

Opioid Related Endocrinopathy

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Abstract

Objective. Millions of patients continue to require opioid analgesics for control of moderate to severe chronic pain, which is a disease that affects more Americans than cancer, heart disease, and diabetes combined. Common opioid adverse effects include constipation, sedation, and nausea. A lesser-known sequelae is opioid induced androgen deficiency (OPIAD). The objective of this review was to better characterize the effects of opioids on the endocrine system.

Methods. Published data were evaluated to identify links between opioid use and hypogonadism, as well as to describe proposed physiological mechanisms.

Results. Chronic opioid use may predispose to hypogonadism through alteration of the hypothalamic-pituitary-gonadal axis as well as the hypothalamic-pituitary-adrenal-axis. The resulting hypogonadism and hypotestosteronism may contribute to impaired

sexual function, decreased libido, infertility, and osteoporosis- none of which may be clinically recognized as opioid related.

Conclusions. OPIAD is a recognized consequence of long-term opioid therapy. Patients initiated or maintained on opioids should be queried about symptoms that might suggest hypogonadism including irregular menses, reduced libido, depression, fatigue, and hot flashes or night sweats. Some clinicians recommend assessment of baseline testosterone levels prior to initiating therapy. Additional data appear necessary to formulate guidelines regarding the diagnosis and management of OPIAD. Options include, rotating, reducing the dose or type, or cessation of opioid therapy or adding hormonal supplementation in the form of androgen replacement therapy. There are multiple formulations of testosterone available for replacement therapy, which is usually guided by laboratory measurements.

Key Words. OPIAD; Androgen Deficiency; Chronic Pain; Testosterone; Opioid therapy; Endocrinopathy

Introduction

Pain is a major public health issue that is estimated to cost society more than \$500 billion annually [1]. This directly correlates to a recent study that reported that as many as 39 million people in the US (12% of the population) have persistent pain [2]. As a result of the number of individuals experiencing persistent pain, the National Institute of Health reported that approximately 200 million prescriptions for opioids were dispensed in 2013, a trend that has grown by over 50% over the last 10 years, and by nearly 100% since 2000 [3].

Almost all patients requiring chronic opioid therapy develop side effects, the most common of which affect the gastrointestinal and central nervous systems (CNS) [4,5]. Although tolerance develops to many of the CNS side effects over time (i.e. sedation), resolution of opioid-induced bowel dysfunction does not typically occur with continued use [4]. "Long-term opioid use has also been associated with other adverse effects and toxicities such as peripheral edema, immune

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suppression, hyperalgesia, sleep apnea, and myoclonus—many of which are not fully appreciated” [6].

Another lesser-known side effect of mu opioid analgesics is endocrinopathy, which can contribute to impaired sexual function, decreased libido and infertility, and be associated long term with osteoporosis and osteopenia. Furthermore, signs of opioid endocrinopathy often go unreported and therefore are not monitored clinically. While testosterone levels are commonly perceived to solely function as a regulator of male libido and erectile function, it also serves other useful biological functions including “muscle maintenance, exercise tolerance, and prevention of osteoporosis” [7]. A finding of interest to pain clinicians is that testosterone appears to be involved in endogenous opioid activity. It is fundamental for the binding of opioid receptors, activation of dopamine, and norepinephrine activity, as well as maintenance of blood-brain barrier transport [8,9]. Deficient testosterone may manifest as poor control of pain, lack of energy, and disturbance of sleep [10]. Men and women with low testosterone are at increased risk for inflammation, poor tissue healing, and compression fractures [7,11].

Long-acting opioids for the treatment of chronic pain often result in opioid induced androgen deficiency (OPIAD). “In a case-control study of 40 male cancer survivors it was found that 90% of those on opioid treatment were hypogonadal compared with only 40% of the control group” [12]. Another study of patients receiving chronic intrathecal opioids described hypogonadism with significantly decreased sex hormones, sexual dysfunction, and decreased quality of life [13]. In addition, it has been suggested that, “when compared with daily use of short acting opioids, daily use of long-acting opioids increases the risk of hypogonadism in men” [14].

While the limited retrospective data suggests “that clinically significant hypogonadal effects can be anticipated when opioid dose ranges exceed 100–200 mg of oral morphine equivalents daily; it is possible that even lower doses may create these effects,” [15] with the greatest risk ascribed to patients taking opioid analgesics for longer than 30 days [16].

