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The Effects of Opioids on the Endocrine System: An overview

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ABSTRACT

Background: Opioids commonly used for pain relief may lead to hypogonadism, which is characterised by suppression of production of the gonadotropin releasing hormone (GnRH) resulting in inadequate production of sex hormones.

Objective: To highlight the effects of opioids on the endocrine system and the development of hypogonadism.

Method: A narrative literature review of studies investigating hypogonadism in patients undertaking opioid therapy was carried out. MEDLINE, EMBASE and Cochrane Library were searched for relevant articles using a combination of both indexing and free text terms.

Results: The suppression of GnRH leading to a decrease in sex hormones has been described as the principal mechanism of opioid induced hypogonadism. However, there is no consensus on the threshold for the clinical diagnosis of hypogonadism.

Conclusion: Evidence indicates that chronic opioid use can lead to hypogonadism. Clinicians should be aware of symptomatology associated with hypogonadism and should regularly monitor patients with appropriate laboratory investigations.

INTRODUCTION

The hypothalamic-pituitary-gonadal (HPG) axis plays an important role in the development and regulation of the reproductive system. Gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus in a pulsatile fashion, which regulates the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. In males, LH regulates the number and function of Leydig cells in the testis and hence the production of testosterone, whereas FSH stimulates Sertoli cell division and spermatogenesis. In females, FSH stimulates the differentiation of granulosa cells in the ovaries and LH stimulates the production of androgens by the theca cells, and of oestradiol and progesterone by mature granulosa cells and corpus luteal cells. Testosterone in males and oestradiol in females have a negative feedback on the pituitary inhibiting gonadotropin secretion. Opioids and prolactin reduce the pulsatile activity of GnRH inhibiting LH and FSH secretion from the pituitary.[1]

Pharmacological analgesic opioids are derived from the medicinal poppy plant *Papaver Somniferum*. These analgesics have been used for centuries to relieve acute and chronic pain.[2] Common side-effects of these drugs include sedation, dizziness, constipation, urinary retention, itchiness, nausea and respiratory depression.[3,4] Hypogonadism is one of the least recognised and investigated side-effect of opioids.[5] Although patients are generally forthcoming in reporting health related complaints to physicians, some patients may associate symptoms of hypogonadism such as decreased libido, tiredness, loss of muscle mass and strength to the pain condition or may not feel comfortable discussing some of the symptoms with the treating physician, therefore making it difficult to identify hypogonadism without routine laboratory investigations.[6]

The aim of this review is to appraise the effects of opioids on the endocrine system and the potential link between opioids and hypogonadism.

METHODS

A review of studies examining hypogonadism in patients undertaking opioids was carried out. MEDLINE (Ovid), EMBASE (Ovid) and the Cochrane Library (Wiley) databases were searched for relevant articles published up to May 6th, 2016. A combination of both indexing and free text terms was used including opioids, hypogonadism, testosterone, endocrine, androgen, luteinising hormone and follicle stimulating hormone. Studies were selected for

inclusion if they investigated hypogonadism, low testosterone or low oestrogen in chronic pain patients undertaking opioid therapy. The search was restricted to articles published in English. A hand-search of reference lists of studies meeting the inclusion criteria was also performed.

DIAGNOSIS OF HYPOGONADISM

Male hypogonadism may result from either primary testicular failure (primary hypogonadism) or secondary testicular failure (secondary hypogonadism) due to hypothalamic or pituitary disease. Primary hypogonadism is characterised by low serum testosterone and high serum LH and FSH concentrations, whereas secondary hypogonadism is characterised by low serum testosterone and inappropriately low serum LH and FSH. In females, primary ovarian failure results in low oestrogen levels and elevated FSH, while in secondary hypogonadism, low oestrogen and FSH levels are observed.

