The Impact of Opioids on the Endocrine System

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Objectives: Opioids have been used for medicinal and analgesic purposes for centuries. However, their negative effects on the endocrine system, which have been known for some times, are barely discussed in modern medicine. Therefore, we conducted a systematic review of the impact of opioids on the endocrine system.

Methods: A review of the English language literature on preclinical and clinical studies of any type on the influence of opioids on the endocrine system was conducted. Preliminary recommendations for monitoring and managing these problems were provided.

Results: Long-term opioid therapy for either addiction or chronic pain often induces hypogonadism owing to central suppression of hypothalamic secretion of gonadotropin-releasing hormone. Symptoms of opioid-induced hypogonadism include loss of libido, infertility, fatigue, depression, anxiety, loss of muscle strength and mass, osteoporosis, and compression fractures in both men and women; impotence in men; and menstrual irregularities and galactorrhea in women. In view of the increased use of opioids for chronic pain, it has become increasingly important to monitor patients taking opioids and manage endocrine complications. Therefore, patients on opioid therapy should be routinely screened for such symptoms and for laboratory abnormalities in sex hormones.

Conclusions: Opioid-induced hypogonadism seems to be a common complication of therapeutic or illicit opioid use. Patients on long-term opioid therapy should be prospectively monitored, and in cases of opioid-induced hypogonadism, we recommend nonopioid pain management, opioid rotation, or sex hormone supplementation after careful consideration of the risks and benefits.

Key Words: opioid, pain, hypogonadism, hormones, testosterone

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"(Opium) has kept, and does now keep down the population: the women have fewer children than those of other countries…the feeble opium-smokers of Assam…are more effeminate than women."

Charles Alexander Bruce, "Report on the manufacture of tea and on the extent and produce of the tea plantations in Assam." Calcutta, 1839.

Opioids have been used for medicinal and analgesic purposes for millennia, and today remain a critical part of the medical armamentarium against pain, diarrhea, cough, and other symptoms. Unfortunately, although barely discussed in the modern medical lexicon, opioids have negative effects on the endocrine system, which have been observed for at least a century. These effects (Table 1) include decreased testosterone production in men, with loss of libido and other expected effects, and menstrual irregularities and infertility in women. In view of the increased use of opioids for chronic pain, it has become increasingly important to recognize and manage their endocrine complications.

PHYSIOLOGY OF OPIOID-ENDOCRINE INTERACTIONS

The hypothalamic-pituitary-gonadal axis, which controls the production of the primary sex hormones, testosterone (androgen) and estradiol (estrogen), begins with the secretion by the hypothalamus of gonadotropin releasing hormone (GnRH) (Fig. 1). GnRH stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH). These 2 hormones are released into the systemic circulation and stimulate the gonads—the testes and ovaries—to secrete testosterone or estradiol, respectively. It should also be noted that estradiol is also secreted by the testes through the aromatization of testosterone[1] and that testosterone is secreted by the ovarian theca cells.[2] These sex hormones then exert a negative feedback on the hypothalamus and pituitary to control the secretion of GnRH, LH, and FSH. Testosterone and estrogen support normal sexual and reproductive development and behavior.

The hypothalamic-pituitary-gonadal axis is modulated by a complex series of outside influences as well. Opioids are one of a number of such influences. Evidence suggests that opioids, both endogenous and exogenous, can bind to opioid receptors primarily in the hypothalamus, but potentially also in the pituitary and the testis, to modulate gonadal function.[3–8] Opioids have been shown to decrease the release of GnRH or interfere with its normal pulsatility at the level of the hypothalamus, resulting in a decreased release of LH and FSH from the pituitary and a secondary fall in gonadal steroid production, that is, hypogonadism. Direct effects of opioids on the testis, including decreased secretion of testosterone and testicular interstitial fluid, have also been documented.[9] Opioid receptors have also been localized in ovarian tissue cultures and opioids have been shown to directly suppress ovarian steroid production in vitro.[10] Opioids have been shown to increase pituitary release of prolactin in preclinical studies,[11] which, in turn, decreases testosterone secretion, although (as indicated below) prolactin secretion is generally not affected in clinical studies. Lastly, opioids have also been shown to alter the adrenal production of dehydroepiandrosterone (DHEA), an important precursor of both testosterone in men and estradiol production in women.[12]