Methadone is another opioid analgesic with significant endocrinopathic effects, particularly on testosterone levels in men. A direct relationship exists between methadone intake and testosterone reduction. “Data revealed that for each 10-mg increase in methadone dose, there was a 0.97 ng/dL (0.03 nmol/L) decrease in testosterone level ($P = 0.003$), suggesting that men who are on higher methadone doses are more likely to have a greater suppression of testosterone. By comparison, no effect of opioids on women was found; testosterone level was significantly associated with methadone dose in men only. The authors recommended that testosterone levels be checked in men prior and during metha-

done and other opioid therapy, in order to detect and treat hypogonadism associated with opioids” [5].

Pathophysiology

The pituitary gland is controlled by the hypothalamus and releases hormones into the circulation utilizing a negative feedback mechanism based on levels of estrogens and testosterone. GnRH (gonadotropin releasing hormone) triggers the anterior pituitary to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates Leydig cells to produce testosterone in the testes and estrogen in the ovaries, while FSH stimulates Sertoli cells to produce androgen binding globulin and inhibin. In this feedback system, levels of testosterone and inhibin negatively impact the levels of LH, FSH, and GnRH.

Opioids act as an inhibitor of GnRH secretion in the hypothalamus resulting in reduced testosterone levels. In addition to well-known hypothalamic effects, it is theorized that “opioid-induced hypogonadism is likely not entirely centrally mediated, and that peripheral sites may contribute to its occurrence as well” [17]. This theory was tested in a study in male rats, where the authors sought to understand the hormonal effects in peripheral tissues such as the liver and testes by studying the gene expression of the enzymes that break down testosterone [18]. They considered that in addition to binding directly to androgen receptors, testosterone can be converted by the enzyme 5-alpha reductase to dihydrotestosterone or by aromatase to estradiol which acts on estrogen receptors. “A single subcutaneous injection of morphine in rats significantly altered these enzymes centrally in the brain and peripherally in the testes and liver; and testosterone was greatly reduced in the plasma and brain in opioid-treated subjects as well” [18].

In another publication, Aloisi stated that although morphine has a depressant effect on testosterone and cortisol in just a few hours following administration, these effects are quickly reversible in a matter of hours or days once opioid administration is discontinued [19].

Evidence supports the notion that the hypothalamic-pituitary-gonadal axis becomes “rapidly suppressed following one week of intrathecal opioid administration, and within hours of heroin or methadone exposure” [20]. As mentioned, these changes are reversible with discontinuation of the opioid. Opioids decrease pulsatile secretion of gonadotropin-releasing hormone, leading to the development of hypogonadism [6]; however, other mechanisms have also been hypothesized such as increased sex hormone-binding globulin production, which decreases available free testosterone [21].

A study by Rhodin et al. compared chronic pain patients ($n = 39$) treated with mu opioid agonists for greater than 12 months to a control group ($n = 20$) of pain patients not on opioids. In this study, “serum estradiol in females

and serum testosterone in males were used to measure the pituitary-gonadal axis. In comparing the two groups, their studies showed lower levels of testosterone as well as significantly lower values of peak LH and FSH in the opioid group. The majority of men had significant sexual dysfunction, such as decreased libido and impotence in the opioid-treated group compared with the control group. Lower peak values of LH and FSH in women suggested an inhibitory effect of the opioids on the hypothalamic-pituitary levels with secondary effects on estradiol and testosterone levels. The results suggested hypofunction of both the hypothalamic-pituitary-gonadal-axis and the hypothalamic-pituitary-adrenal-axis, as well as higher prolactin levels in 42% of the opioid-treated group, compared with no effect in the control group. Another important difference between the opioid treated and the control group was the levels of prolactin. All patients in the control group had normal prolactin levels, contrasting with the opioid-treated group, in which 16 of 39 patients (42%) had supernormal values of prolactin, an effect often seen with low testosterone levels" [22].

Another publication documented hypogonadism with decreased LH/FSH levels in both males and females as early as 1 week after starting opioid therapy, with LH levels more affected in males [23].

These authors stressed that while the data of these androgen deficiency studies have been limited and included mostly small study populations, the prevalence appears to be high among opioid users, with 75–100% of the opioid population studied with symptoms and/or chemical evidence of hypogonadism [24].

In addition to testosterone levels, DHEAS (dehydroepiandrosterone sulfate) represents a sensitive marker for adrenal insufficiency in the hypothalamic-pituitary-adrenal-axis, and "lower levels of DHEAS in an opioid-treated group of females were indicative of hypoadrenalism induced by opioids. The low DHEAS can result in additional sexual disturbance and fatigue in both sexes" [25]. Females who had chronically taken opioids had serum DHEAS levels significantly lower than those who had not (51.2 mcg/dL vs 113.3 mcg/dL, $P < 0.01$) [25].