EFFECTS OF OPIOIDS ON THE ENDOCRINE SYSTEM

Male hypogonadism following the use of opioids

Opioid-induced hypogonadism is characterised by low serum levels of testosterone, LH and FSH which is associated with decreased libido, impotence, reduced body hair, poor muscle strength and fatigue.[7-10] Several studies have indicated that opioids result in low levels of testosterone and hypogonadism in men regardless of the route of administration, i.e. whether oral, intrathecal or transdermal (Table 1).[11-15] It has also been reported that the use of intrathecal opioids in men causes suppression of both LH and FSH and consequently serum testosterone levels leading to hypogonadism.[16] Amongst the various opioids prescribed, studies have suggested that buprenorphine has one of the least inhibitory effects on sex hormones due to its nature as a partial ϒ agonist.[17,18]

It has been suggested that patients on long-term opioids are at an increased risk of developing hypogonadism compared to those treated with short term opioids.[18,19] These authors suggested that the suppressive effect by long acting opioids could be due to the sustained serum drug levels, whereas serum levels with the short acting opioids may vary throughout the day allowing intermittent GnRH and LH suppression.

Although low serum testosterone is the principle reason for opioid-induced hypogonadism, it is important to consider other factors which may affect testosterone levels.[11,20] For

example, it is well established that testosterone levels progressively decline with age and may be affected by smoking, lack of physical exercise and high BMI.[21-24]

Table 1: Studies investigating opioid induced hypogonadism in men

Study	Type of Study	Intervention	Participants	Results	Conclusion
Abs et al.[12]	Retrospective study	Intrathecal opioids	29 men	Decrease libido in 23 of 24 men was observed. Serum testosterone levels were below 9 nmol/L in 25 men of 29 men.	Majority of the 29 men in the study receiving Intrathecal opioids developed hypogonadotropic hypogonadism.
Aloisi et al.[13]	Cross sectional study	Intrathecal opioids	4 men short term and 6 men long term	Testosterone levels were observed to be low in day 7 and continued to decrease until day 23 in short term opioid treated men (morphine 0.5-1.2 mg/day). In long term opioid (0.5-2.5 mg/day), similar effect of reduced testosterone levels was observed (0.99 VS 2.47ng/ml).	The observations indicate that men on long term opioids have significantly reduced testosterone levels in comparison to men on short term Intrathecal opioids. The study suggests that the testosterone levels were observed to be in the range of those underlying hypogonadism.
Duarte et al.[16]	Cross sectional study	Intrathecal opioids	20 men	17 men had biochemical hypogonadism and 15 had free testosterone levels of <180 pmol/L and 2 with 180pmol/L and 250 pmol/L.	The observation suggests an association between intrathecal opioids and hypogonadism, with 85% of men developing biochemical hypogonadism.
Fraser et al.[15]	Cross sectional study	Oral opioids	12 men	75% of 12 men were identified to have a high prevalence of hypogonadism. 83% of men had total testosterone levels below the age specific range.	The study demonstrated that long term oral opioids for chronic pain had a high prevalence rate of hypogonadism in men.
Finch et al.[11]	Cross sectional study	Intrathecal opioids	20 men	Testosterone levels were found to be below the normal range of 10 to 35 nmol/L (4.9 ± 1.1 nmol/L) and was	Gonadotropin levels were observed to be low in male patients suggesting testosterone suppression in the

				significantly lower than the male control group (12.2 ± 1.6 nmol/L)	central inhibition of hypothalamic GnRH or FSH and LH. Men had clear evidence of low levels of serum testosterone.
Rubinstein et al.[18]	Retrospective cohort study	Short term and long term opioids	81 men	745 of men were found to be hypogonadal on long term opioids in comparison to 345 of men that were on short term opioids that were diagnosed as hypogonadal.	High prevalence of hypogonadism was observed in opioid users according to the duration of the use of opioids.

