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Scientific Statement

Exogenous Opioids and the Human Endocrine System: An Endocrine Society Scientific Statement

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Abstract

The use and misuse of opioids are a growing global problem. Although the effects of these drugs on the human endocrine system have been studied for decades, attention on their related clinical consequences, particularly on the hypothalamic-pituitary system and bone health, has intensified over recent years. This Statement appraises research data related to the impact of opioids on the gonadal and adrenal function. Whereas hypogonadism is well recognized as a side effect of opioids, the significance of their inhibitory actions on the hypothalamic-pituitary-adrenal system and the occurrence of clinically relevant adrenal insufficiency is not fully elucidated. The often-inconsistent results of studies investigating how opioids affect the secretion of GH, prolactin, arginine vasopressin, and oxytocin are assessed. The accumulating evidence of opioid actions on bone metabolism and their negative sequelae on bone mineral density and risk of fracture are also reviewed. In each section, available data on diagnostic and management approaches for opioid endocrine sequelae are described. This Statement highlights a plethora of gaps in research associated with the effects and clinical consequences of opioids on the endocrine system. It is anticipated that addressing these gaps will improve the care of people using or misusing opioids worldwide. The Statement is not intended to serve as a guideline or dictate treatment decisions.

Key Words: opioids, opiates, hypothalamic-pituitary, hypopituitarism, hypogonadism, bones

Abbreviations: AVP, arginine vasopressin; BMD, bone mineral density; CNS, central nervous system; DHEAS, dehydroepiandrosterone; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; GHS-R1a, GH secretagogue receptor type 1a; ITT, insulin tolerance test; MME, morphine milligram equivalent; MMT, methadone maintenance therapy; MOR, mu-opioid receptor; OUD, opioid use disorder; PRL, prolactin; S-DDD, Defined Daily Dose for Statistical purposes.

Introduction

Opiates are a class of medicine derived from the opium poppy, a plant that has been used for several millennia as an analgesic by a vast number of segments of human race (1). The naturally occurring alkaloids of opium and the drugs synthesized from it are described as "opiates,"? whereas all natural or synthetic chemicals that bind to opioid receptors are included in the term "opioids."? Their first reported use was around 4000 BCE, when opium poppy (*Papaver somniferum)* was cultivated in Mesopotamia by the Sumerians, though since that time, many opioid products have been derived from opium poppy and synthetically created, with the majority produced to relieve various types of pain (1). Opioids may also be misused because of their euphoric effects. Increasing opioid use and shifts in the illicit drug supply toward high-potency synthetic opioids have resulted in a public health crisis with a dramatic increase in overdose mortality (2–6).

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This Scientific Statement focuses on the effects of exogenous opioids on the human endocrine system, on the evidence related to the clinical significance of these actions, and on the optimal diagnostic and management approach of opioid-induced endocrinopathies. The Statement specifically depicts the landscape of opioids in cancer and noncancer pain and of opioid use disorder (OUD) and presents data on the impact of these drugs on the hypothalamic-pituitary system and on bone health. It also identifies important gaps in our knowledge on this topic highlighting directions for future research.

Opioids in Cancer and Noncancer Pain and Opioid Use Disorder

Opioid Use for Analgesia

Prescription opioids are used to manage chronic or acute pain. However, the risks of prescription misuse, OUD, and overdose have been a growing concern globally (7).

United States opioid prescribing catapulted in the late 1990s and into the early 2000s (2, 8, 9). Corresponding with the significant climb in the annual number of overall opioid prescriptions was a similarly appearing upswing of opioid-related overdose deaths (8–10). Later, as opioid prescribing rates declined, there was a transition in use and death from nonmedical prescription opioid use to illicit opioids, which at first was heroin, and then, as fentanyl penetrated the drug supply, became nearly entirely supplanted by fentanyl-related analogs (3, 4, 10–14). Three distinct waves of opioid mortality have been described in the current overdose crisis; the first began with increased prescribing of opioid pain relievers (natural and semisynthetic opioids and methadone) in the 1990s, the second started in 2010 and was dominated by heroin, whereas the third started in 2013 and was driven predominantly by illicitly manufactured fentanyl and related analogs (15). In recent years, co-use of stimulants with opioids has risen, leading to what some experts are now calling the fourth, polysubstance wave of the overdose crisis (12, 16, 17).

Because of the rise in opioid-related overdose deaths and the widespread, and often unmonitored, prescribing of opioids, several guidelines and policies were developed to try to endorse monitoring strategies, optimize dosing procedures, enhance risk mitigation, and curb opioid prescribing in an attempt to decrease overdose death rates (18–25). Specifically, the Centers for Disease Control and Prevention published their opioid prescribing guidelines in 2016 (19), which was followed by dramatic changes in third-party payer, legislative, and health care system level policies, often limiting overall doses of opioids that could be used for chronic noncancer pain and emphasizing the need to utilize other modalities to treat pain (26).

