

Narrative Review


Opioid-Induced Androgen Deficiency (OPIAD)
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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: None.

Manuscript received: 12/02/2011
Accepted for publication: 02/10/2012

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Opioid therapy is one of the most effective forms of analgesia currently in use. In the past few decades, the use of opioids as a long-term treatment for chronic pain has increased dramatically. Accompanying this upsurge in the use of long-term opioid therapy has been an increase in the occurrence of opioid associated endocrinopathy, most commonly manifested as an androgen deficiency and therefore referred to as opioid associated androgen deficiency (OPIAD). This syndrome is characterized by the presence of inappropriately low levels of gonadotropins (follicle stimulating hormone and luteinizing hormone) leading to inadequate production of sex hormones, particularly testosterone. Symptoms that may manifest in patients with OPIAD include reduced libido, erectile dysfunction, fatigue, hot flashes, and depression. Physical findings may include reduced facial and body hair, anemia, decreased muscle mass, weight gain, and osteopenia or osteoporosis. Additionally, both men and women with OPIAD may suffer from infertility. While the literature regarding OPIAD remains limited, it is apparent that OPIAD is becoming increasingly prevalent among chronic opioid consumers but often goes unrecognized. OPIAD can have a significant negative impact on the the quality of life of opioid users, and clinicians should anticipate the potential for its occurrence whenever long-term opioid prescribing is undertaken. Once diagnosed, treatment for OPIAD may be offered utilizing a number of androgen replacement therapy options including a variety of testosterone preparations and, for female patients with OPIAD, dehydroepiandrosterone (DHEA) supplementation. Follow-up evaluation of patients receiving androgen replacement therapy should include a review of any unresolved symptoms of hypogonadism, laboratory evaluation, and surveillance for potential adverse effects of androgen replacement therapy including prostate disease in males.

Key words: Opioid, hypogonadism, testosterone, endocrine, androgen

Pain Physician 2012; 15:ES145-ES156

Pharmacologic analgesic therapy with opioids is based on the ability of these agents to bind to opioid receptors in the central nervous system (CNS) and in the periphery. Morphine sulfate, through its binding to opioid receptors, is known to act in several body regions from the gut to the brain (1,2). Previous studies have demonstrated that morphine induces a dramatic long-lasting decrease in testosterone, which persists during opioid therapy even if the treatment lasts

for months or years, in both males and females (3). The effect can occur after a few hours, with testosterone concentrations reaching castration levels (< 1ng/mL) (3). Aloisi and colleagues have also shown that once opioid treatment is interrupted, testosterone levels recover in a few hours/days (4,5). Furthermore, spinal (intrathecal or epidural) administration of morphine resulted in a similar reduction in testosterone in both males and females (4).

Testosterone and the Hypothalamic-Pituitary Gonadal Axis

The hypothalamic-pituitary-gonadal (HPG) axis is regulated by a negative feedback mechanism (Fig. 1). Testosterone inhibits the frequency and amplitude of Gonadotropin-releasing hormone (GnRH) release from the hy-

pothalamus and also the secretion of luteinizing hormone (LH) from the pituitary. The Sertoli cells of the testes, in addition to stimulating spermatogenesis, also secrete the glycoprotein hormone inhibin, which provides negative feedback to the pituitary, inhibiting the secretion of follicle stimulating hormone (FSH) (6) (Fig. 1).