Female hypogonadism following the use of opioids

Several studies have shown that women may also be at risk of developing hypogonadism (Table 2).[12,15,25] Symptoms include amenorrhea, oligomenorrhea, failure to conceive and hot flushes.[15]

Fraser et al. showed that 21% of premenopausal women treated with opioids for longer than a year developed menstrual cycle abnormalities, such as oligomenorrhea and amenorrhea.[15] In a study of 32 women treated with intrathecal opioids, 22 women noted a decrease in libido and 7 developed irregular menstrual cycles.[12] In the same study, 18 postmenopausal women had significantly lower serum levels of LH and FSH than controls. It has also been reported that LH and FSH were 30% lower in premenopausal and 70% lower in postmenopausal women consuming sustained-action oral or transdermal opioids.[25]

Bawor et al. found no effect from opioids, including methadone, on testosterone levels in women.[20] However, Daniell et al. observed that testosterone and dehydroepiandrosterone sulfate (DHEA-S) levels are lower in opioid-consuming women compared to controls indicating impaired adrenal androgen production.[25]

Table 2: Studies investigating opioid induced hypogonadism in women

Study	Type of Study	Intervention	Participants	Results	Conclusion
Abs et al.[12]	Retrospective study	Intrathecal opioids	44 women	Decreased libido was present in 22 out of 32 women receiving opioids. All 18 postmenopausal females were observed to have decreased serum LH levels (P<0.001) and FSH levels (P=0.012).	All women in the opioid group developed hypogonadotropic hypogonadism with 15% developing central hypocorticism and 15% developing growth hormone deficiency.
Aloisi et al.[13]	Cross sectional study	Intrathecal opioids	16 women short term and 18 women long term	No significant changes were detected in testosterone levels in women on short term opioids (morphine 0.5-1.2 mg/day), although low levels were present on day 7, 14 and 23. Long term opioids (0.5-2.5 mg/day) did not show any difference and the results were comparable to control.	Observations in the study demonstrated that opioids did not have a significant effect on testosterone levels in women on short term or long term opioids.
Daniell[25]	Cross sectional study	Oral and Transdermal opioids	115 women	Testosterone, oestradiol and dehydroepiandrosterone sulphate were 48-57% lower in the opioid group in comparison to the control group (P< .01-.05). LH and FSH were 30% lower in premenopausal women and 70% lower in postmenopausal women. Oophorectomised women not consuming oestrogen, free testosterone levels were 39% lower in opioid consumers.	The observations suggest a decrease in adrenal androgen levels in most women consuming sustained action oral or transdermal opioids.
Fraser et al.[15]	Cross sectional study	Oral opioids	14 women	21% of 14 premenopausal women indicated hypogonadism with reported amenorrhea. Women that underwent hysterectomy had	Hypogonadism in women was based on self reporting of amenorrhoea. No major findings were present of chronic opioid effect on

				oestradiol levels of 349 pmol/L; therefore the prevalence of hypogonadism was 23%.	menstrual cycle in women.
Finch et al.[11]	Cross sectional study	Intrathecal opioids	29 women	Median oestradiol in premenopausal women were 125 pmol/l. FSH levels were 2U/L and LH levels 1U/L. Whilst postmenopausal women all had normal range of oestradiol. FSH ($p = 0.0037$) and LH ($p = 0.0024$) levels in women were significantly lower in the intrathecal opioid group in comparison to the control group.	Intrathecal opioids showed low levels of oestrogen in women in addition to low levels in pituitary gonadotropins suggesting the development of hypogonadism. This study demonstrated small doses of intrathecal opioids have a profound effect on hypothalamic pituitary gonadal axis.

CONSIDERATIONS

The diagnosis of hypogonadism

The most widely accepted parameter to establish the presence of hypogonadism in men is the measurement of serum total testosterone. The Endocrine Society defines hypogonadism as a failure of the testis to produce physiological levels of testosterone and suggests 10.4 nmol/L (300ng/dl) as the threshold to classify a patient as having a low total testosterone level.[26] However, the International Society of Andrology recommends 8.0 nmol/L (230ng/dl) as the threshold, whereas the American Association of Clinical Endocrinologists recommends 6.9 nmol/L (200ng/dl) as the threshold for diagnosing males with hypogonadism.[27] The lack of consensus on the recommended testosterone threshold for low testosterone brings into question when a patient should be considered for testosterone replacement therapy (TRT).