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TABLE 1. Endocrine Effects of Opioids

Central hypogonadism (also called secondary or hypogonadotropic hypogonadism)
Decreased hypothalamic GnRH
Decreased pituitary LH, possibly FSH
Decreased adrenal DHEAS and testosterone
Decreased estradiol and progesterone (women)
Decreased testicular testosterone (men)
Possible cortisol deficiency
Possible growth hormone deficiency (men)

Effects apply to both men and women unless otherwise noted.
DHEAS indicates dehydroepiandrosterone sulfate; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone.

ENDOCRINE CONSEQUENCES OF OPIOID USE

Opioid-induced Hypogonadism in Animals

Investigations in animals have shown acute and chronic effects of opioids on the endocrine system,[13] including a decrease in testosterone levels via central reductions of LH release (decreased hypothalamic release of LH releasing hormone leading to reduced pituitary release of LH), and peripheral effects on the testicle as well.[14–19] However, not all opioids have the same effect on testosterone levels: in rats, tramadol did not affect plasma testosterone levels and buprenorphine did not affect brain testosterone levels, whereas other opioids tested (morphine and fentanyl) affected both.[20] Tramadol and buprenorphine may not produce as much opioid hypogonadism as other compounds because they are not pure μ agonists and have other properties: tramadol inhibits monoamine reuptake and buprenorphine is a partial μ agonist with potential κ antagonist features.[21]

Opioid-induced Hypogonadism in Opioid-addicted Patients and in Patients Treated for Addiction

Studies in heroin addicts have demonstrated an opioid-mediated decrease in testosterone levels in males, with an associated decrease in LH and/or FSH levels. The latter is referred to as central, secondary, or hypogonadotropic hypogonadism because it is caused by pituitary or hypothalamic dysfunction.[9,22–27] One of these studies showed that testosterone levels had returned to normal 1 month after cessation of heroin use, suggesting that the effect of opioids on the endocrine system is reversible.[27] Several studies in methadone-maintained male patients have shown decreased testosterone and LH levels consistent with central hypogonadism. One of these studies[26] showed a dose-response effect, in that patients on "low dose" methadone (10 to 60 mg/d) had no evidence of testosterone level suppression, whereas patients on "high dose" (80 to 150 mg/d) did. Another study[9] demonstrated a peripheral effect on the testicle, with decreased secretion of testosterone and testicular interstitial fluid, and decreased sperm motility. One case series described amenorrhea and galactorrhea in female heroin addicts.[28]

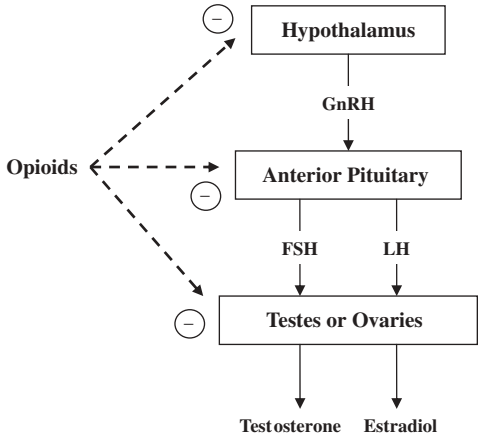

FIGURE 1. Interactions between opioids and the reproductive endocrine system.

Another study[29] compared the endocrine function of 17 men treated with buprenorphine for addiction, 37 treated with high-dose methadone, and 51 healthy controls. Patients treated with buprenorphine had a significantly higher testosterone and a significantly lower frequency of sexual dysfunction compared with patients treated with methadone. The testosterone level of buprenorphine-treated patients did not differ from that of healthy controls. This is the first study suggesting that not all opioids may be alike in terms of endocrine effects in man, although it is not clear that equivalent doses of methadone and buprenorphine were compared in this study.