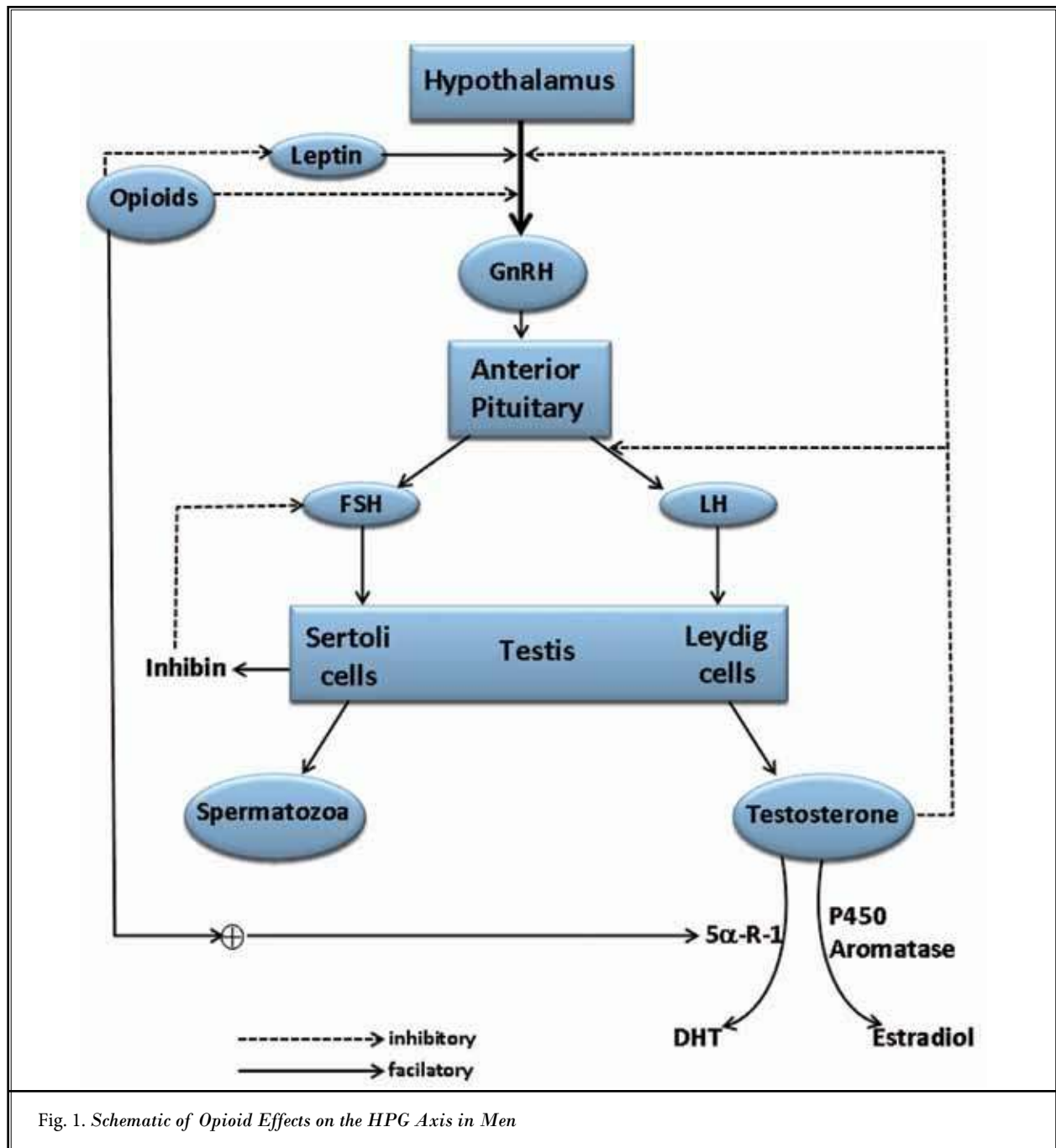


Fig. 1. Schematic of Opioid Effects on the HPG Axis in Men

Testosterone is converted to dihydrotestosterone (DHT) by 5-alpha-reductase enzymes or to estradiol by P450 aromatase in target cells. Testosterone and DHT both bind to the androgen receptor where they exert their biological effects. Approximately 20% of the DHT in the circulation is produced directly by testicular secretion, with the remaining 80% being derived from conversion of testosterone in peripheral tissues (7). Target cells that contain 5-alpha-reductase are concentrated in the prostate, reproductive system, and skin. Aromatase-containing cells predominate in the liver, adipose tissue, and regions of the brain (8,9).

Total serum testosterone is composed of 3 components added together. Roughly half of testosterone is bound to the carrier molecule sex hormone-binding globulin (SHBG), almost all of the remainder is bound to albumin, and 1–2% is unbound or free. Testosterone binds so tightly to SHBG that it is functionally unavailable to cells. In contrast, albumin-bound testosterone dissociates readily, meaning that this component and the free component are available to cells. The term “bioavailable testosterone” refers to a combination of the albumin-bound and free portions (10).

Age-Related Declines in Serum Testosterone

Although wide interindividual variations exist, mean total testosterone (TT) and free testosterone (FT) levels decline with age, whereas DHT and estradiol levels tend to remain relatively constant. At age 75 years, the mean TT level in the morning is about two-thirds of the mean level in men aged 20–30 years, whereas the mean FT and bioactive testosterone (FT plus albumin-bound testosterone) levels are only 40% of the mean levels in younger men. Furthermore, the circadian rhythm of serum testosterone levels is generally lost or attenuated in elderly men (11).

