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Opioids and Pituitary Function: Expert Opinion

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Abstract

Purpose: Opioids are highly addictive potent analgesics and anti-allodynics whose use has dramatically increased in recent decades. The precipitous rise in opioid dependency and opioid use disorder is an important public health challenge given the risks for severely adverse health outcomes. The long-term opioid impact on hypothalamic-pituitary axes is particularly underappreciated among both endocrinologists and primary care physicians. We review the effects of opioids on hypothalamic-pituitary-target gland function and their implications for clinical practice.

Methods: Experts in hypothalamic-pituitary disorders and opioid pharmacology reviewed recently published literature and considered strategies for diagnosing and managing these opioid-induced endocrine effects.

Results: Opioid suppression of hypothalamic-pituitary axes can lead to hypogonadotropic hypogonadism, central adrenal insufficiency, and hyperprolactinemia. These important clinical manifestations are often under-estimated, poorly evaluated, and typically either untreated or not optimally managed. Data on biochemical testing for diagnosis and on the effect of hormone replacement in these patients is limited and prospective randomized controlled studies for guiding clinical practice are lacking.

Conclusions: Patients should be informed about risks for hypogonadism, adrenal insufficiency, and hyperprolactinemia, and encouraged to report associated symptoms. Based on currently available evidence, we recommend clinical and biochemical evaluation for potential central adrenal insufficiency, central hypogonadism, and/or hyperprolactinemia in patients chronically treated with opioids as well as the use of current expert guidelines for the diagnosis and treatment of these conditions.

Introduction

Opium is a mixture of alkaloids extracted from *Papaver somniferum*, a species of poppy with analgesic and anti-allodynic actions; morphine, codeine, and thebaine alkaloids are present in the poppy latex. For many millennia, opium and its derivatives were widely used for medicinal and anesthetic effects [1]. In recent decades, opium has been chemically and physically manipulated to optimize therapeutic efficacy and improve practical routes of administration, and clinicians have been tasked with implementing strategies to minimize adverse effects and mitigate addiction risk.

After morphine was successfully extracted from opium, it was converted chemically to diacetylated morphine (heroin), while paramorphine (thebaine) was converted to oxycodone. In 1995 extended-release oxycodone and subsequently several additional opioids and formulations were developed, all in an attempt to improve on methods to modulate pain [2-4].

Opioids are generally classified into natural compounds, semi-synthetic compounds, and fully synthetic compounds [5]. These act as potent analgesics used by an estimated 5-8 million Americans in the management of chronic pain [6]. Acute use of opioids for 3-7 days is generally not associated with physical dependence, but longer use increases the risk [7].

The precipitous rise in opioid dependency and opioid use disorder in the general population characterizes the so-called opioid epidemic, an important public health problem given the high risks for deleterious health outcomes and excess mortality associated with chronic use, overuse, and abuse of these drugs [6,8,9]. Understandably, researchers have primarily focused on opioid-induced respiratory suppression, which directly increases morbidity and mortality [10-13]. Other key areas of study include opioid-induced euphoria associated with the mesolimbic dopaminergic centers of the brain, which strongly influence undesirable rewarding and addictive behavior. Side effects of opioids, including sedation, dizziness, nausea and vomiting, constipation, delayed gastric emptying, myoclonus, xerostomia, pruritus and muscle rigidity, are well described [6].

By contrast, long-term effects of opioids on the hypothalamic-pituitary axes are highly underappreciated [14]. In a recent survey, only 69% of endocrinologists and 24% of non-endocrinologists could identify opioid-induced endocrine effects, underscoring the importance of a critical review on this topic and the need for clinical management recommendations [15].

This review highlights key pharmacologic properties of opioids that lead to hypothalamic-pituitary effects, identifies different anatomic locations at which opioids elicit these actions, and recommends strategies for diagnosing

and managing these endocrine dysfunctions. Since, to date, no clear opioid effects on TSH and GH axes have been established, we focus on opioid effects on the gonadotrophic and corticotrophic axes, as well as on prolactin [8].

Pharmacology of opioids: effects on overall central nervous system activity and potency

Opioids are characterized by their activity and actions on opioid receptor types expressed throughout the central and peripheral nervous system, as well as other tissues. Of the four primary receptors, mu, delta, kappa, and opioid-receptor-like 1 (ORL1) (**Table 1)** most opioids induce analgesic effects through the mu receptor (MOR) [16,17].