According to the World Drug Report 2020, in 2018, the estimated number of people who had used opioids in the past year was 57.8 million (this figure includes those who had used opiates [30.4 million] as well as those who had misused pharmaceutical opioids) (27). Based on these data, the past-year prevalence of opioid use was 1.2% of the global population aged between 15 and 64 years; prevalence was higher than the global average in North America (3.6%), Australia and New Zealand (3.3%), Near and Middle East and South-West Asia (2.6%), and South Asia (2.0%) (27). It is of note that approximately 20% of the global population aged between 15 and 64 years lives in South Asia and more than one third of the number of opioid users around the world live in this subregion (27). A survey of the European Pain Federation showed that in most of the 25 European countries surveyed, opioid prescriptions increased from 2004 to 2016 with a different rate between the various countries (28). In 2022, the total number of dispensed opioid prescriptions in the United States was 131 778 501, with an opioid dispensing rate of 39.5 per 100 persons; in 2019, these figures were 153 626 197 and 46.8 per 100 persons, respectively (10). The International Narcotics Control Board Report 2022 revealed that the highest consumption of the main opioid analgesics (codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, ketobemidone, morphine, oxycodone, pethidine, tilidine, and trimeperidine) (expressed in S-DDD [Defined Daily Dose for Statistical purposes] per million inhabitants per day) is in developed countries in Europe and North America; for the year 2021, the regional averages were 17 035 S-DDD for North America, 8721 S-DDD for Western and Central Europe, and 7146 S-DDD for Oceania, placing North America as the region with the highest consumption of opioids for pain management in the world (29).

The United States and the world continue to grapple with maintaining the balance between dealing with the worst overdose crisis in the history of humankind and still considering that opioids may be necessary, and therapeutically appropriate, to treat different types of pain. One of the most important ways to help "walk the pain management line"? is to enhance one's understanding of opioid pharmacology and physiochemical characteristics, and how they relate to analgesic and potential adverse effects.

Opioid Use Disorder

OUD is defined as the compulsive use of opioids despite negative consequences and is diagnosed based on criteria using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). A person is diagnosed with OUD if they have experienced at least 2 of 11 symptoms in a 12-month period and the symptoms have led to clinically significant impairment or distress (30). OUD is classified as mild, moderate, or severe depending on the number of DSM-5 criteria met. OUD symptom checklists have been created to support providers in making a diagnosis (31). The 11 diagnostic criteria include evidence of tolerance; withdrawal; using more than intended; difficulty controlling opioid use; spending more time using, recovering from, or seeking opioids; craving or a strong psychological urge to use opioids; using in physically hazardous situations; using despite medical or psychiatric problems caused or exacerbated by opioid use; failing to meet role obligations because of opioid use; continuing to use opioids despite social problems caused by use; and giving up activities because of use (32). Tolerance and withdrawal alone in the context of taking prescribed opioids does not meet criteria for OUD.

In 2021, among individuals aged 12 years and older in the United States, 1.1 million used heroin in the past year, 8.7 million reported misusing prescription opioids, 26 000 reported newly using heroin for the first time in the past year, and 5.6 million people met criteria for OUD (33). Among people who reported misusing prescription opioids, 64% either used more of their own prescription or used opioid pain

relievers without a prescription for the purpose of relieving physical pain. However, 11% used them to feel good or get high and 7% to relax (33). Globally, in 2016 there were an estimated 26.8 million people alive with OUD (34). In 2017 alone, the estimated cost in the United States related to OUD and fatal opioid overdose was $1 trillion because of reduced quality of life and the value of life lost from fatal overdose (35).

Despite touchpoints with the health care system, most people with OUD do not receive treatment, and racial and ethnic disparities persist in treatment access (36–41). Racial and ethnic disparities are also widening in the overdose crisis, with the greatest rates of increase in opioid-related deaths between 2019 and 2020 in the United States seen among Black Americans and American Indian/Alaskan Native populations (absolute rate change of drug overdose deaths between 2019 and 2020: non-Hispanic Black persons 11.9, American Indian/Alaskan Native populations 10.2, White persons 5.5) (42). Social determinants of health exacerbate these racial and ethnic disparities, with greater racial and ethnic disparities in overdose seen in communities with the highest income inequality (42).

OUD is a treatable health condition for which effective treatments exist. Long-term medication treatment with methadone (a full opioid agonist) and buprenorphine (a partial opioid agonist) has been shown to improve remission rates, quality of life and overall health, and to decrease ongoing opioid use, overdose, and mortality (43, 44). In addition to methadone and buprenorphine, a third Food and Drug Administration-approved medication for OUD is extended-release naltrexone, an opioid antagonist, which is a second-line treatment option for the prevention of recurrence of opioid use among individuals who have completed opioid withdrawal management.

Pharmacology of Opioid Analgesics

Opioids primarily exert their physiologic and pharmacologic effects by modulating the endogenous opioid receptor system. This system consists of 4 major opioid receptors (G protein-coupled) including mu-opioid receptors (MORs), kappa-opioid receptors, delta-opioid receptors, and opioid-like receptor one (also known as nociceptin) (44–46). In addition to these main groups, there are several subtypes of each receptor, and the entire receptor system can be susceptible to pharmacogenomic abnormalities, all of which may impact an opioid's ability to modulate such receptors and can help explain individual and site variabilities regarding specific responses to opioids and their overall effects (44–46). Although all 4 receptor types play important roles from a physiologic perspective, most data (especially from an endocrine perspective) continue to revolve around opioids' impact on MORs and the response induced by them.

Most opioids used today act by fully agonizing MORs. All full opioid receptor agonists activate opioid receptors, thereby inducing a conformational change with the receptor and causing several intracellular events that inevitably lead to physiologic effect (47, 48). Other opioids are considered "partial agonists"? at MORs, including buprenorphine and butorphanol, whereby binding to MORs still activates those receptors, albeit to a lesser degree than full agonists (47, 48). The general "amount"? by which receptors are activated by an individual opioid (or any compound) is considered its intrinsic activity (or biological stimulus), and it is usually measured in in vitro studies (47, 48). It is important to note that these studies do not always completely correlate with efficacy/clinical response, which revolves around a particular endpoint (47, 48). Finally, there are opioids that antagonize MORs, such as naloxone, naltrexone, and methylnaltrexone, whereby binding to MORs simply blocks further activity and does not yield any conformational receptor change nor response (47, 48) (Table 1).

