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Title

Opioid-induced endocrinopathies

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Abstract

~~As the use of opioids is becoming a global epidemic and has led to a rise in expanding, so has the occurrence and recognition of their impact consequences on the endocrine system. Nonetheless, opioid-induced endocrinopathies still remain under-diagnosed, mainly due to symptom under-reporting by patients and lack of awareness in clinicians. Hypogonadism is the most well recognised consequence but ~~These include hypogonadism,~~ inhibitory effects on the hypothalamo-pituitary-adrenal axis and negative impact on bone health ~~also require attention.~~ Hyperprolactinaemia may ~~also~~ be detected, whereas, clinically relevant thyroid dysfunction has not been identified. ~~The~~ effects on other hormones have not been ~~as yet~~ clearly defined. ~~At present, consensus or evidence-based guidelines on how to diagnose and manage these endocrinopathies are lacking. A~~ Nonetheless, assessment of gonadal and adrenal function (particularly ~~if in the presence of~~ high index of clinical suspicion), ~~and, as well as~~ evaluation of bone health are advised in these patients. Discontinuation or reduction of ~~the~~ opioid dose and appropriate hormone replacement are management approaches for hypogonadism and hypoadrenalism. ~~Further research is needed to fully elucidate the impact of opioids at all levels of the endocrine system and the optimal management of their consequences.~~ Further research facilitating the development of evidence-based guidelines on the diagnosis and optimal management of opioid-induced endocrinopathies is eagerly awaited.~~

Introduction

Opioids are amongst the most powerful analgesics but they are highly addictive and can be easily abused due to their euphoric effects (Panel 1). Globally, their use has been increasing over the last two decades (Figure 1), with over-prescription of opioid pain relievers being one of the main contributors.¹ Furthermore, in USA, the inappropriate marketing of the sustained-release oxycodone preparation has resulted in abuse of this agent and is a further driving force of the opioid crisis.² The rise of opioid use and misuse has negative impact on public health, not only due to increased number of opioid-associated deaths (Panel 2) but also due to the association of long-acting opioids with elevated risk of all-cause mortality compared with other types of analgesics.³

The increased use of opioids has been associated with an expanding occurrence and recognition of their side effects. Although the significant actions of endogenous opioids on the neuroendocrine axes have been known for more than 40 years,^{4,5} endocrinopathies caused by their analogues still remain under-diagnosed in clinical practice, mainly because of symptom under-reporting by patients and lack of awareness in clinicians, leading to serious consequences.^{6,7} In addition, no consensus or clinical guidelines are available on how to diagnose and manage the opioid-induced endocrinopathies.

The aim of this review is to describe the effects of exogenous opioids on the endocrine system and their underlying mechanisms, to provide an algorithm for the diagnosis and management of opioid-induced endocrinopathies and to identify areas needing further research.

Hypothalamo-Pituitary-Gonadal Axis

Hypogonadism is a well-recognised side-effect of opioids on endocrine system. Opioids inhibit the pulsatile gonadotropin-releasing hormone secretion from the hypothalamus and subsequently the secretion of gonadotropins (mainly luteinising hormone and to a lesser extent follicle-stimulating hormone) from the pituitary and of sex steroids from the gonads.^{28,29} Direct negative action of opioids on testicular function has also been suggested.³⁰

The impact of long-term opioids on the hypothalamo-pituitary-gonadal (HPG) axis has been extensively studied (especially in males) and variable prevalence of hypogonadism has been reported, depending on type, dose, route and duration of administration of the opioid, as well as on the patient group assessed. A meta-analysis found significantly reduced testosterone levels in men on opioids compared to controls.³¹ This meta-analysis included a heterogeneous group of studies with opioids offered for different reasons, and no sub-analyses according to type, dose, route and duration of administration were performed.

The negative effects of opioids on HPG axis in heroin and methadone addicts, and in addicts on methadone maintenance treatment are known for more than 40 years.^{32,33} Prevalence of hypogonadism ranges between 50 and 85% in heroin and methadone addicts^{32,33} and is around 40% in those on methadone maintenance therapy^{34,35}. In opium addicts, testosterone and gonadotropin levels are lower than in controls,^{36,37} with one study reporting hypogonadism in 93% (26/28) of the males.³⁷

Long-term opioid use in patients with chronic non-cancer pain results in hypogonadism, regardless of administration route (oral, intraspinal or transdermal).³⁸ A systematic review evaluating the impact of opioids in men with chronic non-cancer pain found prevalence of hypogonadism between 19 and 86%, depending on the testosterone threshold defining hypogonadism, with the majority of studies reporting overall prevalence >50%.³⁹ Another

systematic review, including however only 165 cases, showed that 23 to 81% of women aged 18-55 years on oral or intrathecal opioids for chronic non-cancer pain had oligo/amenorrhoea.⁴⁰ Furthermore, a study from a large UK primary care database on women aged 18 to 55 years found that long-term opioids for chronic non-cancer pain was associated with higher risk of oligo/amenorrhoea [hazard ratio (HR) 1.13; 95% CI, 1.05-1.21) and of menopause (HR 1.16; 95% CI, 1.10-1.23) compared to short-term opioid use;⁴¹ no difference in risk of low libido or infertility was found. It should be noted that in chronic non-cancer patients, other factors may also contribute to the hypogonadism and need to be taken into account, including pain, comorbidities, concurrent medications and patients' age.