MOR couples with G-proteins within plasma membranes and its activation induces a cascade of intracellular effects, leading to cellular hyperpolarization and inhibition of neuronal activity, all of which potentiate analgesic and anti-allodynic opioid effects [18,19]. The clinical activity of different opioids may vary not only due to their distinctive intracellular mechanisms, but also based on the specific tissues in which they bind to MORs. Thus, opioid binding to MORs in the spinal cord, limbic system, thalamus, midbrain, and afferent neurons, enables analgesic activity and pain attenuation [20,21]. By contrast, MORs activation in the medullary chemoreceptor trigger zone can be associated with nausea and vomiting, while activation within the ventral tegmental area and nigrostriatal cortex can be associated with euphoria and potential addiction. MOR activation within the pre-Bötzinger complex and parabrachial nucleus can lead to respiratory suppression, elevation of carbon dioxide levels, and attenuation of responses to carbon dioxide accumulation [21,20,22]. Most of these effects, as well as those on endocrine function described below, require opioid activity at MORs and the ability to penetrate the blood brain barrier (BBB) [23-26].

These characteristics play an important role in considering agonism, antagonism, and partial agonism of opioids, as well as their potency and binding affinity. A MOR full agonist leads to complete induction of the intended analgesic effects, as well as full induction of specific side effects. In contrast, a MOR partial agonist, leads to lesser induction of intended and unintended effects, and an antagonist that binds MORs without subsequent downstream activity or action and that can prevent the agonist from binding and inhibit its activity. Intrinsic activity determines agonist vs antagonist designation based largely on *in vitro* assessment of potency describing the amount of drug needed to activate the receptor, and potency in a clinical setting that describes efficacy and toxicity.

Binding and lipophilicity are also important properties that determine opioid potency and resultant clinical efficacy. Binding affinity describes the chemical attraction between the opioid and the MOR and is typically measured by the equilibrium inhibition constant which is reflected by K_i. The lower the K_i, the greater the binding affinity [27],

and the greater the number of MORs bound and activated, the greater the clinical response. However, binding affinity does not necessarily directly influence cellular intrinsic activity. The opioid buprenorphine, for example, is often characterized as a partial agonist at MORs due to its lower intrinsic activity [27,28] despite having one of the highest MORs binding affinities [29]. Analgesic actions of an opioid depends on its ability to penetrate the BBB, which, in turn, is dependent on the degree of lipophilicity [26]. The degree to which a substance is lipid soluble is described by the logarithm of the partition coefficient (log P), or the concentration ratio of the substance in a given electrical state in equilibrium between two immiscible solvents [24]. Thus, the greater the partition coefficient, the greater the ability to penetrate the CNS to induce analgesia and certain toxicities, [23,25,30]. As shown in **Table 2**, fentanyl, sufentanil, and buprenorphine are among the most lipophilic opioids and as such, are among the most potent.

In addition to binding affinity and lipophilicity, the volume of distribution can also affect equianalgesic dose between opioids and therefore influence opioid-induced effects on hypothalamic-pituitary function. In general, the risk of opioid side effects increases with higher doses. Morphine milligram equivalent (MME) doses of 50-90 mg/d are typically defined as high. However, as several patient-specific factors may influence opioid potency and toxicity, relative MME is used as a benchmark rather than an absolute cut-off [7,31].

Effect of opioids on the hypothalamus-pituitary-gonadal axis

Opioid use decreases release or disrupts pulsatile secretion of hypothalamic gonadotrophin releasing hormone (GnRH), reducing anterior pituitary secretion of luteinizing hormone (LH) and, to a lesser extent, follicle-stimulating hormone (FSH) and also supressing gonadal sex steroid production resulting in clinical hypogonadism [32,33]. Opioids also inhibit hypothalamic dopamine secretion leading to hyperprolactinemia, thereby contributing to the suppressive actions on the hypothalamus-pituitary-gonadal (HPG) axis [32]. Direct negative effects of opioids on testicular function and sperm quality have also been proposed [34-36].

Most studies of opioid-induced hypogonadism have been conducted in males. The reported frequency of this effect varies widely, from 19% to 86%, and this variation is largely explained by heterogeneity of studied patient groups and their ages; indications for opioid use; opioid type, dose, and route of administration; and diagnostic approach for confirmation of hypogonadism [32,37]. In a meta-analysis of 15 studies with a total of 3250 patients receiving chronic opioids (99.5% males), the weighted mean rate of hypogonadism based on a single morning or random testosterone measurement was 63% (95% CI: 55-70%) [8].

Hypogonadism has been described in 50-86% of men with heroin or methadone use disorder and in 40% of those on methadone maintenance therapy [14]. Although not systematically assessed, amenorrhea and galactorrhea have been reported in females with heroin use disorder [38]. Long-term use of oral, transdermal, and intrathecal opioids in patients with chronic non-cancer pain has been associated with hypogonadism in 19-86% of males (depending on the testosterone cut-off levels used) [37], whereas 23-81% of premenopausal women receiving oral or intrathecal opioids have reported oligo- or amenorrhea [39]. In these patients, effects of pain, other co-morbidities, and/or concurrent medications (e.g. glucocorticoids) on the HPG axis should be considered. The frequency of hypogonadism in patients receiving opioids for malignancy-related pain is difficult to estimate since, in addition to the previously mentioned factors, chemotherapy, anorexia/cachexia, and psychological stress may all suppress the HPG axis [14].