Opioid receptors are expressed throughout the body, including the central nervous system (CNS), peripheral nervous system, and enteric nervous system, among other sites. Opioid actions and clinical responses generally depend on where and which receptor the opioid is activating. Regarding pain pathways, opioid receptors are expressed throughout the descending pain pathways in the cortical and midbrain structures, periaqueductal gray area, limbic system, medulla locus coeruleus dorsal root ganglion, and throughout peripheral afferent neurons as well (45, 46, 53). Binding to MORs throughout those areas is what is primarily associated with pain attenuation and analgesia.

Aside from MORs' presence throughout various pain pathways, they are also present throughout other regions of the body, and their location may help explain specific opioid non-analgesic physiologic effects. Some of the most common opioid-related side effects include delayed gastric emptying, slowed gastrointestinal transit, and constipation, which are all caused by MOR activation throughout the gastrointestinal tract leading to reduction in intestinal secretions, greater fluid efflux from the gastric lumen, anal sphincter paralysis, and reduced peristalsis (45, 46). Opioids can also be associated with nausea and vomiting because of their activation of the medullary chemoreceptor trigger zone within the CNS (45, 46). Opioid activity throughout the ventral tegmental and nigrostriatal cortex, and corresponding communication with other sections of the CNS like the amygdala, are some of the mechanisms thought to allow for opioid-induced euphoria and may be involved in the development of addiction (45, 46, 54). Perhaps the most dangerous side effect of opioid use involves their activity within the pre-Bötzinger complex and parabrachial nucleus, as this is what is associated with suppression of respiratory function and attenuation of the central response to rising carbon dioxide levels, leading to potential cardiopulmonary collapse and death (45, 46, 54). Opioids can also have actions on the hypothalamic-pituitary system, which are one of its most underappreciated side effects and are covered in this Statement.

Distinguishing Between Opioids

There are several key differences between different opioid compounds that are important to recognize, especially as they relate to varying clinical effects and overall potencies. First, it is essential to understand that exogenous opioids are generally classified by how they are created, and then by their base chemical structure that helps determine almost everything about the drug itself. Natural opiates are considered alkaloids that are derived directly from the opium poppy itself and include morphine, codeine, and thebaine (1). Semisynthetic opioids are opioids that are synthesized directly from natural opiates, and include several common ones, such as hydrocodone, oxycodone, hydromorphone, buprenorphine, and heroin (diacetyl morphine), among others (1). Fully synthetic opioids are opioid compounds that are synthesized completely in the laboratory, such as methadone, fentanyl, tapentadol, and tramadol, among others (1). All these opioids can then be further categorized on

Table 1. Properties of commonly used opioid agonists

Opioid	Binding affinity toward MOR	Relative lipophilicity[a]	MME dose[b]	Approximate equivalent does (mg)[c]
Sufentanil	+++++	+++++	−−−	0.02
Buprenorphine	+++++	+++++	1.8 (transdermal patch, μg/h)	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/h)	0.1
Oxycodone	++	+	1.5	4.5
Codeine	+	++	0.15	30-60

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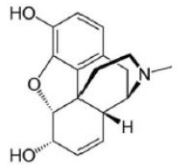
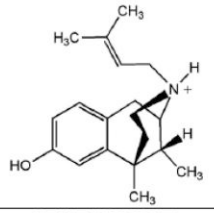
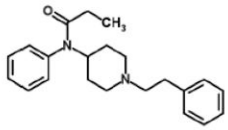
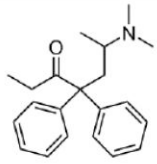
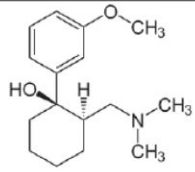
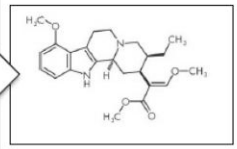
This table should not be used to convert one opioid to another for clinical use.
Abbreviations: MME, morphine milligram equivalent; MOR, mu opioid receptor.
[a]Based on log P, which corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: log P = log (Coct/Cwater). (Values obtained from reference (50)).
[b]From the Centers for Disease Control and Prevention https://cdc.gov/drugoverdose/training/dosing/accessible/index.html (51).
Morphine milligram equivalent (MME) calculators:
https://www.mdcalc.com/morphine-milligram-equivalents-mme-calculator
https://agencymeddirectors.wa.gov/Calculator/DoseCalculator
[c](52).

Table 2. Chemical classes of opioids

Chemical Classes of Opioids (Updated 11/1/2020)

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Pentazocine	Alfentanil Fentanyl Remifentanil Sufentanil Meperidine Diphenoxylate[a] Loperamide[a] **Fentalogues** **Illicit Fentanyl Analogues** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil Others[b]	Methadone Propoxyphene **Mitragynine (Kratom)**	Tapentadol Tramadol 
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK
*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group **6-position is substituted with a ketone group and tolerability is similar to hydroxylation				

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[a]Previously incorrectly listed as "Benzomorphans."?
[b](55).

the basis of their base chemical structures, of which there are 5 major groupings. These include the phenanthrenes, benzomorphans, phenylpiperidines, diphenylheptanes, and phenylpropyl amines (Table 2).