Positive association between opioid use and hypogonadism has also been reported in cancer patients^{42,43} but these results should be interpreted with caution as other factors [pain, chemotherapy, anorexia/cachexia, psychological stress (anxiety, depression)] influence HPG function.⁴⁴ Rajagopal *et al.* found hypogonadism in 90% (18/20) of male cancer survivors (disease-free >1 year) using opioids [morphine-equivalent daily dose (MEDD) \geq 200 mg] compared to 40% (8/20) of subjects in a matched control group.⁴⁵ Median testosterone was significantly lower and sexual dysfunction was worse in the opioid group. However, testosterone measurements were not performed on early morning samples potentially affecting the reliability of hypogonadism diagnosis.

The suppressive effect of opioids on the HPG axis begins as soon as they are administered^{46,47} and their cessation results in axis recovery.^{47,48} The severity of hypogonadism varies depending on dose, duration of action and type of opioid. An inverse association between opioid dose and gonadal dysfunction has been suggested⁴⁹ and is further supported by reports showing reversal of hypogonadism after reduction of opioid dose.³² Androgen deficiency is more likely with long-acting than short-acting opioids.⁵⁰ Furthermore, patients on fentanyl, methadone, and oxycodone have higher odds of androgen deficiency compared to those on hydrocodone.⁵¹ In addition,

buprenorphine and tapentadol, a μ -opioid receptor agonist and norepinephrine reuptake inhibitor used as analgesic, have been associated with milder or no suppressive effects on HPG axis.^{52,53}

Opioid-induced hypogonadism, apart from its well-known multi-system consequences (erectile dysfunction, impotence, decreased muscle mass in men, oligo/amenorrhoea in women, decreased libido, infertility, bone loss, depression in both sexes),^{54,55} may also contribute to poor control of pain and hyperalgesia³⁹.

Management options include discontinuation or reduction of the drug dose or, when this is not feasible, gonadal hormone replacement. The effects of hormone replacement therapy have not been as yet studied in women with opioid-induced hypogonadism and have been addressed only in a few studies in men. In an observational study, testosterone transdermal therapy for 24 weeks in 16 men (aged 34 - 55 years) with opioid-induced androgen deficiency and chronic non-malignant pain improved androgen deficiency symptoms, sexual function, mood, depression and hematocrit.⁵⁶ In the only randomised, double-blind, placebo-controlled trial available, treatment of 65 males (aged between 18 and 64 years) with opioid-induced androgen deficiency and chronic non-cancer pain with transdermal testosterone for 14 weeks resulted in greater improvements in pain sensitivity, sexual desire, body composition and some domains of quality of life compared to placebo;⁵⁷ no difference in the frequency of adverse effects between the two groups was found. Blick *et al.*, in a prospective study of 90 hypogonadal opioid male users, aged between 20 and 77 years and treated with testosterone gel for 12 months, demonstrated improvement in sexual function and mood.⁵⁸ Two smaller studies also reported amelioration in pain and improvement in mood and sexual function with no testosterone-related adverse effects.^{59,60} Most of studies, however, are of short duration and with small sample size not allowing the evaluation of the safety of long-term testosterone replacement in these patients. Interestingly, it has been proposed that clomiphene citrate may be beneficial in the setting of opioid-induced hypogonadism for males desiring preservation of fertility with simultaneous normalisation of testosterone levels.⁶¹

Data on the effects of opioids on fertility are very limited. Daniell reported cessation of menses soon after commencing sustained-action opioid treatment,⁶² and Rhodin *et al.* reported reduced fertility in women on opioids.⁶³ Adverse effects of opioids on semen quality have also been described.^{64,65}

In conclusion, opioid use has inhibitory effect on HPG axis, mainly at hypothalamic level.²⁸ Dose, type and duration of opioid may play a role on the severity of hypogonadism but further studies are needed to elucidate these. Hypogonadism is reversible after discontinuation or dose reduction of opioids. When these options are not feasible, hormonal replacement therapy should be considered aiming to avoid the long-term adverse sequelae of untreated hypogonadism.

Hypothalamo-pituitary-adrenal axis

Opioids exert negative effects on the hypothalamo-pituitary-adrenal (HPA) axis with all three main opioid receptors being implicated.⁵⁵ They mainly act at hypothalamic-pituitary level, where they inhibit corticotropin-releasing hormone (CRH) and antidiuretic hormone (ADH) secretion resulting in decreased adrenocorticotrophic hormone (ACTH) release.⁶⁶⁻⁶⁸ Direct effects on the adrenal function have also been suggested, as administration of naloxone in patients with hypothalamo-pituitary disconnection resulted to higher levels of cortisol (but not of ACTH) compared with saline infusion.⁶⁹ The inhibitory action is evident in both acute and chronic use. Single administration of morphine in normal subjects suppressed basal ACTH and cortisol levels, as well as their peak response to CRH,^{67,68} whilst buprenorphine, hydromorphone and remifentanyl administration attenuated cortisol response to psychosocial or surgical stress.⁷⁰⁻⁷²