The inhibitory effects of these agents are acute [40], and the severity of hypogonadism depends on the dose and type of opioid [41,42]. Longer-acting opioids are associated with a higher potential for androgen deficiency compared with short-acting opioids, likely due to sustained inhibition of the HPG axis [42,43]. Transdermal fentanyl, oral methadone, and oral oxycodone have greater potential for androgen deficiency compared with hydrocodone, possibly because the latter, although derived from codeine and structurally similar to oxycodone, has a lower overall potency for MORs [44]. Buprenorphine influence on the HPG axis determined by its very high binding affinity toward MORs, as well as the fact that the opioid is lipophilic, and exhibits a long half-life, all of which result in high potency at the MOR. Counter-intuitively, buprenorphine , is in fact less frequently associated with hypogonadism or sexual dysfunction compared with other opioid agonists, such as methadone [45,46]. Thus, although only small amounts of buprenorphine are required to elicit an effect, the molecule is considered a partial agonist in terms of its clinical effects, with a lower intracellular response compared to traditional full MOR agonists [47]. Tapentadol, an analgesic centrally acting via both opioid and non-opioid mechanisms, has a lesser impact on testosterone compared to oxycodone/naloxone [48]. Hypogonadism reverses after dose reduction or withdrawal of the opioid [40,49], but the time course for this is not established.

Opioid-induced central (hypogonadotrophic) hypogonadism: clinical results

Hypogonadism in patients receiving opioids may remain undiagnosed, especially in males, due to under-reporting of relevant manifestations by patients and a lack of awareness of this effect by clinicians. However, given the potential adverse sequelae of untreated hypogonadism, timely recognition and management are of importance.

Reduced libido in both sexes, erectile dysfunction in males, and hot flushes and menstrual irregularities in females have been reported [8]; data on the impact of opioids on fertility are limited [50]. Negative effects on bone mineral density have been demonstrated, both due to hypogonadism and as a direct action of these agents on bone formation [32]. Hypogonadism may also be a contributing factor to poor pain control and hyperalgesia [37].

Studies assessing the administration of gonadal hormone replacement involve only male subjects and have provided some promising outcomes; nonetheless, methodological limitations have a potential impact on their quality of evidence. The effect of 24 weeks of testosterone patches was evaluated in an open-label pilot study of 23 males with androgen deficiency on oral sustained release oxycodone or oral methadone for pain [51]. After exclusion of 7 patients who discontinued treatment prior to completion of the trial, improvement in androgen deficiency symptoms, sexual function, mood, depression, and hematocrit was demonstrated. In a group of 9 males treated with epidural morphine for non-cancer chronic pain, testosterone gel administered for 12 months was associated with improvement in the sexual dimension of the Aging Males' Symptoms scale and in the mental index of the SF-36 [52]. In this study, no significant changes in the Profile of Mood State subscale scores or Centre for Epidemiological Studies Depression Scale ratings were identified [52]. In a randomized, double-blind, placebo-controlled parallel-group trial of 65 men with androgen deficiency treated with at least 20 mg/d of hydrocodone (or morphine equivalent dose of another opioid) for at least 4 weeks for chronic non-cancer pain, transdermal testosterone for 14 weeks led to a greater improvement in sexual desire, fat mass, as well as in pressure pain thresholds and mechanical hyperalgesia compared with placebo [53]. In a double-blind, placebo-controlled study, 41 men with non-malignant pain treated for at least 3 months with opioids (at an MME dose of at least 50 mg/d and with total testosterone <12 nmol/L (<346 ng/dL) were randomized to 24 weeks to receive intramuscular testosterone undecanoate or placebo injection given at baseline and at 6 and 18 weeks. Testosterone administration was associated with increased lean body mass and reduced total fat mass, although no change in pain perception was observed [54]. An observational cohort study of males receiving long-term opioids with testosterone <300 ng/dL (<10.4 nmol/L) compared 14,121 patients offered testosterone with 7151 untreated patients. After adjusting for covariates including sociodemographic, specific co-morbidities, and medications, all-cause mortality was lower in men who received testosterone during follow-up of up to 6 years [55]. This group also showed a lower incidence of major adverse cardiovascular events, femoral or hip fractures and anemia.