In a study conducted by Daniell, "DHEAS levels were lower in patients taking opioids than in control subjects in a dose-related pattern, and were below age-specific norms in 67% of users and 8% of controls. ACTH levels were evaluated as normal and were unrelated to opioid use. This further demonstrated that low DHEAS levels resulted from factors other than reduced adrenal ACTH stimulation" [26].

Further studies have revealed opioids inhibitory effect on the hypothalamic-pituitary-adrenal axis, specifically, ACTH and adrenal cortical secretion. Methadone infusion in patients with depression resulted in a progressive decline in serum cortisol levels (baseline 102.9 ng/mL to 26 ng/mL), and cortisol remained suppressed up

to 24 hours after the infusion, with opioids such as transdermal fentanyl having a larger impact than oral morphine [27].

Laboratory Evaluation

Diagnosing opioid-related hypogonadism can be challenging, as endocrine function is affected by several factors including chronic pain, disease comorbidities, other drug therapies, and patient age. Each of these can exaggerate or amplify the impact that opioids have on the HPG axis [28].

Laboratory assessment of potential endocrine disorders is complex and may include "total testosterone, free testosterone, sex hormone binding globulin (SHBG), LH, FSH, DHEAS, and estradiol, and may require more specific evaluation of adrenal function" [29]. As there are no formal guidelines available, it is these authors' opinion that testing should be individualized based on patient signs and symptoms; consultation with an endocrinologist or other specialist may be necessary to confirm the diagnosis until the clinician is proficient with laboratory testing.

Normal male testosterone levels peak at about age 20, and then slowly decline. Testosterone levels are highest in the mornings, especially in younger patients. Levels can fluctuate substantially day to day and androgen status should be based on more than a single measurement [30].

The endocrine systems of women can also be affected by opioids. "Women with hypopituitarism and secondary hypogonadism have been found to have reduced levels of total testosterone, free testosterone, androstenedione, and DHEAS levels as compared with healthy controls" [31]. While women receiving chronic opioid therapy may develop similar symptoms related to testosterone deficiency as men do, there are even fewer studies and certainly no guidelines for the assessment and treatment of opioid related androgen deficiency in women. "Measurements of bone density, estradiol, and free testosterone may guide appropriate therapy" [25].

Management Options and Goals of Therapy for Patients with Opiad

Patients started or maintained on opioids should be queried about symptoms that might suggest hypogonadism including "irregular menses, reduced libido, erectile dysfunction, depression, fatigue, and hot flashes or night sweats" [15]. Some clinicians recommend assessment of baseline testosterone levels prior to initiating therapy [32]. Although data is lacking, "suggested management options for opioid endocrinopathy include discontinuing opioid therapy, reducing the opioid dose, switching to a different opioid or adding hormone supplementation" [6].

Low testosterone levels in chronic pain patients maintained on opioids can be managed with testosterone replacement. Basaria led a clinical trial evaluating “whether testosterone replacement improved pain perception and tolerance, in addition to quality of life in men diagnosed with OPIAD. The study included men aged 18–64 years ($n = 84$) with opioid-induced androgen deficiency and evaluated them both at baseline and after 12 weeks of testosterone supplementation. Participants were randomized to either 5 gm of transdermal testosterone gel or placebo. Sixty-five men completed the study, 36 in the testosterone group, and 29 in the placebo group. Perception of pain was measured using the Brief Pain Inventory questionnaire, while pain threshold and tolerance were measured using Quantitative Sensory Testing. Quality of life was measured by the SF-36 questionnaire. Liquid chromatography/mass spectrometry measured total testosterone, whereby free testosterone was calculated. The study demonstrated that at 12-weeks of hormonal treatment, men randomized to testosterone exhibited significant improvement in pressure pain threshold, mechanical pain intensity, cold pressor pain, as well as emotional mood” [33].

A 2012 observational study investigated the effects of testosterone replacement in patients with OPIAD. Both opioid users and non-users were prescribed testosterone gel 1% and then evaluated for serum levels along with SHBG. The authors concluded that “replacement therapy increased serum testosterone in hypogonadal opioid users and non-users alike” [24]. “This data suggests that testosterone replacement might result in similar improvements in sexual function and mood for hypogonadal opioid users as for non-users” [34].

While testosterone replacement therapy may be beneficial for both men and women for the treatment of opioid related endocrinopathy, clinicians need to recognize the risks that include sleep disordered breathing, lipid abnormalities, hypercalcemia, and polycythemia [15]. Because of the litany of potential side effects from hormonal supplementation, clinicians should monitor the outcomes of treatment over time. “Target testosterone levels are in the range of 400–700 ng/dL for men” [35] and “20–80 ng/dL for women” [36]. Consideration should be given to additional laboratory testing such as total testosterone, complete blood count liver function tests, calcium levels, a lipid profile, and coagulation factors. Hypogonadism has also been known to increase the potential risk for osteoporosis [15], and clinicians “should consider dual-energy x-ray absorptiometry scanning, with repeat evaluation after one to 2 years of testosterone therapy” [35]. Clinicians should also counsel their patients about the effects on fertility as well as reported increases in adverse cardiovascular events.