Although an in-depth comparison between each individual opioid is outside the scope of this Statement, it is important to review some of the most pertinent differences. Certainly, opioid pharmacokinetic and pharmacodynamic variability is

mainly driven by differences in their physiochemical characteristics. Considering most of the opioid-induced analgesia occurs because of opioid actions throughout the CNS and peripheral nervous system, thus requiring transport through the blood-brain barrier, opioids with more lipophilic chemical structures more easily transport through the blood-brain barrier to their sites of action (56–58). This is why lipophilicity is one of the most critical characteristics when assessing measures of potential potency around clinical endpoints. Such opioids with greater degrees of lipophilicity include fentanyl, sufentanil, buprenorphine, and hydromorphone (56–58) (see Table 1 physiochemical properties). In addition to lipophilicity, another important physiochemical characteristic is an opioid's binding affinity, which is defined as the thermodynamically driven chemical attraction between a substance and a receptor, and usually represented by its Ki value (59). Opioids with lower Ki values have greater degrees of binding affinity toward opioid receptors. Once again, buprenorphine, sufentanil, hydromorphone, and oxymorphone have some of the greatest binding affinities toward MORs (59). Not only can these characteristics help define doses used for different opioids from an analgesic perspective (as well as formulations required), but they can help delineate between analgesic efficacy and toxicity risk, including from an endocrine perspective. Buprenorphine, for example, is a lipophilic opioid with significant binding affinity toward MORs and is considered to be highly potent, as low doses (usually in micrograms) are required to produce cellular responses (48, 57, 60). However, because it is a partial agonist (has lower intrinsic activity at MORs), it does not produce as much of a clinical response as full MOR agonists, particularly from a toxicity perspective (48, 57, 60). Thus, comparatively, buprenorphine is associated with plateaued respiratory depressive effects and results in less gonadal axis suppression. Finally, half-life is another key differentiator when it comes to opioid-induced endocrine effects.

Hypothalamic-Pituitary-Gonadal Axis

Effects of Opioids

The inhibitory actions of opioids on the hypothalamic-pituitary-gonadal axis and the subsequent resulting hypogonadism are well recognized. Opioids inhibit pulsatile GnRH secretion from the hypothalamus and the secretion of gonadotropins (mainly LH and to a lesser extent FSH) from the pituitary gland and of sex steroids from the gonads (61–64). They also can inhibit the secretion of dopamine from the hypothalamus leading to hyperprolactinemia, which further contributes to the suppressive action on the hypothalamic-pituitary-gonadal axis (65). Direct negative effects of opioids on testicular function and sperm quality have also been proposed (66–68).

Prevalence of hypogonadism in males on opioids has been reported within variable rates, depending on type, dose, route, and duration of administration of the opioid, diagnostic approach for the confirmation of hypogonadism, as well as on the patient group assessed (65, 69). The first studies on the negative effects of opioids on the hypothalamic-pituitary-gonadal axis involved mainly people addicted to heroin and patients on methadone maintenance treatment, with hypogonadism reported in 40% to 85% of males (70). In female heroin addicts, amenorrhea and galactorrhea have also been described, although this effect has not been systematically looked at in this group (71). In a meta-analysis of 15 studies with a total of 3250 patients (99.5% males) receiving chronic various opioids, the weighted mean rate of hypogonadism (based on a single morning or random testosterone measurement) was 63% (95% CI, 55-70) (72). In another systematic review including 165 women aged 18 to 55 years on oral or intrathecal opioids for chronic noncancer pain, 23% to 81% of them had oligo/amenorrhea (69). In a case control study of 21 women on sustained action oral or transdermal opioids for nonmalignant pain and 16 women not on opioids (but not matched for confounding factors) aged between 30 and 50 years, the levels of estradiol, testosterone, and dehydroepiandrosterone (DHEAS) were significantly lower in opioid users (73). Furthermore, reduced levels of gonadotropins have been found in postmenopausal women on intrathecal opioids for nonmalignant pain (74). It should be noted that when interpreting data on the prevalence of opioid-induced hypogonadism in patients with chronic nonmalignant pain, other confounding factors, like effects of pain, other comorbidities (eg, obesity), and/or concurrent medications need to be taken into account. Hypogonadism has also been reported in patients receiving opioids for cancer-related pain (75, 76) but in this group, in addition to the previously mentioned factors, the underlying malignant disease, chemotherapy, anorexia/cachexia, and psychological stress may have a further negative impact on the axis (77). In a study of male cancer survivors (disease-free for more than 1 year) using opioids (morphine milligram equivalent [MME] daily dose ≥200 mg), hypogonadism was found in 90% of them (18/20), compared to 40% (8/20) of subjects in a matched control group. Median testosterone was significantly lower in the opioid group, although testosterone measurements were not performed on early morning samples, potentially affecting the reliability of the hypogonadism diagnosis (78).

The inhibitory actions of opioids on the hypothalamic-pituitary-gonadal axis occur as soon as they are administered (74, 79, 80) and cessation or reduction in their dose leads to recovery of the axis (79–82), the time course of which is variable (80, 83–85). The severity of hypogonadism depends on the dose and type of opioid (86–88). Long-acting opioids are more likely to cause androgen deficiency than the short-acting ones (89), and transdermal fentanyl, oral methadone, and oral oxycodone have been reported to have higher odds of androgen deficiency compared to hydrocodone (90). Buprenorphine, a partial opioid receptor agonist, is associated with milder effects on the hypothalamic-pituitary-gonadal system (91, 92).