Recommendations for diagnosis and management

Patients treated with opioids should be informed about the possibility of hypogonadism and its clinical manifestations and be encouraged to report associated symptoms. For clinicians, a proposed pragmatic approach includes inquiring about symptoms of hypogonadism prior to opioid initiation and periodically thereafter. If the patient reports relevant symptoms, hormonal investigation should be undertaken. For men, this includes measuring serum testosterone (two morning samples taken before 10.00 am on different days), FSH, LH, and potentially sex hormone binding globulin (SHBG) if needed. However, the published evidence for an effect of different types of opioids on SHBG is not consistent [56-59]. We would not advise screening patients receiving short-term opioids (less than 3 months) because they would typically not be given testosterone replacement. In women with oligo/amenorrhea, measurement of serum estradiol, FSH, and LH is required [60]. If biochemical results suggest hypogonadotrophic hypogonadism, exclusion of other etiologies is required, including measurement of prolactin levels, considerations of potential effects of concomitant medications and co-morbidities, and evaluation for the presence of a pituitary adenoma [32].

If feasible, initial management includes withdrawal or reduction in the opioid dose. As we are unaware of compelling evidence for the frequency of assessing the recovery of the HPG axis after opioid discontinuation, we suggest monthly or bimonthly testing for several months. For patients requiring pain relief, consideration of other therapeutic options by pain management experts is advised. Switching to agents with a potentially lower risk for adverse effect on the HPG axis, such as buprenorphine, has also been suggested.

When these options are not feasible, gonadal hormone replacement should be considered. However, adequately powered and methodologically robust trials in males and females are required to elucidate short- and long-term impact of such treatments on hypogonadism in these patients, as well as impact on pain sensitivity and recovery of those offered methadone as maintenance therapy.

Effect of opioids on the hypothalamus-pituitary-adrenal axis

Opioid-induced secondary adrenal insufficiency is frequently unappreciated and not evaluated [15]. This is likely due to a lack of awareness regarding the effect of opioids on adrenocorticotropic hormone (ACTH) and cortisol, but may also result from overlapping symptomatology between opioid use and adrenal insufficiency, including fatigue, lack of appetite, nausea, vomiting, altered mood, hypotension, and impaired quality of life [61,62].

Opioids regulate the hypothalamus-pituitary-adrenal (HPA) axis via mu, delta, and kappa opioid receptors in the hypothalamus, pituitary, and adrenal glands (**Table 3**). They mainly act centrally to inhibit ACTH secretion,

although a direct effect on the adrenal glands has also been reported [63]. Indeed, ACTH was reduced after treatment with long-acting met-enkephalin analogue in patients with either adrenal insufficiency or Cushing's disease [64], while naltrexone stimulated cortisol and not ACTH in those with hypothalamic-pituitary disconnection [65]. Literature on the biochemical effect of opioids on ACTH and cortisol levels has been reviewed recently and is therefore only briefly discussed here [66,8,14]. This section focuses on clinical effects of opioids on HPA axis function and their management.

Administration of opiates or opioids was shown in a few small clinical trials and case reports to rapidly and dose-dependently inhibit HPA axis activity. Intravenous infusion of β-endorphin decreased plasma ACTH and cortisol in healthy volunteers, with full recovery occurring within 120 minutes from the end of infusion [67]. Morphine sulfate (10 mg) given orally 30 minutes prior to ovine corticotropin-releasing hormone (CRH) injection (1 μg/kg) blunted the ACTH response for up to 60 minutes and the cortisol response for up to 90 minutes, while vasopressin and catecholamine levels were unaltered [68]. Slow release morphine sulfate (30 mg given orally) attenuated the cortisol, ACTH, and β-endorphin response to human CRH, while naloxone (10 mg; but not 4 mg) augmented the response to human CRH [69]. Morphine sulfate (4 mg/kg but not 2 mg/kg) blocked the cortisol stress response during open-heart surgery but did not block cortisol responses to exogenous ACTH [70].

Chronic exposure to opioids also attenuates HPA axis activity. A meta-analysis of 5 studies including 205 subjects evaluated the effect of opioid treatment on HPA axis function using the insulin tolerance test (ITT; 2 studies), $ACTH_{1-24}$-stimulation test (1 study), or morning cortisol only (2 studies) [8]. Across these 5 studies, biochemical adrenal insufficiency was detected in a weighted mean of 15% (95% CI: 6-28%) of patients.