Chronic use of various types or formulations of opioids has been associated with suppression of HPA axis in chronic pain patients. Two studies have assessed the prevalence of central hypoadrenalism [defined as stimulated cortisol levels on insulin tolerance test (ITT) <18 µg/dL] in patients with non-malignant pain on intrathecal opioids. Abs *et al.* found suboptimal cortisol response in 15% (9/61) of those on spinal morphine or hydromorphone [mean daily opioid dose

of 4.8 ± 3.2 mg (range, 0.6–15.0)],⁴⁶ and Valverde-Filho *et al.* reported suboptimal response to ITT in 33% (6/18) of those treated with intrathecal morphine (0.2-10 mg/day).⁷³ In the latter study, hypocortisolism was demonstrated in 50% (9/18) of patients on oral morphine (60-120 mg/day) who, however, had significantly greater cumulative and daily morphine dose compared to the intrathecal group.⁷³ In another series, 6% (3/48) of chronic pain patients on long-term oral and/or transdermal opioids (tramadol, oxycodone, morphine, fentanyl, buprenorphine, dihydrocodeine – median MEDD 68 mg) had blunted response to synthetic ACTH.⁷⁴ Focusing only on those on high-dose opioid analgesia (excluding tramadol and dihydrocodeine), suboptimal cortisol response to synthetic ACTH stimulation was found in 10% (3/33) of the cases; in the non-responders, MEDD was >100 mg.⁷⁴ A recent study assessed the effect of chronic oral and/or transdermal opioid analgesia [mean MEDD 74 mg (range 25–265 mg)] on HPA axis in non-cancer pain patients.⁷⁵ Hypoadrenalism was excluded if basal cortisol was ≥ 250 nmol/L; in those with basal levels <250 nmol/L dynamic testing with ACTH stimulation test (normal response defined as 60 min cortisol >500 nmol/L) and/or overnight metyrapone test were performed. Nine chronic opioid users (22.5%) failed one or both tests, with six of them failing the ACTH stimulation test (15%). Of note, patients with adrenal insufficiency were on significantly higher MEDD of 100 mg compared to 60 mg in the remaining subjects, with none of the latter having abnormal response on stimulation tests.⁷⁵ Finally, decreased levels of the adrenal androgen dehydroepiandrosterone sulfate have been found in patients with chronic non-malignant pain.^{73,75} Whilst these studies have demonstrated biochemical secondary adrenal insufficiency, there are also several case reports of patients on oral opioids (hydromorphone,⁷⁶ tramadol,⁷⁷ diamorphine,⁷⁸ loperamide⁷⁹) presenting with clinical manifestations resembling hypoadrenalism or with adrenal crisis during transdermal fentanyl⁸⁰ or intrathecal opioid administration;⁴⁶ in one case, adrenal insufficiency occurred after acute opioid therapy⁸¹. Discontinuation or dose reduction of these agents improved or restored HPA axis function.^{76,77,79,80}

Suppression of HPA axis has also been demonstrated in opioid drug-addicts on diamorphine maintenance treatment.⁸² In addition, impaired ACTH and cortisol circadian rhythm has been identified in heroin-addicts with reduced basal levels compared to healthy volunteers.⁸³ The clinical significance of these findings remains to be clarified.

Data on the effects of glucocorticoid replacement therapy in patients with opioid-induced hypoadrenalism are limited. Nenke *et al.*, in a placebo-controlled, double-blind, crossover study found that glucocorticoid replacement (hydrocortisone 10 mg/m²/day in three divided doses) in 17 chronic pain patients on long-term analgesia and with mild cortisol deficiency (defined as serum cortisol \leq 350 nmol/L measured 60 min after a cold pressor test) improved wellbeing and analgesic responses compared to controls.⁸⁴ It should be mentioned though that from the 10 patients who were also screened for adrenal insufficiency with an ACTH stimulation test, only one had suboptimal response (serum cortisol \leq 550 nmol/L). Whether the reported improvement in vitality and pain tolerance was due to treatment of the cortisol deficiency or due to the analgesic and anti-inflammatory effects of hydrocortisone remains uncertain. Gibb *et al.* described two patients with symptomatic improvement on hydrocortisone (10 mg am and 5 mg pm) after diagnosis of secondary adrenal insufficiency⁷⁴, whereas no patients with biochemical hypocortisolism were commenced on glucocorticoids in the Lamprecht *et al.*⁷⁵ study.

The necessity of glucocorticoid replacement needs to be reviewed after cessation or reduction of the opioid dose. The exact time interval of HPA axis recovery has not been established and testing includes measurement of morning blood cortisol off glucocorticoid treatment or dynamic assessment of the axis.

In summary, opioids exert inhibitory actions on the HPA axis after either single or chronic administration, which may be dose-related. The accurate prevalence of adrenal insufficiency has not been clearly defined. A prolonged or exaggerated stress response to chronic pain can also be a factor contributing to HPA axis dysfunction.⁸⁵ Although the clinical significance of hypoadrenalism in opioid users (especially in those with mild suboptimal response to dynamic

tests) has not been clarified, the published reports of patients on opioids developing adrenal crises or clinical manifestations resembling those of adrenal insufficiency which improved after glucocorticoid replacement, indicate that in a proportion of them, HPA axis suppression requires attention. Nonetheless, at present, there is uncertainty as to whether routine glucocorticoid replacement is truly indicated or it may cause adverse effects in the long-term.

