

Research Highlights

Highlights from the latest articles on the endocrinological effects of opioid therapy



Opioid therapy can have significant endocrinological effects

Evaluation of: Fraser LA, Morrison D, Morley-Forster P *et al.*: Oral opioids for chronic noncancer pain: higher prevalence of hypogonadism in men than in women. *Exp. Clin. Endocrinol. Diabetes* 117(1), 38–43 (2009).

Daniell HW: Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J. Pain* 9(1), 28–36 (2008).

Opioid medications have been a critical component of the medical armamentarium for the treatment of pain for millennia. As medical practitioners have developed a better understanding of chronic pain, the long-term use of opioid medications for chronic noncancer pain has grown rapidly [1], with courses of treatment initiated that can be expected to last for years [2]. Long-term opioid therapy for chronic pain has gained a reputation for safety and efficacy when used for appropriately selected patients [3]. Indeed, chapters on the use of opioids in recently published textbooks of pain management list constipation as the only common, persistent side effect of well-managed opioid therapy [4,5]. These and other reviews of the pharmacology of long-term opioid treatment often rely on studies of cancer patients who were started on chronic opioid therapy towards the ends of their lives [6].

Years of research and clinical observation have shown that opioids can have significant endocrinologic side effects. The negative effects of opioids on the endocrine system have been integrated into clinical medical practice for nearly a century. The long-standing principle of 'balanced anesthesia' in which the pituitary-mediated stress response to surgery is inhibited by

premedication with opioids depends on the rapid suppressive effect that opioid medications have upon pituitary function [7]. Likewise, a 40-year history of clinical use of opioid antagonists to induce the onset of puberty in hypogonadotrophic individuals has demonstrated that a surfeit of endogenous opioids, such as that encountered in patients with hyperprolactinemia [8] or massive obesity [9], can suppress the release of gonadotrophic hormones.

Pituitary suppression is commonly observed in people exposed to exogenous opioids in both medical and nonmedical settings. Studies of patients undergoing treatment of chronic pain with intrathecal morphine have shown high incidences of hypogonadism [10–12]. While the stress of chronic pain itself can cause gonadal dysfunction [13,14], a marked reduction in gonadal hormones has been specifically associated with the initiation of intrathecal morphine therapy [15]. A community-based study of men on opioid therapy demonstrated a high frequency of hypogonadotrophic hypogonadism [16]. Male cancer survivors who used opioids chronically have been found to have an increased incidence of symptomatic hypogonadotrophic hypogonadism compared with survivors who were not using opioids [17].

In the articles evaluated here, the authors examine the effects of opioids on gonadotrophic hormones.

Daniell, who was one of the first researchers to describe hypogonadism in men being treated for nonmalignant pain, examines the incidence of endocrinopathy in women on sustained-release opioids for nonmalignant pain. He found significant decreases in estradiol, testosterone and dehydroepiandrosterone (DHEA) in women being treated with sustained-action oral or transdermal opioids. The reductions

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of luteinizing hormone and follicle-stimulating hormone that he found indicate that these subjects had hypogonadotropic hypogonadism. In the study of 12 men and 14 women being treated with opioids for nonmalignant pain by Fraser *et al.*, indices of hypogonadism and evidence of osteoporosis was more prominent in men than in women.

Opioid therapy may be the most prominent cause of hypogonadism in non-geriatric men. It is also commonly seen in women on opioid therapy. Hypogonadism is not only a common side effect of opioid therapy, it can also be a serious one. Hypogonadism is a risk factor for clinically significant osteoporosis [18,19], and

may increase the risk of cardiovascular disease [20]. In addition to gonadotrophins, opioids have been shown to influence the release of other pituitary hormones, such as adrenocorticotropic hormone [21], growth hormone [22] and vasopressin [23,24]. Patients receiving opioid therapy should have routine screening for symptoms related to endocrine disorders, although these may be difficult to distinguish from symptoms that are commonly seen in patients with chronic pain [25]. Judicious replacement of testosterone in hypogonadotropic men can be safely carried out using published guidelines [26]. A recent review article details the various endocrine effects of opioids [27].

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Identity of the drug used in opioid therapy may determine extent of endocrinologic side effects

Evaluation of: Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmuller D: Plasma testosterone and sexual dysfunction in men receiving buprenorphine maintenance for opioid dependence. *J. Clin. Endo.* 90(1), 203–206 (2005).

Endogenous opioids appear to have a wide variety of physiologic functions. In the endocrine system, they act as short-range ‘second-messengers’ that give the secretory cells of the pituitary, which don’t have specific receptors for testosterone, estrogen or progesterone, information about serum levels of gonadal hormones. The growing awareness that opioid therapy can suppress gonadotrophic function raises the question of whether different opioid medications have similar suppressive effects. Studies of the long-term use of opioids among heroin users and subjects undergoing methadone maintenance therapy have documented significant endocrinologic side effects. Research involving opioid addicts carried out over 20 years ago associated long-term opioid use with persistent endocrine abnormalities such as hypogonadism [1–3]. Hypogonadism has been associated with both heroin use and with methadone maintenance therapy [4,5]. This appears to be a dose-related effect of the opioid itself [6], and

is rapidly reversed with discontinuation of the drug [7]. This study examined male opioid addicts who had been maintained on methadone or buprenorphine (a partial μ -opioid agonist) for at least 3 months. Patients treated with buprenorphine maintained normal levels of total and free testosterone throughout treatment, which were significantly higher than those of subjects maintained on methadone. The lack of gonadotrophin suppression by buprenorphine may be related to its properties as a κ -opioid antagonist. The increasing popularity of methadone in the long-term therapy of chronic pain may have to be weighed against its high incidence of endocrinologic side effects [8]. Information about the endocrinopathic effects of individual opioid medications will eventually need to be integrated into the guidelines on opioid therapy. Currently, clinical decisions regarding the use of opioids for chronic noncancer pain are being based on weak evidence. Research funding priorities must be set to address these critical clinical needs if the care of patients with chronic noncancer pain is to improve [9].

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