Alterations in ACTH and cortisol levels have been described in both cancer and non-cancer patients treated with morphine. Seventy-three subjects with non-malignant intractable pain receiving intrathecal morphine at a mean daily dose of 4.8 ± 3.2 mg (range, 0.6-15) for 26.6 ±16.3 months had decreased 24-hr urinary free cortisol (UFC) excretion compared to untreated controls, with 19% showing UFC <20 μg/d (550 nmol/d) despite similar baseline levels of morning plasma cortisol, ACTH, cortisol-binding globulin, dehydroepiandrosterone sulfate (DHEAS), plasma renin activity, and 24-hr urinary excretion of aldosterone. Peak serum cortisol levels during ITT were also lower in the opioid-treated group, with 15% showing subnormal peak cortisol [59]. In another study, among 48 patients with non-cancer chronic pain treated with morphine, 8% had baseline morning cortisol ≤3.6 μg/dL (100 nmol/L) and 3 patients showed stimulated cortisol <15.6 μg/dL (430 nmol/L) 30 minutes after $ACTH_{1-24}$ injection, suggesting a

diagnosis of adrenal insufficiency. All 3 were overweight females (body mass index [BMI] 32-38 kg/m^2) in their mid-30s treated with a long-term MME dose >100 mg/d [71]. In a separate case report, opioid treatment of a woman with chronic pain suppressed ACTH and cortisol when MME increased above 50 mg/d [72].

In a study of 40 patients with non-cancer pain treated with opioids for at least 6 months, 22.5% had adrenal insufficiency based on cortisol levels <18 µg/dL (497 nmol/L) measured 60 minutes after $ACTH_{1-24}$-stimulation testing or overnight metyrapone test (adrenal insufficiency was determined if 11-deoxycortisol ≥7 µg/dL and cortisol ≤7 µg/dL the morning after metyrapone ingestion) compared to none in the control group [73]. These 9 patients were receiving a higher mean MME of 100 mg/d versus 60 mg/d in the remaining subjects, and 4 of 5 patients with MME >200 mg/d had secondary adrenal insufficiency, but none were subsequently given glucocorticoid replacement. Among 25 age- and sex-matched controls, none failed $ACTH_{1-24}$-stimulation testing or metyrapone stimulation tests. Random morning cortisol and ACTH were similar between the groups, but opioid users showed significantly lower DHEAS levels and scored lower on GHQ-28 and SF-36 general quality-of-life and health status questionnaires, as well as on the Chalder Fatigue Score survey. Morning cortisol levels moderately correlated with the bodily pain domain on SF-36 but not with fatigue scores.

Interestingly, patients with heroin use disorder treated with buprenorphine 20.5 mg/d (range, 17.4-23.6) demonstrated attenuated ACTH response to metyrapone when compared to controls, in particular in those harboring the *OPRM1* A118G functional allele [74], which has been shown to reduce MOR expression and increase opioid tolerance and overdose vulnerability compared to 118AA homozygotes [75].

In summary, available results indicate that opioid use inhibits HPA axis activity, particularly when taken at higher doses, and that patients on chronic opioid treatment may develop hypocortisolism. Unfortunately, risk factors for opioid-induced adrenal insufficiency remain unclear due to the wide variation in study design, particularly inclusion and exclusion criteria, use of control group, opioid type, dose and duration of treatment, and indications for use. Measures and thresholds utilized to diagnose adrenal insufficiency also vary widely. Indeed, newer immunoassays and mass spectrometry indicate lower thresholds of peak $ACTH_{1-24}$-stimulation test -stimulated cortisol to exclude adrenal insufficiency [76]; thus, accounting for lower cortisol cut-offs, adrenal insufficiency does not appear to be common in opioid users [77]. Whether female gender, increased BMI, or the presence of *OPRM1* A118G allele increase the risk for adrenal insufficiency in opioid users remains to be determined.

Opioid-induced adrenal insufficiency: clinical trials

Opioid-induced symptoms may overlap with those of adrenal insufficiency, including fatigue, dizziness, nausea, vomiting, and low blood pressure, making a clinical diagnosis quite challenging. To our knowledge, studies have not focused on differentiating between symptoms derived from presumed adrenal insufficiency compared to those associated with chronic pain or opioid treatment itself. Furthermore, the optimal validation test and cortisol threshold for the diagnosis and therefore treatment of opioid-induced adrenal insufficiency have not been established. Although case reports describe glucocorticoid replacement in patients receiving chronic opioid treatment who developed adrenal insufficiency [59,71,78,79,49], only two studies specifically address outcomes after glucocorticoid replacement in subjects with opioid-induced adrenal insufficiency.

The first study used the cold pressor test (CPT) to stimulate the HPA axis via nociceptive pathways. However, this test is not validated for the diagnosis of adrenal insufficiency. The effect of hydrocortisone replacement (10 mg/m^2/d in 3 divided daily doses) for 28 days versus placebo was evaluated in 17 patients chronically treated with sustained-release opioid at a MME dose ≥ 20 mg/d for at least 4 weeks and who had plasma cortisol levels ≤12.7 µg/dL (350 nmol/L) [80]. Glucocorticoid replacement improved scores on the SF-36 bodily pain domain and vitality domain, while no improvement was noted when using the AddiQoL survey specific to symptoms associated with adrenal insufficiency. Scores on the Brief Pain Inventory-Short Form and Pain Severity Score surveys did not differ between glucocorticoid replacement and placebo arms, but improvement in general activity, mood, and work was observed on the Pain Interference Score. CPT pain response threshold improved with glucocorticoid replacement, as did CPT tolerance. Systolic, but not diastolic blood pressure, increased with glucocorticoid replacement compared with placebo [80].