Clinical Significance

Typical clinical manifestations of gonadal hormone deficiency have been described in patients with opioid-induced hypogonadism (erectile dysfunction, decreased muscle mass in men, oligo/amenorrhea in women, decreased libido, infertility, bone loss, depression in both sexes) (65, 69, 72). Data on the impact on fertility are limited (93), and adverse effects of these drugs on semen quality have been suggested (68). Hypogonadism may remain undiagnosed, particularly in men, possibly because of a lack of reporting of the relevant symptoms by the patients and the underappreciation of this side effect by the health care professionals.

Interestingly, it has been proposed that opioid-induced androgen deficiency might impair pain control and lead to hyperalgesia (94).

Diagnostic approach

Timely diagnosis of hypogonadism is of major importance. In accord with the Endocrine Society guidelines, screening should be avoided in patients on short-term opioid regimens (95). In contrast, patients on long-term opioid treatment (suggested interval, longer than 3 months) need to be informed about the risk of hypogonadism and encouraged to report relevant symptoms. Also, manifestations of hypogonadism need to be enquired by clinicians and if there is a high index of suspicion, diagnostic investigations should be performed per current guidelines (96).

Management

Given that discontinuation or reduction of the opioid dose reverses their inhibitory effects on the hypothalamic-pituitary-gonadal axis (79–82), this approach is considered to be the first management step, when possible (in parallel, further management options for the pain should be discussed and provided by the relevant experts). The time course of the recovery has not been clearly established and the impact of opioid tapering on hypogonadism has not been explored. Change to buprenorphine, an opioid with milder or no suppressive effect on the axis, could also be another approach. If these are not feasible, gonadal hormone replacement therapy needs to be considered aiming to avoid the negative sequelae of untreated hypogonadism (70, 96).

The effects of gonadal hormone replacement in patients with opioid-induced hypogonadism have been investigated in a small number of studies involving only males and have provided some promising outcomes. Nonetheless, most are of rather short duration posing challenges in the assessment of the safety of this treatment. An open-label pilot study of 23 men on oral sustained-release oxycodone or oral methadone or transdermal fentanyl or oral sustained-release morphine sulfate for pain and with morning free testosterone <50 pg/mL (normal range, 52-280 pg/mL) examined the effects of testosterone patches administered for 24 weeks (5 mg daily for the first 12 weeks and 7.5 mg daily for the second 12 weeks); in the 16 patients who completed the trial, improvement in their androgen deficiency symptoms, sexual function, mood, depression, and hematocrit was demonstrated (97). In a study of 9 males on epidural morphine for noncancer chronic pain and an 8 to 9 AM testosterone level less than 2 to 3 ng/mL (in at least 2 determinations in the previous 3-4 months; normal range, 3.5-8.5 ng/mL), a sachet of testosterone gel (containing 50 mg of testosterone in 5-g gel) was administered daily for 12 months; this treatment was associated with improvement in the sexual dimension of the Aging Males' Symptoms scale and in the mental index of the Short-Form 36 Health Survey, but not in the Profile of Mood State subscale scores or Centre for Epidemiological Studies Depression Scale ratings (98).

In a randomized, double-blind, placebo-controlled parallel-group trial, 65 men on at least 20 mg daily of hydrocodone (or MME dose of other opioid) during a minimum of 4 weeks for chronic noncancer pain and with morning serum total testosterone below 350 ng/dL (measured by liquid chromatography-tandem mass spectrometry) were randomly assigned to receive either 5 g of a transdermal testosterone gel or placebo gel, applied once daily for 3 months. Two weeks after randomization, if total testosterone was below 500 ng/dL, the dose of the testosterone gel was increased to 7.5 g daily. Those on transdermal testosterone showed greater improvement in sexual desire, fat mass, as well as in pressure pain threshold at the thumb and mechanical hyperalgesia compared with the patients on placebo (99). In a double-blind, placebo-controlled study, 41 men with nonmalignant pain on opioids for at least 3 months at a minimum MME dose of 50 mg daily and with an 8 to 10 AM total testosterone level below 12 nmol/L (346 ng/dL) were randomized to have intramuscular testosterone undecanoate 1000 mg or placebo injection at baseline and at 6 and at 18 weeks; at 6 months, in those treated with testosterone, increased lean body mass, and reduced total fat mass, but no change in pain perception were observed (100). In a study of 27 males on opioids for chronic noncancer pain and opioid-induced hypogonadism (total testosterone below 300 ng/dL), 11 of them were offered testosterone supplemental therapy (topical or injectable or subcutaneous implant with no further details on this treatment) and their outcomes were compared with those 16 untreated (101). Data were collected at baseline and follow-up at 6-month periods over 18 months. The testosterone-treated group showed significant improvement in the Numerical Rating Scale pain score and a reduction in the opioid requirements, as quantified by daily MME dose (mean daily MME dose decreased by 21 mg in this group and increased by 2.5 mg in the nontreated one, $P < .05$), and also an improvement in hypogonadal symptoms (assessed by the Androgen Deficiency in Aging Males and the International Index of Erectile Function questionnaires) (101). In a double-blind, placebo-controlled study involving men with noncancer pain treated with opioids for at least 3 months on an MME dose of at least 50 mg daily and with total testosterone below 12 nmol/L (measured 2 times between 8 and 10 AM in the fasting state by liquid chromatography-tandem mass spectrometry), 20 patients were randomly assigned to receive testosterone undecanoate injection 1000 mg and 21 participants to receive placebo (102). The injections were offered at the time of randomization, at 6 and at 18 weeks, and muscle function, gait performance, and body composition were measured before and after 24 weeks of intervention. The trial was completed by 38 participants; 6 of them were not able to complete all tests of muscle function. The testosterone treatment group showed significant increase in the lean body mass, leg lean mass, body weight, and a reduction in the total fat mass compared to placebo. Despite these changes, there was no difference in the muscle function or gait performance. The authors suggested that people with chronic pain are more likely to exhibit sedentary behavior; therefore, the absence of exercise/high-intensity physical activity may explain the lack of association in the observed changes in body composition and muscle function in the testosterone treated participants (102). Finally, in a placebo-controlled, double-blind randomized study, 64 males without diabetes aged between 18 and 64 years on opioid analgesics for chronic noncancer pain (at least 20 mg hydrocodone or MME dose of another opioid) and morning total testosterone below 12 nmol/L (measured by liquid chromatography-tandem mass spectrometry) were randomized to 14 weeks of transdermal testosterone gel (5 g) or placebo gel daily (2 weeks after randomization, if the serum total testosterone level was below 17 nmol/L, the dose of testosterone gel was increased to 7.5 g daily by an unblinded study physician); at the end of the study period, changes in lipid profile, fasting glucose and insulin, homeostatic model assessment for insulin resistance, and C-reactive protein were similar from baseline to the end of treatment in both arms of the study (103). Overall,