Somatotroph axis

The effects of opioids on growth hormone (GH) axis are complex and their underlying mechanisms have not been fully elucidated. Data on pathways involved mainly originate from animal studies suggesting that opioid actions on GH synthesis and secretion are mediated through growth hormone-releasing hormone.⁸⁶

Acute administration of opioids in healthy humans has a dose-related stimulatory effect on GH production; intravenous administration of 15 mg morphine stimulated GH secretion, whilst smaller doses (5 and 10 mg) had no effect.⁸⁷⁻⁸⁹ Studies on the impact of chronic opioid administration have shown conflicting results. Serum insulin-like growth factor 1 (IGF-1) levels were significantly lower in humans on intrathecal opioids (morphine and hydromorphone) for non-malignant pain compared to controls, with 15% (9/62) of the cases demonstrating suboptimal response to ITT (peak GH values <3 µg/L) and 17% (12/72) having IGF-1 concentrations more than two standard deviations below the mean.⁴⁶ However, in another study with chronic pain patients on oral opioids, no abnormal IGF-1 levels or difference in the glucagon stimulated GH response were detected compared with a control group receiving non-opioid analgesia.⁹⁰ Abnormal GH response on ITT has also been described in heroin addicts and methadone patients.⁹¹

In summary, acute administration of opioids increases GH secretion, whereas the available data on the effects of chronic use are inconclusive.

Prolactin

Opioids can stimulate prolactin (PRL) secretion by affecting hypothalamic pathways; inhibition of the tuberoinfundibular dopaminergic system is the most probable mechanism but opioid-induced PRL secretion through serotonergic pathways has also been suggested.⁹²

Acute opioid administration enhances PRL secretion, an effect that can be prevented or attenuated by dopamine agonists.^{93,94} Increased PRL has been found in healthy humans after intravenous administration of morphine at different doses (0.08 mg/kg,⁹⁵ 0.1 mg/kg,⁹⁶ 5 mg,⁹⁷ 10 mg⁵) and in cancer patients after intraventricular or intravenous morphine use.^{98,99} Administration of DAMME (intravenous),⁵ buprenorphine (intravenous),¹⁰⁰ methadone (intramuscular),⁵ oxycodone (intramuscular),¹⁰¹ pentazocine (intravenous)⁵ and fentanyl (intravenous)¹⁰² in normal volunteers also increased PRL; this was dose-dependent with fentanyl and pentazocine.

The effect of chronic opioid use on PRL varies between studies. Increased levels have been found in about 40% of patients on chronic opioids for cancer⁴³ and non-cancer⁶³ pain. However, other studies in patients with non-cancer pain on oral or intrathecal opioids revealed similar PRL levels between opioid-treated patients and controls.^{46,73,90} Significant higher PRL values compared to controls, as well as cases of hyperprolactinaemia have been detected in heroin addicts¹⁰³ and in opium smokers.¹⁰⁴ Finally, variable PRL concentrations have been found in patients on methadone or buprenorphine maintenance treatment (reduced,¹⁰⁵ similar¹⁰⁶ or higher⁹⁴ compared to controls).

In conclusion, although acute opioid administration increases PRL, the effects of chronic opioid use are variable. Hyperprolactinaemia may be present and clinicians should be aware of its potential consequences. Nonetheless, other confounding factors, such as pain, malnutrition and stress, should be considered when interpreting PRL values.

Hypothalamo-Pituitary-Thyroid axis

Acute administration of various opioids (morphine,¹⁰⁷ methadone,⁵ buprenorphine,¹⁰⁷ DAMME⁵) increased serum thyroid-stimulating hormone (TSH) levels in normal subjects, whilst acute intravenous morphine infusion enhanced TSH response to thyrotropin-releasing hormone stimulation (TRH) in normal volunteers¹⁰⁸.

No difference in basal TSH and peripheral thyroid hormones levels has been demonstrated between chronic opioid users and controls. These findings have been verified in subjects on different opioid types (morphine,^{46,73} methadone,¹⁰⁹ diamorphine¹¹⁰), for various conditions (cancer and non-cancer pain, heroin addicts, addiction withdrawal) administered by different routes (intrathecal,^{46,73} oral⁷³). Notably, decreased TSH response to TRH stimulation in patients on chronic opioids compared to controls has been reported in some^{73,109,110} but not all^{46,111} studies. Opium smoking had been correlated with lower TSH levels in addicts compared to healthy subjects.¹¹² However, this was not confirmed in a recent study demonstrating normal thyroid function in both opium smokers and non-addict subjects.¹¹³

Overall, although acute opioid administration increases TSH secretion, there is accumulating evidence that chronic use is not associated with thyroid dysfunction, irrespective of dose and administration route.

Antidiuretic Hormone

The effects of opioids on ADH secretion in humans have not been elucidated. Thus, the results of studies assessing ADH release during different types of surgeries with anesthesia using various opioids regimes have been controversial. Their interpretation is further complicated by the presence of factors potentially influencing ADH secretion, such as pain, differences in the

patients' fluid status, peri-operative complications (haemorrhage, hypotension), co-administration of other agents, and other side effects of opioids.