In the second study, 40 patients with opioid-induced adrenal insufficiency were retrospectively evaluated after treatment with short- and long-acting opioid at a mean MME dose of 105 mg/d (range, 60-200) for a median duration of 60 months (range 3-360) [81]. Diagnosis of opioid-induced adrenal insufficiency was confirmed based on high levels of clinical suspicion, symptoms, and biochemical evaluation, and after exclusion of alternative causes of adrenal insufficiency. Symptoms suggestive of adrenal insufficiency were apparent for a median of 12 months (range 1-132) prior to diagnosis and included fatigue (72.5%), musculoskeletal pain (52.5%), weight loss (42.5%), headache (30%), and abdominal pain and nausea (20%). Other symptoms of adrenal insufficiency, including lightheadedness, vomiting, and diarrhea, were less frequent. No patients presented with an adrenal crisis, but one developed adrenal crisis after the diagnosis of opioid-induced adrenal insufficiency when she developed gastroenteritis and failed to take

adequate glucocorticoid replacement. At diagnosis, median morning cortisol concentration was 3 µg/dL (248 nmol/L) and median ACTH and DHEAS levels were at the lower end of the reference interval. Median peak cortisol during $ACTH_{1-24}$-stimulation test was <16 µg/dL (442 nmol/L), although 11 patients had a normal result. As the cortisol competitive binding immunoenzymatic assay used in this study was recently demonstrated to show lower cortisol values and therefore a lower cortisol threshold on $ACTH_{1-24}$-stimulation test of ~14-15 µg/dL (384-414 nmol/L) [76], some included patients may not have actually had adrenal insufficiency. Nevertheless, a substantial number of patients clearly showed improvements in most common symptoms of adrenal insufficiency following glucocorticoid replacement (95% treated with hydrocortisone; daily doses not reported). Fatigue improved in 48%, musculoskeletal pain in 38%, weight loss in 41%, headache in 17%, and abdominal pain and nausea in 25%. Importantly, 38% ultimately tapered and/or stopped opioid treatment, with HPA axis recovery in 70% of these subjects on biochemical follow-up [81].

These two studies, despite their limitations, suggest that glucocorticoid replacement may be beneficial for patients with opioid-induced adrenal insufficiency.

Recommendations for diagnosis and management

Patients on long term opioid treatment should be evaluated for symptoms and signs of adrenal insufficiency before and periodically after starting chronic opioid treatment. Patients suspected of developing adrenal insufficiency during opioid treatment should be evaluated by measuring morning cortisol and/or $ACTH_{1-24}$-stimulation test. Based on Endocrine Society guidelines for hypopituitarism, morning cortisol <3 µg/dL (83 nmol/L) is highly suggestive of adrenal insufficiency, while cortisol >15 µg/dL (415 nmol/L) is highly suggestive against the diagnosis [60]. More recent studies have suggested slightly different morning cortisol thresholds depending on the assay used. A study comparing morning cortisol to peak cortisol during ITT showed that morning cortisol values <4.6 µg/dL (126.4 nmol/L) supports a diagnosis of adrenal insufficiency while values >16.2 µg/dL (444.7 nmol/L) support adrenal sufficiency using the Roche Cobas cortisol immunoassay [82]. By contrast, another study comparing morning cortisol to cortisol levels at 30 minutes after $ACTH_{1-24}$- injection suggested that morning cortisol values <2.8 µg/dL (78 nmol/L) support the diagnosis of adrenal insufficiency, while values >10.4 µg/dL (282 nmol/L) support adrenal sufficiency using the Abbott Architect immunoassay [83]. However, none of these thresholds were calculated for patients receiving chronic opioid treatment. Therefore, until they are validated in this population, Endocrine Society

hypopituitarism guideline thresholds for morning cortisol should be employed for screening for opioid-induced adrenal insufficiency.