treating hypogonadism with testosterone in men leads to improvement in androgen deficiency symptoms including sexual function, to reduction in fat mass and increase in lean body mass.

Hypothalamic-Pituitary-Adrenal Axis

Effects of Opioids

Acute IV administration of endogenous opioids, such as beta-endorphin (104), enkephalin analogues (105), and pharmacological opioids, such as morphine (106), demonstrates an acute inhibitory effect on ACTH and cortisol levels in humans.

Several early studies examined the hypothalamic-pituitary-adrenal axis of heroin and methadone users, with some variable results (107–109). In a study of 8 pain patients published in 1997, up to 12 weeks of oral sustained release morphine at daily doses ranging from 30 to 240 mg suppressed basal ACTH and cortisol levels; in 2 participants who had 100 mcg of human corticotropin-releasing hormone injected (which is not a standard test for adrenal insufficiency), ACTH and cortisol concentrations showed sufficient increase (110). A landmark study published 3 years later, investigating the effects of intrathecal opioids using the insulin tolerance test (ITT) (the gold standard for the diagnosis of secondary adrenal insufficiency), showed that 15% (9/61) of the patients on intrathecal opioids for nonmalignant pain had secondary adrenal insufficiency (74). Later, cases of symptomatic adrenal insufficiency in people taking opioids began to be described (111–113). However, a 2009 review noted that the clinical significance of the inhibitory effect of opioids on cortisol was unclear and that the clinical consequences of the low cortisol had not been established (114). Soon after, studies on larger cohorts looking at the prevalence of secondary adrenal insufficiency in people using oral or transdermal opioids for chronic nonmalignant pain began to be reported (115–118). These studies were characterized by a high degree of variability in how opioid-induced secondary adrenal insufficiency was defined, and in one of them using the corticotropin-releasing hormone test, in fact, a higher prevalence of secondary adrenal insufficiency in controls with chronic pain not treated with opioids was described (118). A systematic review and meta-analysis examined 52 studies assessing the endocrine effects of opioids (72). The authors included only 5 reports investigating hypocortisolism in the meta-analysis. These studies were heterogenous, with different studies examining cancer and nonmalignant pain patients, different methods of assessing the hypothalamic-pituitary-adrenal axis, whereas two included intra-thecal opioid-treated patients. Among these reports, there was a weighted mean percentage of 15% (95% CI, 6-28) with secondary adrenal insufficiency (72).

An opioid dose-dependent effect on the diagnosis of opioid-induced secondary adrenal insufficiency has been suggested. In a study assessing the effects of long-term oral or transdermal opioids in patients with noncancer pain, an overall rate of secondary adrenal insufficiency of 22.5% (9 out of 40) was reported (defined as failing either an ACTH1-24 stimulation test or an overnight metyrapone test) (116). Using the ACTH1-24 stimulation test alone, the rate of secondary adrenal insufficiency was 15%. No patient on an MME dose of below 60 mg per day showed a suboptimal response (116). In another retrospective cohort study comprising 40 patients considered to have opioid-induced secondary adrenal insufficiency, the minimum MME dose was also 60 mg daily (119). In addition, all cases of patients on long-term oral and/or transdermal opioids for chronic pain found with blunted response to the ACTH1-24 test (3 of 48, 6%) were on a dose higher than the MME of 60 mg per day (115). However, other studies have reported secondary adrenal insufficiency in people on lower opioid doses, including a cross-sectional one examining the hypothalamic-pituitary-adrenal axis function of 102 patients on various opioids (117). Nine patients (9%) were diagnosed with secondary adrenal insufficiency (6 based on a combination of clinical assessment, basal morning cortisol, ACTH, and DHEAS levels and 3 after an ACTH1-24 stimulation test), and their minimum MME dose was 20 mg daily. Overall, there was a significant difference in cumulative opioid exposure but not daily dose, between patients considered to have secondary adrenal insufficiency vs those with a normal hypothalamic-pituitary-adrenal axis (117).