More carefully designed studies in healthy volunteers, controlling for some of these confounding factors, have also provided inconsistent results. Acute intravenous administration of 1 mg DAMME (but not 0.5 mg) inhibited ADH release caused by osmotic stimulation (hypertonic saline infusion) compared to controls,^{114,115} whilst intramuscular administration of 0.5 mg DAMME reduced urinary ADH concentrations in healthy subjects compared to placebo.¹¹⁶ In addition, acute administration of asimadoline, a κ -opioid receptor agonist, at various doses (1, 5 and 10 mg) in normal subjects suppressed plasma ADH during 2.5% saline infusion in six out of eight patients receiving the highest dose (10 mg) compared to placebo.¹¹⁷ In contrast, a single intramuscular dose of spiradoline, another κ -opioid receptor agonist, had no effect on plasma ADH in healthy volunteers compared to placebo.¹¹⁸

On the other hand, other studies suggest that acute opioid administration increases ADH levels. Fentanyl intravenous infusion in healthy subjects increased plasma ADH in a dose-dependent manner,¹¹⁹ whilst intravenous administration of meptazinol (1.4 mg/kg) increased plasma ADH in three out of six normal subjects;¹²⁰ it should be noted, however, that these three individuals reported nausea after the opioid administration. Nausea and the potential opioid-induced hypotension may have contributed to the increase in ADH levels.

The only published study on the effects of diamorphine maintenance treatment on ADH in opiate-dependent patients is by Glahn *et al.* and showed reduced levels in patients compared to controls.⁶⁶

In summary, the impact of exogenous opioids on ADH in humans has not been clearly understood necessitating well-designed studies taking into account the impact of other factors influencing ADH secretion.

Oxytocin

In animal and *in vitro* studies opioids inhibit oxytocin secretion from the magnocellular neurons of the neurohypophysis (mainly through κ -receptors) and they also suppress the magnocellular cell activity in the supraoptic nucleus (through κ - and μ -receptors).¹²¹ However, data on the effects of exogenous opioids in humans are scarce mostly focusing in women during gestation or labour.

Intravenous morphine or intrathecal sufentanil in women at first stage of labour reduced plasma oxytocin levels,^{122,123} whilst intravenous morphine suppressed oxytocin response in breast-feeding women after delivery.¹²⁴ In contrast, intrathecal fentanyl and intravenous morphine did not alter plasma oxytocin compared to controls in women with late pregnancy but not in labour.^{125,126}

Overall, the limited data on opioids' effects on oxytocin in humans are of unknown clinical significance.

Bones

Exogenous opioids have negative effects on bone metabolism and result in low bone mineral density (BMD). Although the underlying mechanisms have not been completely characterised, opioids may reduce BMD indirectly, by causing hypogonadism, and directly, by affecting bone turnover.¹²⁷ Incubation of human osteoblast-like cells (MG-63), which express the three main opioid receptors (μ -, κ - and δ -), with morphine at high doses, led to reduced osteocalcin, an effect prevented by naloxone¹²⁸. No change in osteocalcin levels was observed, however, with a δ -receptor agonist. The opioid-induced inhibition of human osteoblast growth and the low serum osteocalcin levels in heroin addicts also support the negative impact of opioids on osteoblast activity.¹²⁹ Finally, opioid-mediated enhanced osteoclast activity has also been suggested. Balodimos *et al.* reported higher concentrations of beta C-terminal telopeptide (β -CTX) in male

heroin addicts (no details on their sex hormone status available) compared to healthy subjects,¹³⁰ whilst increased β -CTX was also found in men on opioid substitution treatment.¹³¹ However, in other studies with subjects on methadone maintenance therapy, β -CTX levels were not different compared to controls.¹³²

The negative impact of exogenous opioids on BMD has been shown in various groups of patients. In a study of men on intrathecal opioids for chronic non-malignant pain and hypogonadism, osteoporosis was observed in 21% (3/7) and osteopenia in 50% (7/14).¹³³ In another study, osteopenia was found in 50% (6/12) of men and 21% (3/14) of women on chronic oral opioids,¹³⁴ in this report, men had higher prevalence of hypogonadism and longer period of opioid use compared to women. Kinjo *et al.* described significantly reduced BMD in opioid users compared to non-users after adjustment for covariates affecting bone health [smoking, alcohol use, body mass index (BMI), exercise, vitamin D levels, total calcium intake, use of steroids, hormone-replacement therapy],¹³⁵ no data on sex hormones levels were provided. Furthermore, total hip and whole-body BMD tended to be lower in perimenopausal women with amenorrhoea exposed on opioids for chronic non-malignant pain than in the non-exposed ones after adjustment for confounding factors (age, time since menopause, BMI, calcium intake, vitamin D levels and intake, prior fracture, family history of fracture).¹³⁶

Low BMD has been described in addicts on opioid maintenance therapy. A recent study in men on different types of opioid substitution treatment (morphine, methadone and buprenorphine) revealed lower BMD in lumbar spine and hip compared to age- and BMI-matched controls,¹³¹ BMD did not differ according to opioid type. In this report, 29% (31/106) of men older than 40 years had osteoporosis and 48% (51/106) osteopenia, whilst in younger men, low bone mass was found in 66% (25/38).¹³¹ Of note, total and free testosterone levels were decreased in 50% and 62.5% of subjects, respectively. Grey *et al.* found decreased BMD throughout the skeleton in men on methadone maintenance therapy compared to controls but not in women;¹³² blood testosterone was lower in male patients than in controls and in 38% (8/21) of them it was below normal range.