After excluding recent exogenous glucocorticoid use, opioid-treated patients with lower morning cortisol levels and symptoms and/or signs of adrenal insufficiency should be further evaluated with a morning plasma ACTH level and an $ACTH_{1-24}$-stimulation test. As $ACTH_{1-24}$-stimulation test cutoffs have not been systematically validated in patients treated chronically with opioids, we recommend that the criteria for serum cortisol thresholds after $ACTH_{1-24}$ stimulation should follow the established cutoffs of 14-15 µg/dL (386-413 nmol/L) with mass spectrometry and second-generation cortisol immunoassays at 30 minutes, and probably 18 µg/dL (500 nmol/L) at 60 minutes [84,76,85]. Importantly, it is not advisable to measure baseline cortisol or to perform $ACTH_{1-24}$-stimulation test shortly after acute opioid administration, such as in hospitalized patients, as suppression of the HPA axis may be reversible within hours and glucocorticoid treatment may not be required.

If a biochemical diagnosis of opioid-induced adrenal insufficiency in a patient with clinical symptoms suggestive of adrenal insufficiency has been established, hydrocortisone treatment should be started immediately. As for other types of adrenal insufficiency, treatment should be initiated at 15-20 mg per day, divided into 2-3 doses, with the highest dose taken in the morning. The dose can be determined by the clinical presentation and may be adjusted for body weight or body surface area [86]. Patient education regarding sick day rules, stress doses, and the need for an emergency kit should follow current guidelines [60].

Adrenal insufficiency symptoms and response to hydrocortisone treatment should be followed and re-evaluated periodically, particularly after discontinuation of opioid treatment. Treatment should be stopped after demonstrating HPA axis recovery. However, if no improvement is observed, clinical and biochemical re-evaluation of adrenal insufficiency by an endocrinologist should be performed to determine whether regular hydrocortisone treatment is required.

Effect of opioids on prolactin

Opioids can cause hyperprolactinemia in both males and females, likely by inhibiting the tuberoinfundibular dopaminergic system [87]. Acutely high prolactin levels induced by opioid administration can be reversed by dopamine agonists [88], while effects of chronic opioids on prolactin levels are variable. A recent meta-analysis of 7 studies comprising 354 patients [8] reported higher prolactin levels in four studies of patients using opioids [59,89-

91]; 43% of 14 patients treated with opioids for cancer-associated pain for at least one month with a MME dose ≥25 mg/d [91] developed hyperprolactinemia.

Recommendations for diagnosis and management

Given the risk for hyperprolactinemia in patients treated with opioids, clinicians should inquire about associated signs and symptoms, specifically hypogonadism and galactorrhea. The diagnosis of opioid-induced hyperprolactinemia should follow Endocrine Society recommendations for drug-induced hyperprolactinemia [92].

If possible, measurement of prolactin levels should be repeated after an adequate period of opioid withdrawal determined by the known duration of action to prove etiology of hyperprolactinemia [92]. If opioid discontinuation is not feasible, no other obvious cause of hyperprolactinemia is identified, and/or the onset of the hyperprolactinemia does not clearly coincide with opioid initiation, imaging should be performed to exclude a prolactinoma or other lesions compressing the pituitary stalk [92].

No treatment is necessary in patients with opioid-induced hyperprolactinemia if they are asymptomatic or if galactorrhea is mild and not bothersome. However, if symptoms are of concern, and if opioid discontinuation is not feasible, administration of a dopamine agonist or sex steroid replacement for hypogonadal symptoms can be considered [92].

Summary

Opioids potently affect pituitary hormone secretion, attenuating sex hormones and cortisol production and increasing prolactin levels. Long-term opioid use may result in adrenal insufficiency and hypogonadism in both males and females. These important clinical manifestations are often underestimated, poorly evaluated, and typically untreated. Information on the use of biochemical tests for diagnosis and on the effect of hormone replacement in these patients is limited and prospective randomized controlled studies are needed to guide clinical practice. Based on currently available evidence, we recommend clinical and biochemical evaluation to exclude central adrenal insufficiency, central hypogonadism, and/or hyperprolactinemia in patients chronically treated with opioids as well as the use of current expert guidelines for the diagnosis and treatment of these conditions.

Executive Summary Box

- Opioids suppress the HPG and HPA axes - this may lead to hypogonadotrophic hypogonadism and central adrenal insufficiency. Hypogonadism may also be caused by opioid-induced hyperprolactinemia. The presence of these disorders should be considered in patients receiving long-term opioid treatment.
- Patients with symptoms of hypogonadism, adrenal insufficiency, and/or hyperprolactinemia should be evaluated as per published expert guidelines, including measurement of serum sex steroids, prolactin, and morning cortisol levels and $ACTH_{1-24}$-stimulation as needed to confirm the diagnosis of adrenal insufficiency.
- Symptomatic patients with biochemical evidence for hypogonadism, adrenal insufficiency, and/or hyperprolactinemia should be treated according to published expert guidelines and by an endocrinologist together with an expert in pain management.

Compliance with Ethical Standards

Disclosure of Potential Conflicts of Interest: The interests listed below were not directly related to the work submitted for publication but are provided for completeness.