Opioid-induced Hypogonadism in Patients With Chronic Pain on Opioid Therapy

In the pain arena, several studies of patients undergoing intrathecal opioid use for nonmalignant pain, compared with patients with a comparable pain syndrome not on opioid therapy, have documented hypogonadism associated with low LH values and normal or low FSH levels in both men and women.[29–34] These laboratory findings, which indicate hypogonadotropic hypogonadism, were associated with decreased libido (men and women), impotence in men, and irregular or absent menses (oligorrhea or amenorrhea) in women. Symptoms were reported to have improved in most patients with hormone supplementation. In none of these studies were prolactin levels elevated, suggesting that prolactin is not significantly associated with opioid-mediated hypogonadism in humans. In premenopausal women, chronic oligorrhea or amenorrhea may lead to infertility, osteoporosis, and potentially increased cardiovascular risk.[35] In postmenopausal or oophorectomized women, the opioid-induced reductions in testosterone and adrenal DHEA levels may both contribute to diminished libido and depressed mood.[12]

Three studies have been published on the effect of long-term oral opioid therapy in men with chronic pain. In the first study,[36] endocrine function was measured in 54 patients on sustained-release opioids and in 27 healthy controls. Hormone levels were much lower in opioid users than in control patients in a dose-related pattern ($P < 0.0001$ for all comparisons). Total testosterone levels were subnormal in 74% of the opioid group, with an apparent dose-response effect. Of the men who reported normal erectile function before opioid use, 87% reported severe erectile dysfunction or diminished libido after beginning their opioid therapy. A recent study from the same group showed clinically significant improvements in hypogonadal symptoms, sexual function, and mood in men with opioid-induced androgen deficiency (termed OPIAD[37]) who were treated with transdermal testosterone patches.

The second study[38] showed abnormally low testosterone levels in cancer survivors taking opioids for chronic pain. In a follow-up case-control study,[39] 20 cancer survivors on opioids were compared with 20 matched controls—cancer survivors not on opioid therapy. In the opioid group, 90% exhibited hypogonadism, compared with 40% in the control group. Median testosterone levels, LH levels, but not FSH levels, were statistically significantly lower in the opioid group. Importantly, these laboratory abnormalities were associated with clinically significant consequences: sexual desire (measured by the Sexual Desire Inventory), anxiety and depression (measured by the Hospital Anxiety and Depression Scale), and overall quality of life [measured by the Functional Assessment of Chronic Illness Therapy with general and fatigue subscales (FACT-G/FACIT-F)] were all significantly lower in the opioid group than in the controls.

A recent study showed that women consuming sustained-action oral or transdermal opioids for the control of noncancer pain have a decrease in FSH and LH accompanied with a profound inhibition of ovarian sex hormones (estradiol) and adrenal androgen [testosterone and dehydroepiandrosterone sulfate (DHEAS)] production.[40] A decrease in DHEAS was also found in men taking opioids for nonmalignant pain, suggesting that opioids may also decrease adrenal function.[12]

Hypogonadism and Pain Sensitivity

Interestingly, 1 preclinical study in rats[41] demonstrated that reducing testosterone levels by castration significantly increased sensitivity to pain (as measured by 2 standard assays—the tail flick and hot plate tests). This increase in pain sensitivity was reversed by testosterone supplementation. Other preclinical studies have demonstrated that hypogonadism can interfere with the antinociceptive actions of opioids, although the effects are not entirely consistent across studies.[42] These observations raise the hypotheses that the phenomena of opioid-induced hyperalgesia and even of opioid tolerance in man may be in part accounted for by (1) increased pain sensitivity produced by hypogonadism or (2) interference with opioid analgesia by the reduction in gonadal hormones. The only evidence to our knowledge addressing these issues in humans is quite indirect. A randomized placebo-controlled study[43] was conducted to evaluate the efficacy of transdermal testosterone versus placebo in 53 female patients with AIDS wasting syndrome (a syndrome associated with markedly decreased serum androgen levels). Pain scores were captured incidentally with the pain item on the SF-36 quality of life survey. A trend toward improved pain score ($P = 0.059$) was observed in 1 of the 2 testosterone treatment groups compared with placebo.