In another study assessing BMD in the same group of patients, osteoporosis was shown in 61% (20/33) and 20% (12/59) of men and women, respectively, and osteopenia in 36% (12/33) and 54% (32/59), respectively;¹³⁷ methadone dose and duration of maintenance treatment were not associated with lower BMD and details on the sex hormone status of the subjects were not available. Milos *et al.* showed lower BMD in the total-hip in young females on methadone substitution compared to age- and BMI-matched controls but no difference at femoral neck and lumbar spine parameters;¹³⁸ the duration of heroin use and methadone intake was not associated with any BMD parameter. In this series, 82% (9/12) of subjects had amenorrhoea and 36% (4/11) were on oral contraceptive pill.

Finally, significant lower vertebral BMD compared with healthy age- and sex-matched controls has been found in male chronic heroin users;¹³⁹ this group also had lower testosterone compared to controls. Notably, the former heroin users had no difference in their BMD or testosterone levels compared to the control group. It should be pointed out that illicit drug users and patients on opioid substitution therapy may also have other factors contributing to low BMD, like smoking, increased alcohol intake, liver disease, low BMI or malnutrition and HIV infection.

Exogenous opioids use has also been associated with increased risk of fractures. A meta-analysis published in 2007 showed 38% ([relative risk (RR) 1.38; 95% CI, 1.15-1.66] increase in bone fracture risk in chronic opioid users,¹⁴⁰ whilst a more recent one (2015) identified significant, positive association between opioid consumption and overall fracture risk (RR 1.88; 95% CI, 1.51-2.34) but with substantial heterogeneity amongst the included studies.¹⁴¹ Focus on hip fractures revealed RR of 1.36 (95% CI, 1.11-1.67) and 2.00 (95% CI, 1.84-2.19) in each study, respectively.^{140,141} The positive correlation between opioid use and hip fracture risk was also confirmed in the meta-analysis by Ping *et al.* [RR of 1.54 (95 % CI, 1.34-1.77)]; however, the analysed studies were substantially heterogeneous.¹⁴² The opioid dose associated with increased fracture risk varies widely amongst studies.¹⁴³⁻¹⁴⁵

A further factor contributing to increased fracture risk is the high risk of falls due to opioid-induced central nervous system effects (sedation, dizziness). The fact that this risk has been found higher during the early stages of opioid use, before opioids' detrimental action on bones is established, has led to the suggestion that having a fall is the main etiology for the increased fractures.¹⁴³ This is further supported by a study showing that the risk of falls and subsequently of fractures in patients due to persistent musculoskeletal pain did not differ between opioid use and non-use groups.¹⁴⁶ Finally, limitations in mobility of patients with chronic pain can also be a contributing factor.

In summary, exogenous opioid use is associated with low BMD and increased fracture risk, mainly attributed to high risk of falls, to the negative effects of opioids on bone metabolism and to hypogonadism.

Monitoring, Diagnostic and Management Algorithm

Opioid-induced endocrinopathies remain underdiagnosed in clinical practice, mainly due to under-reporting of the symptoms by the patients and to lack of awareness in many clinicians. Healthcare professionals prescribing opioids should be familiar with these side effects and discuss them with the patients at the initiation and during maintenance of treatment; this discussion will also influence balanced decisions on the benefits and drawbacks of these medications, particularly if long-term use is considered. In addition, these patients should be appropriately monitored for opioid-induced endocrinopathies. Currently, evidence-based guidelines for monitoring, diagnosing and treating endocrine adverse effects in patients with chronic opioid use are not available and a proposed algorithm based on the published literature is shown in Figure 2.

Taking into account the high prevalence of hypogonadism with chronic opioid treatment, all relevant patients require assessment for symptoms/signs of sex steroid deficiency. In agreement with the recent Endocrine Society guidelines, screening should be avoided in patients on opioids for short-term.¹⁴⁷ On clinical suspicion of hypogonadism, hormonal investigations should be performed for confirmation of secondary hypogonadism (with other causes being excluded). Discontinuation or reduction of the opioid dose should be the first management step. Change to buprenorphine, an opioid with milder or no suppressive effect on the HPG axis, could also be another approach. If these are not feasible, gonadal hormone replacement therapy is advised aiming to avoid potential adverse sequelae of untreated hypogonadism.

With regards to hypoadrenalism, patients on opioids should be monitored for clinical manifestations of adrenal insufficiency and if there is high index of suspicion, measurement of morning blood cortisol levels is required, followed, if indicated, by dynamic assessment of the HPA axis. If hypoadrenalism is confirmed, treatment with glucocorticoids should be initiated. In such cases, cessation or reduction of the opioid dose needs to be considered and following this, reassessment of HPA axis for potential recovery should be performed.