Effects of Testosterone Deficiency on Male Sexual Function

Sexual interest and activity, and erectile rigidity and duration decline in men as they age. Erectile dysfunction (ED) is seen with an age-stratified incidence of 1.9% at 40 years and 25% or greater by age 65 (12). The reported incidence of endocrinopathy as the etiology of ED is 1–35% (13). Interestingly, the prevalence of abnormally low serum testosterone levels, even among men with ED, has historically been reported to be low (roughly 6% in urology clinics). The majority of studies show that ED has a clear association with aging, but no consistent correlation of total testosterone levels with

erectile function has been identified. The role testosterone plays in human penile erectile physiology is unclear, and so far appears to be different from its effects in animal models. The physiology of erection depends on the integrity of corporal smooth muscle (14). In a variety of experimental conditions, orchiectomy has been associated with decreased smooth muscle content and increased interstitial collagen in the penis (15). At the cellular level, the absence of testosterone reduces nitric oxide synthase and nitric oxide production. Recent clinical recommendations have been made regarding assessment of testosterone levels in patients in whom phosphodiesterase type 5 inhibitor therapy fails. Although no direct link has been made to cavernosal muscular atrophy or penile neurological control, it may be that testosterone not only affects sex behavior but also subtly changes a number of physiological parameters directly regulating erectile activity.

HYPOGONADISM

Hypogonadism may be congenital or acquired, and has many causes. The pathophysiologic mechanisms underlying hypogonadism involve either gonadal failure or failure of the hypothalamus or pituitary to release adequate stimulatory hormones for the gonadal production of sex hormones. Gonadal failure may be referred to as primary hypogonadism or hypergonadotropic hypogonadism (e.g. low testosterone; high pituitary gonadotropins), while insufficiency of hypothalamic and/or pituitary gonadotropin release results in hypogonadotropic hypogonadism, also known as secondary or central hypogonadism (e.g. low testosterone, and low to low normal LH/FSH). Common causes of primary hypogonadism in men include testicular infections (such as the mumps), exposure to radiation and certain forms of chemotherapy, and the use of some drugs (e.g. ketoconazole) (16). Secondary hypogonadism may occur as a result of conditions such as hemochromatosis, pituitary tumors, and exposure to drugs such as corticosteroids or opioids (17).

Diagnosis of hypogonadism

The diagnosis of hypogonadism remains a clinical one, and therefore is still very much an art. Subjective symptoms suggestive of androgen deficiency with characteristic signs on physical examination may lead one to suspect hypogonadism, which can then be confirmed by testing with demonstration of low serum testosterone levels. The most characteristic symptom of low testosterone is diminished libido, which, taken in

conjunction with signs of testicular atrophy on physical examination, is highly specific for hypogonadism when observed in patients with ED (18). However, focusing on these "characteristic" or "classic" signs and symptoms alone may lead one to miss many men who are androgen deficient and who might be well served by testosterone replacement therapy (18). Sexual symptoms due to low testosterone include ED, difficulty achieving orgasm, reduced intensity of orgasm, diminished ejaculatory volume, and reduced sexual sensation in the genital region, particularly the penis. Non-sexual symptoms of hypogonadism may include reduced sense of vitality or "energy," increased fatigue, decreased attention, depressed mood, reduced motivation, vasomotor instability, weight gain, and decreased muscle mass or strength. Note that these symptoms are not specific to androgen deficiency, and so one should maintain a high index of suspicion of hypogonadism when trying to correctly diagnose the cause of these broad symptoms (18).

Signs of androgen deficiency may include testicular atrophy, anemia, reduced facial hair growth, infertility (in both men and women), menstrual irregularities, muscle hypotrophy, reduced bone mineral density (osteopenia or osteoporosis), and changes in body composition (increased fat mass and reduced lean body mass). Low testosterone has also been associated with the metabolic syndrome, a set of risk factors for cardiovascular disease (19).

The Endocrine Society defines male hypogonadism as a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa caused by disruption of one or more levels of

the HPG axis (20).

There are no absolute testosterone levels below which a man can unambiguously be stated to be hypogonadal. The Endocrine Society recommends 300 ng / dl (10.4 nmol / l) as a good level to consider as the lower limit of normal total testosterone. The American Association of Clinical Endocrinologists (AACE) suggests 200 ng/dl (21), and the International Society of Andrology (ISA), International Society for the Study of Ageing Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), and American Society of Andrology (ASA) recommendations suggest 230 ng / dl as the threshold below which patients will usually benefit from testosterone replacement treatment (22).