Opioid Effects on Other Endocrine Functions

Several studies have examined the possibility of opioid-induced alterations of other endocrine functions. In general, it does not seem that opioids alter thyroid function in any meaningful way.[44,45] Opioids have been found in several studies to decrease cortisol levels and cortisol responses to adrenocorticotropic challenges[29,46,47]; however, the clinical significance of this is unclear. Interestingly, in 1 study, 15% of patients developed hypocortisolism and 15% developed growth hormone deficiency.[29] Although 1 patient with hypocortisolism developed an Addisonian crisis, the clinical consequences of low cortisol levels observed in several studies of opioid therapy have not been established. Hypogonadism from any cause has also been shown to affect the serum lipid profile in men, although the consistency and clinical importance of these effects is uncertain.[48]

In summary, a number of lines of evidence in animals and humans (including the settings of opioid addiction, opioid addiction treatment, intrathecal opioids, and oral opioids for chronic pain) clearly demonstrate that opioids suppress gonadal hormone secretion in males and females. Opioids seem to mediate their effects on gonadal hormones primarily via central mechanisms (acting on the hypothalamus and pituitary), although a peripheral component may be involved as well. Some studies have found a dose-response effect of opioids on the endocrine system, with increasing opioid doses resulting in increased testosterone suppression. OPIAD seems to have important clinical consequences, including decreased sexual desire and performance, increased anxiety and depression, and reduced quality of life. Preclinical data suggest that it may also be associated with increased pain sensitivity (which could counteract the analgesic effects of opioids). On the basis of limited data, these opioid effects seem reversible. Opioids also in some studies seem to affect the endocrine system in other ways, including decreasing cortisol and growth hormone levels (Table 2). Interestingly, all opioids may not have the same effect on the endocrine system as buprenorphine did not seem to affect testosterone levels in 1 clinical study.

DIAGNOSIS OF OPIOID-INDUCED ENDOCRINOPATHY

The signs and symptoms of hypogonadism are well known (Table 2) and include decreased libido, tiredness, depressed mood, hot flashes or night sweats, loss of muscle mass and strength, infertility, and osteoporosis and fractures in men and women; decreased erectile dysfunction in men; and abnormal menses in women.[5,32,49–51] In women with low testosterone levels, decreased libido may be reflected by a decrease in sexual thoughts, fantasies, sexual receptivity and activity, arousal, orgasm, and pleasure.[52,53] However, many of these symptoms are also widespread in patients with chronic pain.[54–57] Thus, in patients on opioids for chronic pain, these symptoms, if elicited at all, may be attributed to the chronic pain and its associated conditions, and the possibility of hypogonadism not entertained. Therefore, all patients on opioid therapy for chronic pain

TABLE 2. Symptoms of Hypogonadism

Decreased libido
Erectile dysfunction (men)
Infertility
Depression and anxiety
Decreased muscle mass and strength
Tiredness or fatigue
Hot flashes and night sweats
Amenorrhea, irregular menses, galactorrhea (women)
Osteoporosis and fractures
Pain?
Decreased opioid effect?

Effects apply to both men and women unless otherwise noted.

should be assessed prospectively for symptoms that could be potentially related to opioid-induced hypogonadism (Table 2). Although there are no available standards for laboratory monitoring of patients on opioids for chronic pain, endocrine monitoring should be routine in such patients (Table 3). Laboratory testing should include total and free testosterone (or sex hormone binding globulin), LH, FSH (optional), and DHEAS in both men and women and estradiol in women. Although LH levels are generally low or inappropriately normal in patients with opioid-induced hypogonadism, a magnetic resonance imaging is not needed to rule out pituitary tumors in this setting as the opioid use is the likely cause of the hormonal changes.[58] Monitoring of bone density should also be considered in patients at risk for osteoporosis, as patients with fractures associated with hypogonadism often have no other symptoms of hypogonadism,[49] and a high prevalence of osteoporosis has been described in patients on methadone maintenance.[59] The diagnosis of hypogonadism is made by low levels of testosterone, with a customary cutoff of total (bound and free) testosterone < 300 ng/dL in men and < 20 ng/dL in premenopausal women. The diagnosis and treatment of hypogonadism in a patient on opioid therapy should take into account the fact that other causes of hypogonadism (eg, menopause, ovariectomy, castration, past mumps or other infections, other medications, and alcohol) may be present; if not, opioids should be the presumptive cause of hypogonadism.