Patients on chronic opioid use should be assessed for clinical features of hyperprolactinaemia and if this is confirmed, other confounding factors, like pain, malnutrition and stress need to be taken into account when interpreting the results. If other causes of hyperprolactinaemia have been excluded and high PRL is finally attributed to opioid use, management should be offered only in the presence of relevant clinical manifestations. As with the other endocrinopathies, discontinuation or reduction of the opioid dose are the first options.

Assessment of BMD is required in patients on chronic opioids, especially if hypogonadism or other risk factors for compromised BMD are present. Management includes opioid cessation and treatment of osteopenia/osteoporosis according to the current guidelines.

Long-term opioid use is not related with thyroid dysfunction and screening is not indicated.

Finally, data on the effects of chronic opioid use on GH, ADH and oxytocin are limited or inconsistent making provision of clinical recommendations not possible.

Outstanding Questions and Future Research

Despite the accumulating evidence on the effects of opioids on the endocrine system, there is still a plethora of areas requiring clarification posing difficulties in the development of safe and cost-effective guidelines.

Further studies are required to establish the true prevalence of hormonal abnormalities with different types, doses, routes and duration of use of opioids, the effects of partial agonists (like buprenorphine) and the clinical significance of the suppressive effects on the HPA axis. Well-designed prospective studies taking into account confounding factors (e.g. presence of other comorbidities, concomitant medications or pain) will clarify the long-term benefits and risks of hormonal replacement and its effects on other areas (including pain sensitivity, potential for reduction in required opioid dose, impact on recovery of patients on methadone for opioid use disorder). The effects of opioids on fertility deserve additional studies. Finally, further research is required to establish the impact of opioids in GH, ADH and oxytocin secretion and the underlying mechanisms of their negative action in bone metabolism and health.

Conclusions

Exogenous opioids have multiple effects on the endocrine system. Although hypogonadism is their most well-recognised side effect, their inhibitory effect on HPA axis and the negative impact on bone health should not be overlooked. Long-term opioid use does not seem to affect the thyroid function but can be responsible for hyperprolactinaemia, whilst the effects of opioids on GH, ADH and oxytocin secretion have not been as yet clarified. Further research is needed to

fully elucidate the impact of opioids at all levels of the endocrine system and the optimal management of their consequences.

Contributors

AF and SVU performed the literature search. AF, SVU and NK contributed to the interpretation of the literature. AF and NK wrote the manuscript with input from SVU. NK supervised the overall preparation of the review. All authors approved the final submitted version.

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Panel 1

Types, Pharmacology and Use of Opioids

Opium is obtained from the unripe seedpods of the opium poppy (*Papaver somniferum*), and its use was first reported around 4000 BC, when the opium poppy was cultivated in lower Mesopotamia by the Sumerians. The term “opiates” is used for the natural alkaloids of opium, like morphine, and the synthetic drugs derived from these, such as codeine and heroin, whilst

“opioids” refers to all chemicals binding to opioid receptors. Opioids can be classified in three categories: i) natural compounds (morphine, codeine, papaverine and thebaine), ii) semi-synthetic compounds [e.g. diamorphine (heroin), hydromorphone, hydrocodone, oxycodone, oxycodone, buprenorphine], and iii) fully synthetic compounds (fentanyl, pethidine, tramadol, alfentanil, methadone, remifentanyl).⁸ The endogenous opioid system constitutes a different category and consists of opioid peptides that derive from proteolytic cleavage of large protein precursors, including proopiomelanocortin, preproenkephalin and preprodynorphin, which are the precursors of β -endorphin, enkephalins and dynorphin, respectively.⁹

Opioids exert their actions by binding to opioid receptors (expressed in central and peripheral neurons and in neuroendocrine, immune and ectodermal cells) which belong to the class A gamma subgroup of seven transmembrane G protein-coupled receptors.¹⁰ Although many opioid receptor subtypes have been proposed, μ -, κ - and δ - are the main ones; nociceptin/orphanin opioid peptide (NOP) receptor is the most recently discovered member of the opioid receptor family.^{11,12} The actions of the most commonly used opioids on these receptors are shown in Table 1.

In clinical practice, opioids are primarily used as analgesic agents. Although μ -receptor is the main target for opioid analgesics, δ - and κ -receptors also regulate pain and analgesia;¹¹ the involvement of NOP receptor is under investigation.¹² Some types (codeine, morphine and methadone) are also used in chronic cough (especially in patients with lung cancer),¹³ whilst some μ -receptor agonists (loperamide, codeine) and mixed opioid receptor agonists/antagonists are used for diarrhoea-predominant irritable bowel syndrome.¹⁴ Morphine has been used for a long time to relieve pain, dyspnoea and anxiety in patients with acute myocardial infarction or pulmonary oedema but, nowadays, its use has been significantly decreased due to possible elevated morbidity and mortality risk in these patients.^{15,16} Finally, heroin is used as a recreational drug due to its euphoric effects.