Ancillary Diagnostic Tools

Screening questionnaires on hypogonadism in men are gradually improving. The more commonly used screens are the Aging Male Symptoms Scale (AMS), Androgen Deficiency in the Aging Males Questionnaire (ADAM), and Massachusetts Male Aging Survey Questionnaire (MMAS), which are intended for the screening or diagnosis of hypogonadism as well as for the evaluation of its therapeutic results. Morley et al (23) compared these questionnaires in 148 men using bioavailable testosterone as the "biochemical gold standard" for the diagnosis of hypogonadism, and found the sensitivity to be 97% for the ADAM, 83% for the AMS, and 60% for the MMAS. Specificity was 30% for the ADAM, 59% for the MMAS, and 39% for the AMS. The ADAM and the AMS may be useful screening tools for hypogonadism (23). The authors recommend using the ADAM (24) (Table 1).

Table 1. *Androgen deficiency in ageing males (ADAM) questionnaire (24-Morley 2000)*

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?
If the answer is 'yes' to question 1 or 7, or at least 3 of the other questions, low testosterone may be present.

(24)- Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, Perry HM 3rd. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000; 49: 1239-1242.

Common Comorbidities

Higher rates of hypogonadism than those seen in the general population are associated with various common diseases or conditions. The Hypogonadism in Males (HIM) study calculated odds ratios for the occurrence of hypogonadism in conjunction with some common conditions including obesity (2.3), diabetes mellitus (2.09), hypertension (1.84), hyperlipidemia (1.47), osteoporosis (1.41), and asthma or chronic obstructive pulmonary disease (1.40) (25).

Opioid-Induced Androgen Deficiency (OPIAD)

The occurrence of significantly reduced testosterone levels during morphine administration has largely been attributed to the inhibitory action of morphine on GnRH secretion in the hypothalamus (26,27). This inhibition causes decreased gonadotropin production, and consequently, gonadal hormone secretion. It appears that morphine-induced hypogonadism is likely not solely centrally mediated and that peripheral active sites may also contribute to its occurrence. Aloisi and colleagues (28) investigated whether changes in testosterone catabolic enzymes contribute to the occurrence of hypogonadism during morphine administration. They demonstrated that a single subcutaneous injection of morphine significantly altered 5-alpha reductase type 1 and/or P450-aromatase mRNA expression in different body regions (28). The finding of increased expression of one or both of these enzymes in the brain as well as in the liver and testis suggests a catabolic effect of morphine on testosterone. It therefore appears that following opioid administration, testosterone is not only produced to a lesser degree because of reduced gonadotropin secretion, but it is also metabolized to a greater extent, with a combined effect of significantly reduced blood and brain testosterone levels (Fig. 1). While low serum testosterone levels often correlate with low CNS testosterone levels (as observed in castrated animals), experimental data in formalin injected rats suggests that CNS levels of testosterone can be depressed even when serum testosterone levels are normal (29). In the CNS, glial cells may play an important role in supplying neurons with testosterone. Ceccarelli and colleagues (30) have shown that *in vitro* supplementation of glial cells with exogenous testosterone strongly increases the cellular content of testosterone. Exposure of glial cells to morphine results in significant reductions in cellular testosterone levels; however, pretreatment with exogenous testosterone prevents this effect (30). It ap-

pears that morphine exposure increases the activity of aromatase in glial cells, which is responsible for the conversion of testosterone to estradiol, thus causing reductions in testosterone levels. This suggests that levels of testosterone in neurons may respond dynamically (and perhaps bi-directionally) to levels of testosterone in glia and that exposure of glia to morphine may reduce the availability of testosterone to neighboring neurons.

Most research on OPIAD has centered on the use of intrathecal opioids or has been done in individuals undergoing treatment for heroin addiction (31-37). Several studies conducted on patients with chronic pain have also demonstrated that repeated use of oral opioids may predispose to the development of hypogonadism (38-42). Both neuraxial and enteral opioid administration have been shown to cause significant reductions in serum sex hormone levels, which may lead to clinically significant sexual dysfunction and decreased quality of life (33,41). Retrospective studies in subjects on chronic opioid therapy have shown that many of these patients manifest a pattern of central hypogonadism, which is frequently associated with the development of a depressed mood (43).