MANAGEMENT OF OPIOID-INDUCED ENDOCRINOPATHY

There are no accepted standards for the management of presumptive opioid-induced hypogonadism; therefore, clinical judgment must be relied upon. In patients who seem to have opioid-induced hypogonadism, several considerations will influence treatment decisions (Table 4).

The first step is to determine to which extent the laboratory abnormalities are clinically important by assessing sexual function, libido, mood, and the other symptoms noted above. For patients with symptoms or even in patients with laboratory abnormalities and unclear clinical status, the first option is to switch treatment. The physician should explore nonopioid pain management options such as transcutaneous electrical nerve stimulation, behavior therapies, injections, radiofrequency, spinal and peripheral nerve stimulation, and nonopioid pharmacologic agents (pain specialists can be consulted to determine the best nonopioid options). If these techniques are not adequate, the physician may consider opioid rotation. There is currently no information regarding whether opioid hypogonadism improves with opioid rotation. However, like other opioid side-effects that seem to occur idiosyncratically between patients,[60] hypogonadism may occur with different degree with different opioids in any individual patient; thus, we suggest that clinicians consider opioid rotation to potentially find an opioid that induces minimal or no hypogonadism in a particular patient. For instance, switching to buprenorphine is a possible option that requires further exploration as this opioid has shown to induce fewer hypogonadism symptoms in preliminary studies. In some patients, opioid rotation should be fairly straightforward and, therefore, may be a reasonable initial plan. In other patients, such as those on high doses or those who have failed multiple opioids, opioid rotation may be difficult and testosterone supplementation may be more appropriate.

Hormone therapy (HT) with testosterone should aim at increasing total serum testosterone concentrations to within the normal physiologic range of 300 to 1000 ng/mL for men.[37,61–63] Sex HT in women conventionally includes estrogen (oral or transdermal dosage forms) and progestin (to protect the uterus). At present, there are no approved modalities for treating OPIAD in women. In premenopausal women, HT with estrogen and progestational agents or oral contraceptives may ameliorate the endocrine function. Using over-the-counter DHEA supplements may be a consideration with monitoring testosterone levels. Indeed, symptomatic women receiving conventional HT may potentially benefit from testosterone and/or DHEA therapy at appropriate replacement doses, although such approaches are still considered experimental.

Several formulations of testosterone are available, including intramuscular injections, transdermal patches,

TABLE 3. Diagnosis of Opioid-induced Endocrinopathy

Clinical evaluation: symptoms (Table 2)
Laboratory evaluation
Total testosterone
Free testosterone
SHBG
LH
FSH (optional)
DHEAS
Estradiol (women)
Cortisol (women)
Bone density (optional)
Rule out other causes of hypogonadotropic hypogonadism
Alcoholism
Idiopathic gonadotropin or GnRH deficiency
Pituitary-hypothalamic injury
Tumors
Trauma
Radiation
Hemochromatosis
Corticosteroid therapy

DHEAS indicates dehydroepiandrosterone sulfate; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin.

TABLE 4. Management of Opioid-induced Hypogonadism

Consider nonopioid pain management options (eg, TENS, behavior therapies, injections, radiofrequency, nerve stimulation, and nonopioid drugs)
Consider opioid rotation
Consider strategies that allow opioid dose reduction
Concomitant nonopioid analgesics
Nonpharmacologic modalities
Testosterone supplementation (men)
Consider consultation with an endocrinologist
Choose formulation and dose
Transdermal gel
Transdermal patch
Intramuscular injection
Monitor prostate-specific antigen and prostate examination in men
Monitor clinical and laboratory results

TENS indicates transcutaneous electrical nerve stimulation.