The finding of a possible but inconsistent dose-dependent effect is compatible with the pharmacodynamics, pharmacokinetics, and pharmacogenomics of opioids. In a study of cancer patients, there was a 2-fold difference in the steady state oxycodone concentration among 10 patients taking an oral identical dose (120). In another study examining pharmacogenomics, it was shown that inherited polymorphisms in the CYP2D6 enzyme determined opioid metabolism (121). In this study, 54% of patients were extensive metabolizers, 41% intermediate, and 5% poor metabolizers. Poor metabolizers had the highest steady state drug concentrations. There was a clear relationship between steady-state drug concentration and degree of analgesia, and 80% of those reporting side effects had impaired CYP2D6 metabolism (121). Extrapolating these studies to the opioid effects on the hypothalamic-pituitary-adrenal axis, it is a reasonable hypothesis that a concentration threshold may exist for hormonal inhibitory effects. In turn, the concentration depends on several factors, such as drug dose, absorption, and metabolism. This potentially explains some of the variability in dose threshold that has been reported to be associated with opioid-induced secondary adrenal insufficiency. The variable prevalence of opioid-induced secondary adrenal insufficiency may in part relate to the number of poor metabolizers in the generally small cohorts. The key point is that there is unlikely to be a simple relationship between drug dose, plasma drug concentration, and hypothalamic-pituitary-adrenal axis inhibition across a broader cohort of patients because of individual differences in absorption and metabolism. The interaction between drug concentration and opioid receptor expression then finally determines the extent of hormonal suppression.

Clinical Significance

Despite the millions of people worldwide using oral and transdermal opioids, the number of those diagnosed with opioid-induced secondary adrenal insufficiency is low, and there have been only very few published cases of adrenal crisis (112, 119, 122). As well as common symptoms of cortisol deficiency, such as fatigue, nausea/vomiting, musculoskeletal pain, weight loss, headache, and light-headedness (119), less common but well recognized manifestations, such as hypercalcemia (123) and hypoglycemia (124) have been described. Both opioid use and the pain syndromes may result in a broad spectrum of symptoms and signs that impact health-related

quality of life, including physical function, sexual function, mental health, and fatigue hindering the interpretation of the relationship between health-related quality of life and hormonal data (116, 124). Nevertheless, there is evidence that secondary adrenal insufficiency (in the context of pituitary disease) itself impacts aspects of health-related quality of life, including pain, which may be alleviated by increased glucocorticoid doses (125).

Diagnostic approach

In routine clinical practice, the most frequently used tests of hypothalamic-pituitary-adrenal axis function are the basal morning cortisol and the ACTH1-24 stimulation test (126). Low serum DHEAS has also been proposed as an adjunct test for adrenal insufficiency (127). As previously mentioned, ITT is considered the gold standard for diagnosing secondary adrenal insufficiency, although it has some limitations (128). There are data indicating that the overnight metyrapone test is a more sensitive test for secondary adrenal insufficiency than the ACTH1-24 stimulation test (129). However, a prospective study comparing the diagnostic accuracy of the ACTH1-24 stimulation test, overnight metyrapone test, and ITT to diagnose secondary adrenal insufficiency after pituitary surgery found no significant differences between them, when requirement for glucocorticoid replacement at 6 months was the critical end point (130).

Most of the published studies examining the prevalence of secondary adrenal insufficiency amongst opioid users have used the measurement of morning cortisol with or without the 250 mcg ACTH1-24 stimulation test. Lamprecht et al used morning cortisol and the 250-mcg ACTH1-24 stimulation test (applying a locally validated cutoff for the 60-minute cortisol), as well as the overnight metyrapone test, although because of the reluctance of the patient group to attend morning appointments, not every participant with a morning cortisol of below 9.1 mcg/dL (250 nmol/L) had both dynamic tests (116). The cutoff for a "normal"? morning cortisol varied with different studies and cortisol assays from 3 mcg/dL (83 nmol/L) (131) to 10 mcg/dL (276 nmol/L) (117). The two studies by Li et al used a combination of morning cortisol, ACTH, and DHEAS, suggestive symptoms, and an ACTH1-24 stimulation test in selected cases, and their sampling window was between 7 AM and 10 AM (117, 119). There is a considerable diurnal decrease in cortisol concentrations across this time frame. In a study in which cortisol sampling was undertaken every 10 minutes for 2 hours between 7 AM and 9 AM, there was a median difference of 6.4 mcg/dL (177 nmol/L) between an individual's highest and lowest cortisol across the 2-hour window (130). Thus, there is a significant physiological disparity between a "morning"? cortisol drawn at 7.30 AM compared with 9.30 AM. The heterogeneity in the diagnostic criteria for opioid-induced secondary adrenal insufficiency, cortisol assay variability, and a wide sampling window make direct comparison of morning cortisol levels between studies difficult. For example, in a study that included people both on and not on opioids, a cortisol of below 10 mcg/dL (276 nmol/L) was 100% sensitive to diagnose adrenal insufficiency in outpatients, but the specificity was only 54% (131).