Unfortunately, prospective, randomized, controlled clinical trial data regarding the occurrence of OPIAD in humans is virtually non-existent (43). In the only prospective study on this subject performed to date, Roberts et al (35), evaluated sex hormone suppression by intrathecal opioids and demonstrated that HPG axis-suppression occurred within one week of initiation of intrathecal opioids in study subjects (35). It appeared that many of the study subjects had a history of ongoing oral opioid exposure prior to the initiation of the trial, though the degree of previous opioid exposure was not clearly defined. Some degree of sexual dysfunction was present in most of the subjects at the time of enrollment into the study, and the mean baseline testosterone level was slightly below the reference range, possibly as a result of prior opioid use. Over the course of the 12-week study, reduced sexual activity was observed in all subjects, and there was a significant decrease in the mean serum testosterone level from baseline, supporting the hypothesis that intrathecal opioid administration causes suppression of sex hormone secretion.

The administration of long-acting opioids such as methadone, morphine sulfate, fentanyl, and oxycodone for the treatment of chronic pain often results in OPIAD. In a case-control study of 40 cancer survivors it

was found that 90% of those on opioid treatment were hypogonadal compared with only 40% of the control group (40).

Studies have demonstrated a direct correlation between testosterone deficiency and chronic opioid use (39-41). Androgen deficiency during prolonged opioid administration can occur in female as well as male patients. Women with hypopituitarism and secondary hypogonadism have been found to have markedly reduced levels of TT, FT, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) levels as compared to healthy controls (44,45). Suppression of adrenal androgen production may play a role in addition to the induction of hypogonadotropic hypogonadism (46). The hypothesis of opioid-related suppression of adrenal androgen production is supported by the finding of reduced dehydroepiandrosterone (DHEA) and DHEAS levels among chronic opioid consumers (46).

Testosterone deficiency appears to be underdiagnosed in women (47). Women receiving chronic opioid therapy may manifest a similar constellation of symptoms related to testosterone deficiency as men do; however, these symptoms may go undiagnosed due to under appreciation of this phenomenon by both patient and practitioner (43).

The absolute threshold of opioid dosing associated with the development of hypogonadotropic hypogonadism remains unclear, though it does appear there is a correlation between higher opioid doses and the development of hypogonadism (37,48). The limited retrospective human data available suggests that clinically significant hypogonadal effects should be anticipated when opioid dose ranges exceed 100 - 200 mg of oral morphine equivalents daily; however, it is possible that even lower doses may create these effects (43). Additionally, the duration of opioid exposure required to induce changes of clinical consequence to the HPG axis is unclear, but the highest risk appears to be among patients receiving significant opioid doses for longer than one month (49). Suppression of the HPG axis appears to occur rapidly after exposure to opioids, and has been documented one week following initiation of intrathecal opioid administration, and within hours of heroin or methadone exposure (35,37,41). It seems that opioid-induced endocrinopathy is reversible, as recovery of normal serum testosterone levels has been observed as soon as a few days after cessation of opioid therapy, even among long-term users (31,41,48).

Aloisi and colleagues (50) evaluated 9 male chronic pain patients who developed hypogonadism during

treatment with epidural morphine at baseline and for a year during androgen replacement therapy. The daily administration of testosterone increased total and free testosterone and DHT levels as measured after 3 months of therapy. These levels remained high through the conclusion of the 12 month study period. Pain rating indexes in the form of the Italian Pain Questionnaire (QUID), which is a reconstructed version of the McGill Pain Questionnaire, progressively improved from months 3 to 12, while other pain parameters (VAS, Area%) remained unchanged. The AMS sexual dimension and SF-36 Mental Index significantly improved over time, with overall study results suggesting that continual, long-term use of testosterone supplementation can induce a general improvement in the male chronic pain patient's quality of life (50).

RECOMMENDATIONS FOR PATIENTS WITH OPIAD

There should be a high index of suspicion for the development of hypogonadism in patients who receive opioid therapy for longer than a few weeks (43). Doses exceeding approximately 100 mg of oral morphine equivalents daily may be more likely to trigger the onset of OPIAD than lower opioid doses (49). Since suppression of the HPG axis has been observed as early as one week after the initiation of intrathecal opioids, and limited data exist regarding opioid dosing thresholds required to induce hypogonadism, it would seem prudent to evaluate any patient manifesting symptoms of hypogonadism for signs of OPIAD regardless of opioid doses consumed or duration of therapy (35,43). Patients who chronically consume opioids should be asked about symptoms such as reduced libido, erectile dysfunction, depression, fatigue, hot flashes or night sweats, and irregular menses (43). Laboratory testing to assess for the presence of opioid-induced hypogonadism may include TT, FT, SHBG, LH, FSH, DHEAS, and estradiol (E2) (48). Other causes of hypogonadism such as menopause, surgical absence of gonads, prior history of mumps exposure, and exposure to alcohol and other drugs that might affect gonadal function should also be considered when making this assessment (48). Women should be adequately estrogenized (they should have normal ovarian function or be on established estrogen replacement therapy) before a diagnosis of androgen deficiency is established (51,52). Any patient who is prescribed chronic opioid therapy should be given adequate informed consent that addresses the issue of opioid-associated endocrinopathy as a consequence of

this therapy, including symptoms that may occur with its development (49,53,54).