TABLE 5. Monitoring of Patients on Testosterone Supplementation

Symptoms of hypogonadism
Free and total testosterone and SHBG
Rectal examinations and prostate-specific antigen
Complete blood count
Lipid profile

SHBG indicates sex hormone binding globulin.

and transdermal gel. The majority of the clinical trial data and experience involves intramuscular injections, but the transdermal formulations are more acceptable to most patients. Therefore, a reasonable approach is to begin with a transdermal formulation and switch to injections in patients who are unable to normalize testosterone levels with transdermal formulations. It must be remembered that testosterone supplementation is not free of side-effects, including local site reactions, decreases in high-density lipoproteins-cholesterol levels, abuse and misuse, and various hematologic abnormalities, particularly polycythemia. In men, oligospermia, priapism, male pattern baldness, and gynecomastia may occur; in women, menstrual irregularities, acne, hirsutism, and virilization. Perhaps most worrisome is the potential for stimulation of growth, benign or otherwise, of the prostate gland. Although exogenous testosterone has not been firmly linked to the development of prostate cancer, patients must be monitored (rectal examinations and prostate-specific antigen levels) for such effects. The possibility of abnormalities in serum lipids should be monitored, because decreases in high-density lipoprotein levels are common in men receiving testosterone therapy (Table 5).

HT for women is available via patches, tablets, creams, troches, intrauterine devices, vaginal rings, gels, or, more rarely, by injection. HT for women may contain various doses of estrogens, progestin (a progesterone analog), and experimental use of testosterone or DHEA. However, HT may increase the risk of cardiovascular disease and breast cancer. Given these complexities, consultation with an endocrinologist may be helpful.

CONCLUSIONS

Opioid-induced hypogonadism owing to central suppression of hypothalamic secretion of GnRH is probably common in both male and female patients on long-term opioid therapy for either addiction or chronic pain. Potential symptoms include loss of libido, infertility, fatigue, depression, anxiety, loss of muscle strength and mass, osteoporosis and compression fractures in both men and women; impotence in men; and menstrual irregularities and galactorrhea in women. Thus, clinicians should consider this issue in weighing the risks and benefits of long-term opioid therapy in comparison with other pain management options such as behavior therapies, injections, radiofrequency, nerve stimulation, and nonopioid pharmacologic agents.

Patients on long-term opioid therapy should be routinely screened for such symptoms and for associated laboratory abnormalities in sex hormones. If opioid-induced hypogonadism is detected, physicians should first consider the following options (in this order): (1) nonopioid pain management options, (2) opioid rotation, and (3) sex hormone supplementation (which should be offered after careful consideration of the risks and benefits and consultation with an endocrinologist). Patients who undergo testosterone supplementation should be regularly assessed to monitor the risks and benefits. Further research is needed to better define the incidence and prevalence of this phenomenon, its natural history, whether opioid rotation is beneficial, whether certain opioids are more problematic than others, treatment, and whether opioid hypogonadism can antagonize the benefits of analgesic treatment.

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REFERENCES

1. de Ronde W, Pols HA, van Leeuwen JP, et al. The importance of oestrogens in males. *Clin Endocrinol*. 2003;58:529–542.
2. Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. *Fertil Steril*. 1994; 62:20–27.
3. Cicero T. Effects of exogenous and endogenous opiates on the hypothalamic-pituitary-gonadal axis in the male. *Fed Proc*. 1980;39:2551–2554.
4. Drolet G, Dumont EC, Gosselin I, et al. Role of endogenous opioid system in the regulation of the stress response. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001;25:729–741.
5. Genazzani AR, Genazzani AD, Volpogni C, et al. Opioid control of gonadotrophin secretion in humans. *Hum Reprod*. 1993;8(suppl 2):151–153.
6. Grossman A, Moult PJ, Gaillard RC, et al. The opioid control of LH and FSH release: effects of a met-enkephalin analogue and naloxone. *Clin Endocrinol*. 1981;14:41–47.
7. Jordan D, Tafani JAM, Ries C, et al. Evidence for multiple opioid receptors in the human posterior pituitary. *J Neuroendocrinol*. 1996;8:883–887.
8. Veldhuis JD, Rogol AD, Samojlik E, et al. Role of endogenous opiates in the expression of negative feedback actions of androgen and estrogen on pulsatile properties of luteinizing hormone secretion in man. *J Clin Invest*. 1984;74:47–55.
9. Cicero TJ, Bell RD, Wiest WG, et al. Function of the male sex organs in heroin and methadone users. *N Engl J Med*. 1975;292:882–887.
10. Kaminski T. The involvement of protein kinases in signalling of opioid agonist FK 33-824 in porcine granulosa cells. *Anim Reprod Sci*. 2006;91:107–122.
11. Yen SSC, Quigley ME, Reid RL, et al. Neuroendocrinology of opioid peptides and their role in the control of gonadotropin and prolactin secretion. *Am J Obstet Gynecol*. 1985;152: 485–493.
12. Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioids: evidence for opioid-induced inhibition of adrenal androgen production. *J Pain*. 2006;7:901–907.
13. Pfeiffer A, Herz A. Endocrine actions of opioids. *Horm Metab Res*. 1984;16:386–397.
14. Adams ML, Sewing B, Forman JB, et al. Opioid-induced suppression of rat testicular function. *J Pharmacol Exp Ther*. 1993;266:323–328.
15. Cicero TJ, Meyer ER, Bell RD, et al. Effects of morphine on the secondary sex organs and plasma testosterone levels of rats. *Res Commun Chem Pathol Pharmacol*. 1974;7:17–24.
16. Cicero TJ, Wilcox CE, Bell RD, et al. Acute reduction in serum testosterone levels by narcotics in the male rat: stereospecificity, blockade by naloxone and tolerance. *J Pharmacol Exp Ther*. 1976;198:340–346.
17. Clark JT, Gabriel SM, Simpkins JW, et al. Chronic morphine and testosterone treatment. Effects on sexual behaviour and