Although there are no generally accepted lower limits of normal levels, there is a general agreement that a total testosterone level above 12.0 nmol/L (350ng/dl) does not require substitution. There is also consensus that patients with serum total testosterone levels below 8.0nmol/L (230ng/dl) will usually benefit from testosterone replacement therapy.[21] If the serum total testosterone level is between 8.0 and 12.0nmol/L, repeating the measurement of

total testosterone with sex hormone-binding globulin (SHBG) to calculate free testosterone may be helpful.

The serum sample for total testosterone determination should be obtained between 0700 and 1100 h. Since there are known variations between assay methods, it is imperative that the practitioners use reliable laboratories and are acquainted with the reference ranges for testosterone for their specific laboratory. The measurement of free testosterone should be considered when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in obese men. There are no generally accepted lower limits of normal for free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 225 pmol/l (65 pg/ml) can provide supportive evidence for testosterone treatment. Measurements of serum LH will assist in differentiating between primary and secondary hypogonadism and serum prolactin is indicated when the serum testosterone is lower than 5.2 nmol/l (150 ng/dl) or when secondary hypogonadism is suspected.

Subsidiary diagnostic tools

Validated questionnaires have been developed to assess symptoms associated with androgen deficiency, such as Aging Male Survey (AMS) and Androgen Deficiency in the Ageing Male (ADAM).[28] The AMS evaluates the severity of symptoms over time but is also designed to measure changes in symptoms before and after TRT.[29] The ADAM tool is designed to detect men at risk for androgen deficiency but it does not provide information about the severity of symptoms.[30] Although sensitive, these questionnaires have been shown to have low specificity. Morley et al. compared the most commonly used questionnaires in148 men using bioavailable testosterone (BT) as the bio-chemical ‘‘gold standard’’ for the diagnosis of hypogonadism, and found the sensitivity to be 97% for the ADAM and 83% for the AMS.[29] Specificity was 30% for the ADAM and 39% for the AMS. Despite having low specificity, the AMS and other male hypogonadism questionnaires may be useful to assess the presence and severity of symptoms and for monitoring the clinical response to TRT.

Testosterone Replacement Therapy (TRT)

TRT should be considered in men with symptoms of hypogonadism and low serum testosterone with the aim of restoring normal testosterone levels. Studies have demonstrated that in addition to restoring the normal level of testosterone, TRT improves body

composition. Further benefits may include an increase in muscle mass as well as stabilisation of other endocrine functions.[31,32] In addition to physical and biomechanical benefits of TRT, a recent study reported a significant improvement in mood amongst opioid users after TRT.[33] Other long term and short term studies on hypogonadal men receiving TRT have also shown similar improvements in sexual function as well as improvements in symptoms of depression.[34,35]

Kaergaard et al. suggested that patients with low testosterone levels could score higher on pain scores.[36] English et al. also suggested that low dose transdermal testosterone therapy may provide some analgesic effects.[37] A study conducted on 16 men on testosterone patch therapy suffering from opioid induced androgen deficiency (OPIAD) showed a substantial improvement in sexual function and mood.[14] Although many studies have found benefits in the use of TRT in patients suffering from opioid induced hypogonadism, not all studies have demonstrated positive outcomes.

Huggins and Hodges identified a relationship between TRT and prostate cancer.[38] The authors reported that TRT was a contributing factor of the metastasis of prostate cancer to bone and that tumour growth rate was enhanced with the therapy. Several studies emerged shortly after which contradicted these findings. A systematic review by Shabsign et al. highlighted possible prostate cancer risk with TRT for hypogonadism.[39] In this systematic review, 11 placebo controlled and 29 non placebo controlled studies of men with no prostate cancer history and 4 studies of hypogonadal men with history of prostate cancer were included. The authors concluded that there was no evidence that testosterone replacement therapy increases the risk of prostate cancer in hypogonadal men.[39] In addition to this systematic review, a prospective study was conducted to evaluate the possible risk associated with sex hormones in serum and prostate cancer. This prospective study of 3886 men with prostate cancer and 6438 control subjects, examined the risk of prostate cancer based on serum concentration of sex hormones.[40] The findings of this study suggest that there was no association between serum concentration of sex hormones and the risk of prostate cancer. Although studies have concluded that there may be no risk of prostate cancer, we cannot neglect the fact that TRT may potentially cause adverse effects. Most common adverse effects appear to be acne and gynecomastia. However, recently developed testosterone therapy is alleged not to cause gynecomastia in patients.[41,42] Polycythaemia, an increase number of red blood cells, has also been linked with TRT.[43] It is thus recommended that