Androgen Replacement Therapy

Both men and women diagnosed with opioid-associated endocrinopathy may be treated with androgen replacement therapy (ART). Any patient who is offered testosterone replacement therapy should be educated about the potential side effects of this treatment including polycythemia, sleep apnea, local site reactions, and reductions in serum high-density lipoprotein (HDL) levels (43). Potential contraindications to the use of ART may include known hypersensitivity to the drugs, males with known or suspected carcinoma of the prostate, women who are or who may become pregnant, and patients with uncontrolled sleep apnea, hematocrits exceeding 50 percent, or those who have significant cardiac or hepatic disease. Women being prescribed testosterone replacement therapy should be informed of the potential for virilization (hirsutism, clitoral enlargement, acne, muscular development, and deepening of voice) and also of the possibility of an increased risk for the development of breast cancer during treatment (55). Women of child-bearing potential should be counseled regarding the potential for virilization of a female fetus should they become pregnant while receiving ART (45,51,56). Men receiving testosterone replacement therapy should be informed of possible side effects to include male pattern baldness, gynecomastia, priapism, and oligospermia/azoospermia, and they must be monitored for the development of prostate disease, including BPH and prostate cancer (20). Patients with pre-existing benign prostatic hypertrophy should be monitored for worsening symptoms/signs. Target testosterone levels during ART in men are in the range of 400 - 700 ng/dL (20). Target testosterone levels for women receiving ART are not well defined in the literature, but ranges of 20 - 80 ng/dL appear to be reference ranges used in most laboratories to define "normal" female testosterone levels (the lower end of the range representing levels seen in postmenopausal women and the higher end of the range those seen in premenopausal women) (57).

The most common adverse effects of testosterone therapy found in a recent meta-analysis of 51 studies evaluating testosterone therapy in men were increased hemoglobin and hematocrit levels and slightly decreased serum HDL levels (58). The incidence of death or major cardiovascular adverse events did not differ

significantly between the testosterone-treated group and patients receiving placebo in these studies. A data safety monitoring board terminated a recent placebo-controlled study evaluating testosterone therapy in elderly men with limited mobility because of an increased incidence of cardiovascular events in the testosterone-treated group (59). Basaria and colleagues (59) reported a high prevalence of underlying cardiovascular disease in the study subjects, and they felt that a lack of a consistent pattern in the adverse events and small overall number of events might have been due to chance. Therefore, caution was advised in extrapolating these results to other populations, particularly younger men who are hypogonadal and who do not have cardiovascular disease (59).

ART may also be associated with other potential adverse effects. ART should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Androgens conceivably may promote sleep apnea, especially in certain patients who may be at increased risk or have a predisposition for sleep apnea. Androgens may change insulin sensitivity and decrease blood glucose with the potential to lower insulin requirements in diabetic patients. Additionally, patients on anticoagulation may have changes in anticoagulant activity that may require more frequent monitoring of international normalized ratio (INR)/prothrombin time. Also, the use of testosterone with adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention.

Patients receiving ART should be periodically reassessed for ongoing symptoms of hypogonadism, and should undergo monitoring of laboratory tests (TT, FT, SHBG, lipid profile, liver function tests, complete blood count, serum calcium concentrations, INR, prothrombin time) and digital rectal examination and prostate-specific antigen screening in men. Since the risk of osteoporosis and related fractures is increased in both males and females who manifest hypogonadism, bone density assessment should be considered in all individuals identified with opioid-associated hypogonadism (48,60-63). The Endocrine Society clinical practice guidelines recommend assessment of bone mineral density in men with severe androgen deficiency or low trauma fracture via dual-energy X-ray absorptiometry scanning (DEXA), with repeat evaluation after one to 2 years of testosterone therapy (20,43). Goals of ART may be to restore a normal (or the patient's baseline) body composition, bone density, libido, and mood (18).