Mônica R. Gadelha: Speaker for Recordati Rare Diseases, Novartis, Ipsen and Crinetics; Principal Investigator - Clinical trials for Recordati Rare Diseases, Novartis and Crinetics;
Scientific advisory board for Novartis, Crinetics, Ipsen and Novo Nordisk.

Niki Karavitaki: Speaker for Pfizer, Ipsen, HRA Pharma, Recordati Rare Diseases, - Investigator for Pfizer, Ipsen, Shire – Scientific Advisory Board for Pfizer, Ipsen, Recordati Rare Diseases.

Jeffrey Fudin: Lecturer (non-speakers' bureau) for Abbott Laboratories; Speakers bureau, consulting, advisory boards for AcelRx Pharmaceuticals; Collaborative publications, consulting, advisory boards for BioDelivery Sciences International; Educational studio recording for Collegium Pharmaceutical; Consulting for Firstox Laboratories; Collaborative non-paid poster presentations for GlaxoSmithKline (GSK); Advisory Board for Hisamitsu America; Advisory Board for Hikma Pharmaceuticals; Collaborative non-paid publications for Scilex Pharmaceuticals; Speakers' bureau, consultant, advisory boards for Salix Pharmaceuticals; Lecture, non-speakers' bureau for Torrent Pharmaceuticals.

Jeffrey Bettinger: National Advisory Board: Hisamitsu America, Inc; Scientific Advisory Board: PainScript.

Hershel Raff: Consultant for Corcept Therapeutics; Consultant for Cerium Pharmaceuticals.

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Table 1: Opioid Receptor Types and Effects of Activation.

Opioid receptor	Intended effects when activated	Adverse effects when activated
Mu	• Analgesia • Anti-allodynia	• Respiratory depression • Euphoria/abuse liability • Reduced peristalsis and gastric secretions • Depression and anxiety • Nausea, vomiting • Tolerance/dependence
Delta	• Analgesia	• Respiratory depression • Reduced peristalsis and gastric secretions • Dependence • Rewarding
Kappa	• Analgesia • Anti-allodynia	• Reduced peristalsis and gastric secretions • Depression, anxiety, increased suicidal tendencies • Dysphoria • Immunosuppression
Opioid receptor like 1 (ORL1)	• Enhanced spinal analgesia • Anti-allodynia	• Reduction in opioid-rewarding effects • Reduction in potential for tolerance

Adapted from The Science of Opioids: Evaluating New Therapies to Optimize Opioid Stewardship (pharmacytimes.com) (https://AST.pharmacytimes.com/view/the-science-of-opioids-evaluating-new-therapies-to-optimize-opioid-stewardship)

Table 2: Properties of Commonly Used Opioid Agonists.

This table should not be used to convert one opioid to another for clinical use.

Opioid	Binding Affinity Toward MOR	Relative Lipophilicity[a]	MME Dose[b]	Approximate Equivalent Dose (mg)[c]
Sufentanil	+++++	+++++	---	0.02
Buprenorphine	+++++	+++++	1.8 (transdermal patch, μg/hr)	0.3
Hydromorphone	++++	++	4.0	1.5
Oxymorphone	++++	+	3.0	1.5
Levorphanol	++++	++++	11.0	2-3
Morphine	+++	+	1.0	10
Fentanyl	+++	+++++	2.4 (transdermal patch, μg/hr)	0.1
Oxycodone	++	+	1.5	4.5
Codeine	+	++	0.15	30-60

MME, morphine milligram equivalent; MOR, mu opioid receptor.
[a]Based on log P, which corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: Log P = Log (C_{oct}/C_{water}). [Values obtained from reference [93]]
[b] From the Centers for Disease Control and Prevention
https://cdc.gov/drugoverdose/training/dosing/accessible/index.html
Morphine Milligram Equivalent (MME) Calculators:
https://www.mdcalc.com/morphine-milligram-equivalents-mme-calculator
https://agencymeddirectors.wa.gov/Calculator/DoseCalculator
[c]Schumacher MA, Basbaum AI, Naidu RK. Opioid Agonists & Antagonists. In: Katzung BG, Vanderah TW. eds. *Basic & Clinical Pharmacology*, 15th ed. McGraw Hill; 2021.

Table 3: Normalized gene expression of opioid receptor subtypes in HPA axis

Opioid receptor subtype		Normalized expression		
Gene	Opioid receptor	Hypothalamus	Pituitary	Adrenal
OPRM1	mu	2.3	0.6	3.4
OPRK1	kappa	6.2	0.8	0.7
OPRD1	delta	1.3	0.5	2.4

From Human Protein Atlas (http://www.proteinatlas.org)