Although OPIAD is a recognized consequence of long-term opioid therapy, testosterone supplementation is not officially approved for this indication. When electing to treat using androgen replacement therapy, goals to be considered include restoration of libido, bone den-

sity, and mood. There are multiple formulations of testosterone available for replacement therapy, which is usually guided by measured laboratory parameters. Individual laboratories will have different cutoff values for normal levels based on their own specific assays, but for adult men, a eugonadal range of 280–800 ng/dL is recommended [36]. For replacement therapy, the target should be in the mid-normal range, avoiding levels greater than normally found in the body [37].

A 2015 safety announcement by the U.S. Food and Drug Administration cautions that “prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions (hypogonadism due to disorders of the testicles, pituitary gland, or brain) and confirmed by laboratory tests. They stated that the benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if symptoms seem related to low testosterone” [38].

Testosterone replacement therapy is also not approved for use in female patients [38]. When used off-label, Tennant recommends that the starting dosage in females is no more than one-fourth to one-third of the starting male dosage [7].

Another potential therapy for women with OPIAD is DHEA, which is a natural precursor hormone produced by the adrenal glands. It is available as an over-the-counter supplement that is not closely regulated, making the actual content of DHEA highly variable. Although there is no standard dose, “it is recommended that women take a 50 mg dose of DHEA daily if this is to be used as a hormonal supplement” [37]. Clinicians may consider ordering plasma DHEA levels to assist with supplementation, which remains controversial for the treatment of OPIAD and underreported in the medical and pain management literature.

In 2010, the Endocrine Task Force updated its recommendations and stressed that clinicians’ diagnose androgen deficiency only in men expressing signs and symptoms consistent with low serum testosterone levels. These recommendations were not specific to OPIAD. They suggested morning total testosterone as the initial diagnostic test, with repeat confirmation as necessary. Additionally, they suggested “measurement of free testosterone levels in some men in whom total testosterone is near the lower limit of normal or in whom SHBG abnormality is suspected” [35].

The Endocrine Task Force proposed “supplemental testosterone therapy for men with symptomatic androgen deficiency. Goals include improving sense of well-being, libido and sexual function as well as maintaining muscle mass and bone mineral density. They recommend against starting testosterone therapy in certain patients including those with breast or prostate cancer or those at high risk for prostate cancer” [35]. Other cautions for testosterone replacement include hematocrit greater

Table 1 Symptoms and signs suggestive of androgen deficiency in men (Adapted from Bhasin et al. [35] *NOT SPECIFIC TO OPIOIDS*)

Reduced Sexual Desire or Ability	Breast Pain, Gynecomastia	Loss of Body Hair
Small or Shrinking Testes	Infertility	Low Bone Density
Hot flushes, Sweating	Reduced Muscle Mass	Poor Concentration or Mood Disturbance

Derived from: *J Clin Endocrinol Metab*, June 2010, 95(6):2536–2559 *Endocrine Society Clinical Guidelines: Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes* (reference #35 in the article).

than 50, untreated severe obstructive sleep apnea, or poorly controlled heart failure. With supplemental therapy, “clinicians should target plasma testosterone levels to the mid-normal range, choosing prescription therapies based on patient preference, treatment burden, and cost” [35]. As with any disease state, patients’ symptoms and laboratory parameters should be monitored over time and therapies adjusted accordingly.

Conclusion

Although recognized as related to long-term opioid therapy, the diagnosis and treatment of OPIAD is poorly understood and often overlooked by clinicians. Both the hypothalamic-pituitary-gonadal and the hypothalamic-pituitary-adrenal axes are involved, and recognizing endocrine dysfunction can be a diagnostic challenge in both men and women. Clinicians should be mindful that opioids, along with other comorbidities including age, pain, chronic illness, and other medications, contribute to hypogonadism.

Signs and symptoms of androgen deficiency including erectile and sexual dysfunction, hot flashes or irregular menses, mood disturbance, fatigue, and night sweats should be assessed when evaluating chronic pain patients on long term opioid therapies. Routine testing and treatment for OPIAD may be warranted; more formal recommendations or guidelines by a dedicated pain

management or endocrinology task force would benefit patients affected by this condition.

[Table 1 lists common symptoms of androgen deficiency in men].

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