AVAILABLE ART FORMULATIONS

There are multiple formulations of ART that might be particularly well suited to various individual patients (Table 2). It should be noted that testosterone replacement therapy is not approved by the U.S. Food and Drug Administration (FDA) for use in female patients and doses of testosterone replacement for this patient population have not been well established. If chosen for the treatment of OPIAD in women, testosterone should be dose reduced substantially relative to doses used in men (often to less than 10% of the dose recommended for men).

Attempts should be made to match the most appropriate treatment formulations to the individual patient. According to most studies, the eugonadal range of serum testosterone in adult men is considered to be in the range of 300–1000 ng/dl (the AACE recommends 280–800 ng/dl). It is generally considered best to aim for a testosterone level in the mid-normal range, avoiding excessive supraphysiological peaks (20,64,65).

DHEA

DHEA may be used in women diagnosed with OPIAD. It is available as an over-the-counter supplement in

most pharmacies and health food stores. Due to lack of regulation of these supplements by the FDA to comply with good pharmaceutical practice, the actual content of DHEA may be highly variable from one supplement to another (52,56). It is recommended that women take a 50 mg dose of DHEA daily if this is to be used as ART(66). Follow-up laboratory evaluation of DHEA levels is recommended and will help further guide adjustment of this therapy (52,56).

Intramuscular Testosterone Injections

Testosterone injections have been used for at least 50 years and are often the lowest cost option available for treatment (67). A characteristic of injected testosterone esters is that serum testosterone levels rise to supraphysiological levels after injection, and then gradually decline into the hypogonadal range by the end of the dosing interval. These swings in testosterone levels may be associated with parallel variations in breast tenderness, sexual activity, emotional stability (anger or depression), and general well being (fatigue) (67).

Testosterone cypionate for intramuscular injection is the oil-soluble 17 (beta)-cyclopentylpropionate ester of testosterone. Each mL contains testosterone

Table 2. Testosterone formulations

Brand Name	Formulation(s)	Dose
-----	Intramuscular injections (testosterone enanthate or testosterone cypionate)	75–100 mg weekly or 150–200 mg every 2 weeks
Striant	Muco-adhesive Buccal tablets	30 mg tablet applied to the buccal mucosa every 12 h
Testopel	Subcutaneous pellets	6–10, 75 mg pellets implanted subcutaneously every 4–6 months
Android, Testred, Virilon	Oral capsule or tablet (methyl testosterone)	Should not be used for the treatment of hypogonadism because of risk of liver toxicity and hepatocellular carcinoma
Androderm	2.5 mg/24 hr patch; 5 mg/24 hr patch	5 mg once nightly
Andro Gel 1%	2.5 g packet of gel (25 mg testosterone); 5 g packet of gel (50 mg testosterone)	one 5 g packet of gel (50 mg of testosterone) once daily (4 pump presses) [shoulders, upper arms and/or abdomen]
Andro Gel 1.62%	Each Actuation delivers 1.25 g of gel (20.25 mg of testosterone per pump actuation)	2.5 g of gel (40.5 mg of testosterone) (2 pump presses) [shoulders and upper arms]
Axiron	metered-dose pump containing 10 mL of solution (30 mg of testosterone solution per 1.5 mL actuation) for transdermal use in axilla	60 mg (2 actuations) once daily
Fortesta	metered-dose pump containing 60 g (10 mg of testosterone gel per 0.5 g pump actuation) for transdermal use	40 mg (4 actuations) once daily

cypionate 200 mg, benzyl benzoate 20%, and benzyl alcohol 0.9% (as a preservative) in cottonseed oil. Approximately 90% of a dose of testosterone cypionate is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites, while about 6% of a dose is excreted in the feces, mostly in the unconjugated form. The half-life of testosterone cypionate when injected intramuscularly is roughly 8 days, and it is generally administered at 2-week intervals. Patients experiencing adverse effects from this regimen may better tolerate administering half the usual dose once every week.

Transdermal Testosterone Patches

These are applied at night and generally provide a good approximation of normal circadian plasma testosterone levels (67). Patches are applied once a day (in the evening) to nongenital skin on the back, abdomen, thighs or upper arms (67).

Transdermal Testosterone Gels

These are hydroalcoholic gels of 1% testosterone that are applied once a day to the upper arms and shoulders or to the abdomen (67). One concern with the use of gels is that testosterone can be transferred from the patient to his partner or children after skin contact. To minimize this risk, patients should be instructed to wash their hands with soap and water after applying the gel, cover the site of application with clothing after the gel has dried, and wash the application site when skin-to-skin contact is expected (67).