dopamine metabolism in male rats. *Neuroendocrinology*. 1988;48:97–104.
18. Wiesenfeld-Hallin Z, Sodersten P. Spinal opiates affect sexual behavior in rats. *Nature*. 1984;309:257–258.
19. Yilmaz B, Knoar V, Kutlu S, et al. Influence of chronic morphine exposure on serum LH, FSH, testosterone levels, and body and testicular weights in the developing male rat. *Arch Androl*. 1999;43:189–196.
20. Ceccarelli I, De Padova AM, Fiorenzani P, et al. Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. *Neuroscience*. 2006;140:929–937.
21. Bliesener N, Albrecht S, Schwager A, et al. Plasma testosterone and sexual function in men on buprenorphine maintenance for opioid dependence. *J Clin Endocrinol Metab*. 2005;90:203–206.
22. Daniell HW. Narcotic-induced hypogonadism during therapy for heroin addiction. *J Addict Dis*. 2002;21:47–53.
23. Fachinetti F, Volpe A, Farci G, et al. Hypothalamus-pituitary-adrenal axis of heroin addicts. *Drug Alcohol Depend*. 1985;15: 361–366.
24. Khan C, Malik SA, Iqbal MA. Testosterone suppression by heroin. *J Pak Med Assoc*. 1990;40:172–173.
25. Malik SA, Khan C, Jabbar A, et al. Heroin addiction and sex hormones in males. *J Pak Med Assoc*. 1992;42:210–212.
26. Mendelson JH, Mendelson JE, Patch VD. Plasma testosterone levels in heroin addiction and during methadone maintenance. *J Pharmacol Exp Ther*. 1975;192:211–217.
27. Mendelson JH, Mello NK. Plasma testosterone levels during chronic heroin use and protracted abstinence. A study of Hong Kong addicts. *Clin Pharmacol Ther*. 1975;17:529–533.
28. Pelosi MA, Sama JC, Caterini H, et al. Galactorrhea-amenorrhea syndrome associated with heroin addiction. *Am J Obstet Gynecol*. 1974;118:996–970.
29. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85:2215–2222.
30. Doleys DM, Dinoff BL, Page L, et al. Sexual dysfunction and other side effects of intraspinal opiate use in the management of chronic non-cancer pain. *AJPM*. 1998;8:5–11.
31. Finch PM, Roberts LJ, Price L, et al. Hypogonadism in patients treated with intrathecal morphine. *Clin J Pain*. 2000;16:251–254.
32. Paice JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. *J Pain Symptom Manage*. 1994;9:126–131.
33. Paice JA, Penn RD. Amenorrhea associated with intraspinal morphine. *J Pain Symptom Manage*. 1995;10:582–583.
34. Winkelmuller M, Winkelmuller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. *J Neurosurg*. 1996;85:458–467.
35. Berga SL, Loucks TL. The diagnosis and treatment of stress-induced anovulation. *Minerva Ginecol*. 2005;57:45–54.
36. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002;3:377–384.
37. Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid induced androgen deficiency (OPIAD). *J Pain*. 2006;7:200–210.
38. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. *J Pain Symptom Manage*. 2003;26:1055–1061.
39. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer*. 2004;100:851–858.
40. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain*. 2008;9:28–36.
41. Forman LJ, Tingle V, Estilow S, et al. The response to analgesia testing is affected by gonadal steroids in the rat. *Life Sci*. 1989;45:447–454.
