDS wasting syndrome; this study measured pain as a secondary outcome and demonstrated reduced pain scores compared with placebo.

Other factors besides opioid use may affect the hypothalamic-pituitary-gonadal axis and/or reduce sex hormone levels; therefore, a differential diagnosis must be conducted to determine the cause of the hypogonadism. For example, drugs outside the opioid class—alcohol, chemotherapy, glucocorticoids, cimetidine, ketoconazole, marijuana, neuroleptics, and spironolactone—can lower sex hormone levels. Illnesses, including liver and kidney diseases, also can have a similar effect.

**EFFECT OF OPIOIDS ON THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS**

The hypothalamic-pituitary-adrenal axis is another endocrine system that can be affected by opioids. The cascade for this system is initiated with the release of corticotropin-releasing hormone (CRH) from the hypothalamus, targeting the pituitary. The pituitary is then stimulated to release adrenocorticotropic hormone (ACTH), which enters the systemic circulation and induces the adrenal glands to produce 2 hormones, cortisol and dehydroepiandrosterone (DHEA). Cortisol is important for mounting stress responses, including responses to disease; DHEA is an important precursor to testosterone in men and to estradiol in women.

The effects of chronic opioid use on the hypothalamic-pituitary-adrenal system are not as well characterized as the effects on the hypothalamic-pituitary-gonadal axis; it is known that opioids inhibit the hypothalamic-pituitary-gonadal axis on multiple levels, starting with the production of CRH. Reduced levels of CRH lead to reduced secretion of ACTH from the pituitary. Opioids also reduce the capacity of the pituitary to respond to CRH, and directly interfere with adrenal gland production of cortisol and DHEA independent of central nervous system downregulation.

Evidence in the literature suggests that opioids interfere with the release of adrenal androgens such as DHEA. A dose-related effect on adrenal androgen production was noted in a controlled study of 152 participants: 66 consumed opioids regularly for pain and 86 used opioids rarely. Low DHEA blood levels were observed in the majority (67%) of patients taking opioids, but in only 8% of controls (P < .001). Often, the level of DHEA deficiency seen was severe enough to be symptomatic when observed in other diseases that have associated adrenal insufficiency, including symptoms such as fatigue, depression, weakness, and sexual dysfunction.

Similarly, multiple studies of adrenal cortisol production have demonstrated low cortisol levels in healthy participants given morphine, and in patients on systemic or intrathecal opioids for acute or chronic pain, although it is unclear how clinically important or prevalent it is. Potential mechanisms of opioid-induced adrenal insufficiency include direct adrenal suppression and central suppression of CRH and/or ACTH production. Case reports have documented the occurrence of Addisonian crises experienced by patients taking opioids.

**MONITORING AND TREATMENT**

Standards have not been established for monitoring and treating opioid-induced hypogonadism or hypoadrenalism. Based on the literature and clinical experience, however, patients taking opioid therapy equivalent to ≥100 mg of morphine daily should be monitored for the development of hypogonadism. Patients may not necessarily report symptoms of hypogonadism, such as sexual dysfunction, menstrual irregularities, or fatigue. Therefore, monitoring should include specific questioning regarding these effects (Table 1). Toward this end, standardized questionnaires have been developed, by the St. Louis University Androgen Deficiency in Aging Male (ADAM) study, the Aging Males’ Symptoms Scale (AMS), and the Massachusetts Male Aging Study (MMAS), demonstrating sensitivities of 97%, 83%, and 60%, respectively.

In addition, laboratory tests can be useful to check endocrine system function. Total and free testosterone levels, as well as blood concentrations of sex hormone–binding globulin, LH, FSH, DHEA sulfate (DHEAS), and estradiol
Currently there is no consensus in the literature as to whether patients taking opioids chronically should have routine BMD screenings. However, guidelines do recommend BMD screenings every 2 years for patients presenting with hypogonadism.57

When a differential diagnosis identifies opioid-induced hypogonadism, one option for management is the discontinuation of opioid therapy. Discontinuing opioids can lead to renormalization of testosterone levels within 1 month of halting therapy, according to a study in heroin addicts.26 It is unclear whether this option is viable in patients with chronic pain, but it should be offered. Less clear, however, is the possible contribution and effect of comorbidities on hypogonadism. Also poorly understood is the effect of pain itself on the development of hypogonadism. Because so many variables that are not well understood have the potential to contribute to hypogonadism, baseline testing of hormone levels, if possible prior to initiating opioid therapy, can help discern the potential causes of hypogonadism. If discontinuation of opioids is pursued, alternative therapies for managing pain are available. Nonopioid treatment for pain, such as transcutaneous electrical nerve stimulation, behavior therapies, injections, radiofrequency, spinal and peripheral nerve stimulation, or nonopioid pharmacologic agents can be tried individually or in combination.2