Axiron topical solution is supplied as a metered-dose pump that delivers 30 mg of testosterone per pump actuation. The recommended starting dose is 60 mg (one pump for each axilla) applied once daily at the same time each morning after showering or bathing. If a deodorant or antiperspirant is used, it should be applied at least 2 minutes before applying Axiron. The axilla should be clean and dry at the time of application. Axiron is supplied in a metered dose pump and is applied to the skin using an applicator. Axiron is flammable until dry. Caution should be taken to minimize secondary transfer of the drug by skin-to-skin contact. Patients should wait 3 minutes after application, until it is dry, before contacting anything. After 14 days, the dose can be adjusted (in a range of 30 - 120 mg per day) based on serum testosterone concentrations measured 2 - 8 hours after application.

Fortesta (testosterone) gel is supplied in a metered dose pump and is applied directly to the skin using one

finger to gently rub the gel into the skin. As with Axiron, Fortesta is flammable until dry (roughly 3 minutes postapplication) and contact of the area with water should be avoided for at least 2 hours postapplication. The starting dose of Fortesta is generally 40 mg of testosterone (4 pump actuations) applied topically to the nongenital skin of the thighs once daily in the morning. The dose can be adjusted between a minimum of 10 mg of testosterone (one pump actuation) and a maximum of 70 mg of testosterone (7 pump actuations) on the basis of total serum testosterone concentrations measured 2 hours postapplication. The dose should be titrated based on the serum testosterone concentration from a single blood draw 2 hours after application obtained approximately 14 days and 35 days after starting treatment or following dose adjustments.

Davis and colleagues (68) evaluated the effects of exogenous testosterone gel in a metered-dose transdermal spray in premenopausal women reporting diminished sexual function. The primary outcome was the mean number of self-reported satisfactory sexual events (SSEs) over 28 days at week 16. The frequency of SSEs, total number of sexual events (every 4 weeks), scores from the modified Sabbatsberg Sexual Self-Rating Scale and the Psychological General Well-Being Index, and safety variables were also measured (68). They found that in premenopausal women with reduced libido and low serum-free testosterone levels, a daily 90- μ L dose of transdermal testosterone improves self-reported sexual satisfaction significantly when compared to placebo (68).

Buccal Testosterone Tablets

These mucoadhesive tablets are applied to the gum just above the incisor teeth, and bypass first-pass hepatic metabolism. Tablets must remain in the mouth for a full 12 hours and 2 are needed for the 24 hour dosing period (67).

Subcutaneous Testosterone Pellets

Testosterone pellets are usually implanted under the skin of the lower abdomen using a trochar and cannula or are inserted into the gluteus muscle. Six to 10 pellets are implanted at one time and last 4-6 months, after which a new procedure is required to implant more (67).

Implanted testosterone pellets can normalize testosterone and LH levels and improve symptoms for at least 3 months and up to 6 months in men with hypogonadism, and should be considered as a viable thera-

peutic option for hypogonadal men (69). Testosterone pellets are the only FDA approved form of long-acting testosterone available in the United States (67).

Oral Testosterone Tablets or Capsules

Orally ingested testosterone is hepatically deactivated, but modification to 17-methyl testosterone enhances its oral bioavailability. Although it is an effective oral androgen formulation, it is not recommended in the treatment of hypogonadism due to hepatotoxic side effects and its association with long-term development of liver tumors (67). Currently, there are no oral testosterone preparations available in the United States for the management of hypogonadism.

CONCLUSION

OPIAD is an increasingly recognized consequence of long-term opioid therapy. It occurs due to alterations in the HPG axis induced by exposure to opioids that result in hypogonadotropic hypogonadism. It manifests with loss of libido, sexual dysfunction, and non-specific symptoms such as fatigue and depression,

which may contribute to the low rate of its diagnosis despite its relatively common occurrence. Untreated, patients with OPIAD may suffer reduced quality of life due to these symptoms and may go on to develop further complications such as osteopenia or osteoporosis. Pain practitioners should be aware of this disorder and anticipate the potential for its occurrence among chronic pain patients on recurring opioid prescriptions. Any patient who receives long-term treatment with opioids is at risk for the development of this syndrome and should be monitored accordingly with attention paid to underlying symptoms and signs of OPIAD. Laboratory evaluation may be helpful in establishing this diagnosis once suspected. Both men and women who are identified with OPIAD may be offered hormonal replacement with androgen therapy. Patients started on ART will require periodic follow-up including laboratory evaluation and surveillance for adverse effects from androgen therapy to include polycythemia, reductions in HDL cholesterol, virilization in females, and prostate disease in males.

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