haematocrit and haemoglobin concentration should be closely monitored in patients receiving TRT.

DISCUSSION AND RECOMMENDATIONS

Several studies have indicated that opioids result in low levels of testosterone and male hypogonadism regardless of the route of administration, i.e. whether oral, intrathecal or transdermal. Women appear to be also at risk of developing hypogonadism with menstrual irregularities, reduced libido and hot flushes.

The main mechanism of opioid-induced hypogonadism appears to be suppression of GnRH resulting in low LH, FSH and sex hormones (secondary hypogonadism). In addition, there is evidence of impaired adrenal androgen production in women consuming opioids.[25]

Despite this strong evidence, hypogonadism seems to be under diagnosed in patients treated with opioids. This may be due to under-reporting of symptoms by patients and also the lack of awareness by clinicians that hypogonadism is relatively common in this group of patients. Clinical diagnosis in men is hampered by the lack of specificity of assessment tools and the lack of consensus on the threshold of serum testosterone to diagnose hypogonadism. In women, symptoms of hypogonadism may go unrecognised or may be attributed to other conditions, such as depression.

Untreated, low sex hormones can lead to osteopenia and osteoporosis in both men and women.[44,45] In men, the aim of treatment is to restore normal testosterone levels in order to improve quality of life, sense of well-being, sexual function, muscle strength and bone mineral density.

We recommend that the potential effect of opioids on sex hormones should be clearly explained to patients before commencing treatment and patients should be advised to report symptoms which may be related to hypogonadism. We recommend measuring serum testosterone routinely in men treated with opioids and, if low, this should be confirmed by repeat measurement together with serum LH and FSH. If low serum testosterone is confirmed, we recommend assessment of bone mineral density and consideration of TRT. In women taking opioids, we recommend the measurement of serum oestradiol, LH and FSH in premenopausal women who develop menstrual irregularities.

In conclusion, the use of opioids for the management of pain appears to be on the increase and the available evidence supports the notion that chronic opioid use can lead to hypogonadism. Clinicians should be aware of the symptoms and physical signs associated with hypogonadism. They should regularly monitor these patients with appropriate laboratory investigations and if hypogonadism is confirmed, hormone replacement therapy should be considered.

MAIN MESSAGE

- Long term opioid therapy may induce sexual dysfunction in men and women.
- There is no consensus on the threshold in sex hormones in the diagnosis of hypogonadism.
- Although subsidiary tools are valid in the diagnosis of low androgen levels, the precision and specificity are key issues in the use of these tools.
- Replenishing testosterone with testosterone replacement therapy has been shown to improve testosterone levels in patients; however monitoring is essential to avoid risks of developing other complications.

CURRENT RESEARCH QUESTIONS

- Are different approaches to monitoring or treating hypogonadism associated with improved clinical outcomes?
- Is there a dose-related association between opioid use and hypogonadism?
- What is the best management option for patients with opioid-induced hypogonadism without disregard for their pain relief?

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SELF ASSESSMENT QUESTIONS

1. One of the characteristics of hypogonadism is low levels of testosterone. (True)
2. Aging male survey is a valid questionnaire in measuring male androgen deficiency. (True)
3. Testosterone replacement therapy does not aid in replenishing testosterone levels in hypogonadism patients. (False)
4. Untreated low sex hormones can lead to osteopenia.(True)
5. Symptoms of hypogonadism include decreased libido, impotence and fatigue.(True)

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