Panel 2

Epidemiology of Regular Prescribed Opioid Use and Opioid Use Disorder

The use of opioids has significantly grown over the last 20 years. The overall national opioid prescribing rate in USA, the highest in the world, steadily increased since 2006, reaching its peak in 2012 (81.3 prescriptions per 100 persons), and then decreased to 66.5 prescriptions per 100 persons in 2016.¹⁷ This possibly reflects the change in the opioid prescribing practice amongst the healthcare providers, who became more cautious about the opioid-related risks of addiction and overdose for their patients. Increased prescribing of opioids has been also observed in the rest of the world. Between 2006 and 2016, the opioid prescribing rate in Australia increased by 33.5%, approaching the USA one, whilst the prescription rate of strong opioids rose by 25.3%.^{18,19} Finally, England, although still having the lowest prescribing rate compared with USA and Australia, demonstrated a doubling in the number of prescriptions during the same ten-year period, with the dispensed strong opioids showing increase by 135%.²⁰ Opioid prescription rates (per 100 persons) in USA, Australia and England between 2006 and 2016 are demonstrated in Figure 1a.

Opioid misuse has also been on the rise, as well as the number of patients with “opioid use disorder”. This term has been introduced by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders aiming to replace previous used terms of “opioid dependence and abuse”. It includes signs and symptoms associated with compulsive and prolonged self-administration of opioid substances for no legitimate medical purposes or, in cases of a medical condition requiring opioid treatment, with consumption of excessive doses than those actual needed.²¹ In 2016, 4.4% of USA population aged 12 or more reported opioid misuse in the previous year, with this being highest amongst young persons (aged 18-34); 0.8% of persons aged 12 and older reported opioid use disorder and 0.4% mentioned heroin use in the previous

year, respectively.¹⁷ In Australia, 3.6% of the population aged 14 or older misused pharmaceutical opioids during 2016, whilst the proportion of those used heroin in the previous 12 months has remained stable (0.2%) between 2001-2016.²² In England and Wales, the 2015/16 survey estimated that in the previous year, 7.5% of persons aged 16 to 59 had taken a prescription-only opioid painkiller not prescribed to them, while 0.1% of them reported heroin use.²³

The growing use of opioids has translated into an increased number of opioid-related deaths. In USA, the age-adjusted rate of drug overdose deaths attributed to opioids increased more than 4-times from 2000 to 2016.^{24,25} Between 2013 and 2016, and despite the reduction of opioid prescription rates, an increase of the opioid-related deaths was noticed which was primarily driven by deaths associated with synthetic opioids, especially the illicitly manufactured fentanyl, and to a lesser extent by deaths involving prescription opioids or heroin. However, it should be noted that heroin overdose death rates have more than tripled since 2010.^{24,25} In Australia, the age-adjusted rate of opioid overdose deaths has also increased by 214% from 2006 to 2016. During this interval, the age-adjusted rate of overdose deaths involving synthetic opioids, heroin and natural opioids demonstrated a 10-, 4- and 2-times increase, respectively.²⁶ Finally, in England and Wales there was a 64% increase in the number of deaths attributed to opioids during the same 10-year period. The higher increase of deaths was also due to synthetic opioids, followed by heroin or morphine and natural or other semi-synthetics opioids.²⁷ The age-adjusted opioid overdose death rates (per 100000 persons) in USA, Australia, England and Wales between 2000 and 2016 are demonstrated in Figure 1b.

Search strategy and selection criteria

With the help of a librarian, we performed a comprehensive literature search for articles published in MEDLINE, EMBASE, Cochrane Library and Web of Science up to June 14, 2019.

The following ~~We used the~~ search terms were used: "opioid", "opiate", "opioid agonist", "opiate agonist", "opium", "morphine", "heroin", "diamorphine", "dihydromorphine", "ethylmorphine", "azidomorphine", "normorphine", "hydromorphone", "oxymorphone", "pentamorphone", "morphinone", "codeine", "hydrocodone", "oxycodone", "methadone", "isomethadone", "tramadol", "desmetramadol", "fentanyl", "carfentanil", "buprenorphine" or "opiate", "alfentanil", "remifentanil", "pentazocine", "pethidine", "meperidine" - in combination with each of the terms "pituitary", "hypopituitarism", "androgen", "androgen deficiency", "hypogonadism", "gonadotropin", "testosterone", "oligomenorrhoea", "amenorrhoea", "sexual dysfunction", "fertility", "adrenal", "adrenal insufficiency", "hypoadrenalism", "adrenal crisis", "cortisol", "hypocortisolism", "hypocortisolaemia", "growth hormone", "insulin-like growth factor 1", "prolactin", "hyperprolactinaemia", "thyroid", "TSH", "hypothyroidism", "hyperthyroidism", "vasopressin", "antidiuretic hormone", "oxytocin", "bones", "osteopenia", "osteoporosis", "bone mineral density" and "fracture" ~~endocrine" or "endocrinopathy"~~. We gave priority for inclusion to relevant scientific literature published from 2013 onwards, although selected key older references are also cited. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than this Review has room for.

Legends for figures

Figure 1: (a) Opioid prescription rates (per 100 persons) in England, USA and Australia between 2006 and 2016.¹⁷⁻²⁰ (b) Age-adjusted opioid overdose death rates (per 100000 persons) in England/Wales, USA and Australia between 2000 and 2016²⁴⁻²⁷.

Figure 2: Proposed algorithm for the monitoring, diagnosis and management of endocrinopathies in patients on chronic opioid use.