In men, if the pain relief obtained is inadequate, an alternative option can be the continuation of opioid therapy with the addition of TRT. An open-label, pilot study considered TRT for 23 men with opioid-induced androgen deficiency.48 The men were administered transdermal patches with 5 mg/day testosterone for the first 12 weeks and then patches with 7.5 mg/day testosterone for the second 12 weeks. Among the 16 participants who completed the study, total testosterone and free testosterone levels improved significantly from baseline measurements (P < .001). Measurements in scales of androgen deficiency symptoms (androgen deficiency symptom questionnaire [ADSQ]), sexual function (Watts Sexual Functioning Questionnaire [Watts SFQ]), mood (Psychological General Well-Being Index [PGWB]), and depression (Beck Depression Inventory–II [BDI-II]) also improved, particularly with the 7.5-mg/day patch. Pain intensity scores, as measured on BPI-SF, reduced with therapy, although not statistically significantly, and pain interference with function decreased significantly (P < .05). No significant safety issues were reported.48 Besides the patch, testosterone formulations include gels, buccal tablets, and injectables.18 Further study in randomized controlled trials will lend better insight into the usefulness of this treatment approach for opioid-induced hypogonadism in men.

There are some established complications and some not-yet-validated risks of TRT. The former include local site reactions with transdermal administration methods, hematologic abnormalities such as polycythemia, and lowered sperm counts, while the latter include prostatic hypertrophy.55,58,59

### Table 1 Diagnosis of Opioid-Induced Endocrinopathy

- **Clinical evaluation:** screen for the following symptoms
  - Amenorrhea, irregular menses, galactorrhea (women)
  - Decreased libido
  - Decreased muscle mass and strength
  - Depression and anxiety
  - Erectile dysfunction (men)
  - Hot flashes and night sweats
  - Infertility
  - Osteoporosis and fractures
  - Tiredness or fatigue
  - Decreased opioid effect
  - Pain

- **Laboratory evaluation**
  - Dehydroepiandrosterone sulfate
  - Estradiol (women)
  - Free testosterone
  - Luteinizing hormone
  - Sex hormone-binding globulin
  - Total testosterone
  - Bone density (optional)
  - Follicle-stimulating hormone (optional)

- **Rule out other causes of central hypogonadism**
  - Alcoholism
  - Corticosteroid therapy
  - Hemochromatosis
  - Idiopathic gonadotropin or gonadotropin-releasing hormone deficiency
  - Pituitary-hypothalamic injury
    - Tumors
    - Trauma
    - Radiation

Adapted from Clin J Pain.2

(in women) can be measured.2 For men, blood samples should be taken by a reliable laboratory between the hours of 7:00 and 11:00 AM to account for testosterone circadian variations; if abnormal results are obtained, then measurements should be repeated. Indeed, guidelines released by The Endocrine Society recommend that several measurements be taken using an accurate assay to confirm hormone levels, because of the variability commonly observed and to reduce the risk of a false diagnosis.54,55 Toward this end, new recommendations endorsed by The Endocrine Society and 10 other professional organizations in a meeting convened by the Centers for Disease Control and Prevention (CDC) support the development of a new initiative toward testosterone assay standardization to address issues associated with inaccurate measurements.56 Typically, for men, normal serum total testosterone ranges from 300 to 1200 ng/dL, and free testosterone ranges from 9 to 30 ng/dL (2.0% to 4.8%); individuals may differ, however.18,55 DHEAS levels may be the preferred indicator of opioid-induced endocrinopathy in women because of the variations in gonadotropins over the course of the menstrual cycle, although little research has been conducted in this area.18 Currently there is no consensus in the literature as to
Because of these potential risks, patients should be monitored for development of adverse effects of TRT, such as by regular measurement of prostate-specific antigen (PSA) levels and by digital rectal examination. The Endocrine Society recommends a follow-up visit 3 months after TRT is initiated and then annually thereafter. Because of these potential risks, patients should be monitored for development of adverse effects of TRT, such as by regular measurement of prostate-specific antigen (PSA) levels and by digital rectal examination. The Endocrine Society recommends a follow-up visit 3 months after TRT is initiated and then annually thereafter to check for the development of adverse effects. Moreover, because patients with chronic pain already tend to be prone to sleep apnea, exacerbation of the problem with testosterone supplementation can be problematic. Exogenous testosterone treatment also can worsen infertility. In contrast to previous reports, a 2010 article in The New England Journal of Medicine documented cardiovascular risks associated with TRT. Many of the 106 older adult patients (65 years or older) randomized to take testosterone began therapy with high baseline measurements of cardiovascular disease. Twenty percent of the treatment group had cardiovascular adverse events, such as death, myocardial infarction, or stroke—a 10-fold higher prevalence than that in the placebo group. Additionally, TRT is commonly associated with a risk of lowering high-density lipoprotein cholesterol levels.