42. Stoffel EC, Ulibarri CM, Folk JE, et al. Gonadal hormone modulation of mu, kappa, and delta opioid antinociception in male and female rats. *J Pain*. 2005;6:261–274.
43. Miller K, Corcoran C, Armstrong C, et al. Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. *J Clin Endocrinol Metab*. 1998;83:2717–2725.
44. Chan V, Wang C, Yeung RT. Effects of heroin addiction on thyrotrophin, thyroid hormones and prolactin secretion in men. *Clin Endocrinol*. 1979;10:557–565.
45. Rasheed A, Tareen IA. Effects of heroin on thyroid function, cortisol and testosterone level in addicts. *Pol J Pharmacol*. 1995;47:441–444.
46. Allolio B, Deuss U, Kaulen D, et al. FK 33-824, a met-enkephalin analog, blocks corticotropin-releasing hormone-induced adrenocorticotropin secretion in normal subjects but not in patients with Cushing's disease. *J Clin Endocrinol Metab*. 1986;63:1427–1431.
47. Taylor T, Dluhy RG, Williams GH. Beta-endorphin suppresses adrenocorticotropin and cortisol levels in normal human subjects. *J Clin Endocrinol Metab*. 1983;57:592–596.
48. von Eckardstein A, Kliesch S, Nieschlag E, et al. Suppression of endogenous testosterone in young men increases serum levels of high density lipoprotein subclass lipoprotein A-I and lipoprotein(a). *J Clin Endocrinol Metab*. 1997;82: 3367–3372.
49. Anderson FH, Francis RM, Selby PL, et al. Sex hormones and osteoporosis in men. *Calcif Tissue Int*. 1998;62:185–188.
50. Ebeling PR. Osteoporosis in men. New insights into aetiology, pathogenesis, prevention and management. *Drugs Aging*. 1998;13:421–434.
51. Jackson JA, Riggs MW, Spiekerman AM. Testosterone deficiency as a risk factor for hip fractures in men: a case-control study. *Am J Med Sci*. 1992;304:4–8.
52. Mazer NA, Leiblum SR, Rosen RC. The brief index of sexual functioning for women (BISF-W): a new scoring algorithm and comparison of normative and surgically menopausal populations. *Menopause*. 2000;7:350–363.
53. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril*. 2002;77: 660–665.
54. Flor H, Turk DC, Schotz OB. Impact of chronic pain on the spouse: marital, emotional and physical consequences. *J Psychosom Res*. 1987;31:63–71.
55. Maruta T, Osborne D, Swanson DW, et al. Chronic pain patients, and spouses: marital and sexual adjustment. *Mayo Clin Proc*. 1981;56:307–310.
56. Monga TN, Tan G, Ostermann HJ, et al. Sexuality and sexual adjustment of patients with chronic pain. *Disabil Rehabil*. 1998;20:317–329.
57. Sjogren K, Fugl-Meyer AR. Chronic back pain and sexuality. *Int Rehabil Med*. 1981;3:19–25.
58. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2006;91:1995–2010.
59. Kim TW, Alford DP, Malabanan A, et al. Low bone density in patients receiving methadone maintenance treatment. *Drug Alcohol Depend*. 2006;85:258–262.
60. Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev*. 2004;3:CD004847.
61. Gooren LJ, Bunck MC. Androgen replacement therapy: present and future. *Drugs*. 2004;64:1861–1891.
62. Behre HM, Kliesch S, Leifke E, et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. *J Clin Endocrinol Metab*. 1997;82:2386–2390.
63. McClure RD, Oses R, Ernest ML. Hypogonadal impotence treated by transdermal testosterone. *Urology*. 1991;37:224–228.