To date, there is little evidence regarding the treatment of opioid-induced hypogonadism in women, nor are there any clinical guidelines to direct the management of these patients or any approved modalities for treatment of this condition in women. Conventionally, women with opioid-induced hypogonadism are treated by supplementation with estrogen, progestin, or DHEA, or with oral contraceptives, in formulations including patches, tablets, creams, gels, troches, intrauterine devices, vaginal rings, and injectables. Hormone therapy in women is connected with a risk of cardiovascular disease and breast cancer.

Opioid rotation, the practice of switching opioid therapies, can be considered when managing opioid-induced endocrinopathy, though there is no clear evidence this will be sufficient. There is some evidence, however, indicating that buprenorphine induces less hypogonadism than does methadone in addicted populations. This remains a tentative conclusion, however, as the doses of buprenorphine may not have been equivalent to the methadone doses. Moreover, many opioid side effects are idiosyncratic, so potentially this adverse effect may be opioid-specific too. In 2009, an ad hoc expert committee reviewed the evidence and assembled recommendations for rotating between opioids. Following the calculation of an equianalgesic dose of a new opioid, the experts recommend 2 modifications of the dose to account for potency differences between opioids and to individualize the new opioid dose to the patient and his or her circumstance (Table 2).

No studies have provided evidence suggesting a treatment approach for opioid-induced osteoporosis, although clinical common sense suggests reducing the opioid dose or discontinuing the opioid. Alternatively, a therapy to treat osteoporosis, such as calcium, vitamin D, or a bis-

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Table 2: Guideline for Opioid Rotation

- **Step 1**
  - Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.
  - If switching to any opioid other than methadone or fentanyl, apply an “automatic dose reduction window” of 25%–50% lower than the calculated equianalgesic dose.
    - If switching to methadone, apply a dose reduction of 75%–90% lower than the calculated equianalgesic dose. For individuals on very high opioid doses (e.g., ≥1000 mg morphine equivalents/day), great caution should be exercised in converting to methadone at doses of ≥100 mg/day; consider inpatient monitoring, including serial ECG monitoring.
    - If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the package insert for these formulations.
  - Select a dose closer to the lower bound (25% reduction) or the upper bound (50% reduction) of this automatic dose reduction window on the basis of a clinical judgment that the equianalgesic dose table is relatively more or less applicable, respectively, to the specific characteristics of the opioid regimen or patient.
    - Select a dose closer to the upper bound (50% reduction) of the reduction if the patient is receiving a relatively high dose of the current opioid regimen, is not white, or is elderly or medically frail.
    - Select a dose closer to the lower bound (25% reduction) of the reduction if the patient does not have these characteristics or is undergoing a switch to a different route of systemic drug administration using the same drug.

- **Step 2**
  - Perform a second assessment of pain severity and other medical or psychosocial characteristics to determine whether to apply an additional increase or decrease of 15%–30% to enhance the likelihood that the initial dose will be effective for pain, or conversely, unlikely to cause withdrawal or opioid-related side effects.
  - Have a strategy to frequently assess the initial response and titrate the dose of the new opioid regimen to optimize outcomes.
  - If a supplemental “rescue dose” is used for titration, calculate this at 5%-15% of the total daily opioid dose and administer at an appropriate interval; if an oral transmucosal fentanyl formulation is used as a rescue dose, begin dosing at one of the lower doses, irrespective of the baseline opioid dose.

**ECG** = electrocardiogram.

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phosphonate, could be added to the opioid treatment regimen.

**SUMMARY**
Managing opioid-induced endocrine dysfunction in clinical practice begins with monitoring for symptoms, coupled with appropriate diagnostic tests, in all patients taking long-term opioids. Nonopioid analgesic approaches and/or opioid rotation should be considered in the management of opioid-induced endocrine dysfunction. Furthermore, when supported by a risk-benefit analysis and with appropriate consultation, hormone supplementation may be an option for certain individuals.

**ACKNOWLEDGMENTS**
Research and editorial support was provided by Miller Medical Communications, LLC, and by Rebecca A Bachmann, PhD, of BookishProse.

**AUTHOR DISCLOSURES**
The author of this article has disclosed the following industry relationships:

**Michael J. Brennan, MD, consultant:** Covidien, Endo Pharmaceuticals Inc, Purdue Pharma; *speakers bureau:* Covidien, Endo Pharmaceuticals Inc, inSYS Therapeutics Inc, Johnson & Johnson, Purdue Pharma, Teva/Cephalon; *stockholder:* Apricus Biosciences, Inc., Pfizer Inc, Teva Pharmaceuticals, Zalics.

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