There are no universally agreed-on criteria for the diagnosis of opioid-induced adrenal insufficiency. Manifestations of secondary adrenal insufficiency include fatigue, nausea, vomiting, postural hypotension/light-headedness, cognitive decline, muscle weakness, and arthralgia/myalgia, but these may also be observed in patients on opioids with normal adrenal function. Per the Endocrine Society's guideline, the suggested approach would be to screen with a morning cortisol between 8 AM and 9 AM (96); if this is less than a predefined threshold consistent with the local cortisol assay, to proceed with an ACTH1-24 stimulation test, again using an assay-specific cutoff for the 30- or 60-minute cortisol (131) and keeping in mind its limitations for the diagnosis of recent-onset adrenal insufficiency. The frequency of the hypothalamic-pituitary-adrenal axis assessment in patients on opioids is not known but occurrence of manifestations of cortisol deficiency should prompt investigations for the integrity of the cortisol reserve. It is important to consider that a patient may have other causes of secondary adrenal insufficiency, such as structural pituitary disease, pharmacological doses of glucocorticoids for a variety of medical conditions, or immune checkpoint inhibitors.

Management

Studies reporting on outcomes of patients with opioid-induced secondary adrenal insufficiency following glucocorticoid replacement are scarce. Li et al commenced 95% of patients who met their diagnostic criteria for opioid-induced adrenal insufficiency on hydrocortisone and the remainder on prednisone (119). They reported some improvement in possible manifestations of adrenal insufficiency in 70% of those evaluated; however, analyzing the individual symptoms, none demonstrated more than 50% of patients improving with glucocorticoids. The closest was fatigue, where 14 of 29 patients reported subjective improvement. Relevant but nonspecific symptoms, such as headache, abdominal pain, nausea, vomiting, and light-headedness, were improved in less than 25% of those presenting with them (119). Because this was an uncontrolled study and these symptoms/signs are common in patients on opioids with normal adrenal function, it is not possible to definitively attribute any clinical improvement to the glucocorticoid replacement. There is only a single randomized double-blind crossover trial of glucocorticoid replacement in opioid-induced secondary adrenal insufficiency that utilized a reduced cortisol response to a cold pain stimulus as the inclusion criterion (this test is not validated for the diagnosis of adrenal insufficiency) (132). Five of 17 participants had a morning cortisol below 5 mcg/dL (138 nmol/L), but 9 of 10 in the trial who underwent a 1-mcg ACTH1-24 stimulation test had a normal cortisol response. Therefore, although the participants had low morning cortisol and a reduced hypothalamic-pituitary-adrenal axis response to a cold pain stimulus, most did not have adrenal insufficiency as defined by the ACTH1-24 stimulation test. It is possible the effect of the opioid itself diminishes the painful stimulus resulting in a reduced endogenous axis response. Nevertheless, the study found that physiological glucocorticoid substitution had benefits in improving vitality and perceived pain compared to placebo (132).

Normalization of hypothalamic-pituitary-adrenal axis function can occur rapidly following opioid dose reduction. Unlike the classical scenario of glucocorticoid-induced axis suppression, which can take months or even years from which to fully recover, normal ACTH and cortisol parameters may occur within days to weeks of reducing opioid doses (112, 124). In a group of 7 patients, 6 successfully weaned off opioids completely and were able to cease their hydrocortisone (117).

Therefore, the primary action for managing opioid-induced secondary adrenal insufficiency should be an attempt at opioid withdrawal.

There are no data to underpin a consensus on the need for daily physiological glucocorticoid replacement but for those who are unable to discontinue their opioids or wean to a dose below the threshold that results in opioid-induced secondary adrenal insufficiency, physiological glucocorticoid replacement may be considered. In these cases, the response to treatment needs to be monitored to identify if this had led to clinical improvement. The hypothalamic-pituitary-adrenal axis should be reevaluated after reduction or discontinuation of the opioid. There is a paradox in that opioid use, often at high dose, is prevalent, yet there are relatively low percentages of people with biochemically diagnosed secondary adrenal insufficiency and only very rare instances of adrenal crisis. One possible explanation is that opioids may largely affect basal ACTH/cortisol secretion but less commonly impede the physiological response to stress; therefore, the user is largely protected from the usually very serious consequences of adrenal insufficiency. Consequently, one could consider as a safe and reasonable approach in selected cases to prescribe stress dosing for times of illness but not daily maintenance dosing. Patient education on sick day rules and stress steroid doses should follow current guidelines (96). However, standard management principles applied to pathological primary and secondary adrenal insufficiency may not be universally inferred to opioid-induced secondary adrenal insufficiency. Demonstration of benefit through an appropriately powered double-blind randomized controlled trial of maintenance hydrocortisone vs placebo, with provision for standard stress dosing in the placebo group in the event of significant stress or illness, would answer this question.

GH Axis

Effects of Opioids

Studies evaluating the effects of opioids on the GH axis in humans are limited and data supporting a robust and consistent effect are insufficient (70).

Single dose administration of opioids has a dose-dependent stimulatory action on the GH axis (133). This acute effect seems to be mediated through the GHRH (134). Other mechanisms may also be implicated, as when a Met-enkephalin analogue G-DAMME was administered in combination with a maximally stimulatory dose of a GHRH analogue in healthy men, an enhancing effect of the GHRH-induced GH release was observed (135).

In contrast, data on the long-term impact of opioids on the somatotroph axis are contradictory. In a systematic review, the effects of opioids on the GH axis were reviewed from 4 studies involving 225 patients with either cancer or noncancer pain (72, 74, 75, 118, 136). The limited number of included reports and the different protocols used to assess GH deficiency did not allow definite conclusions to be obtained (72). The study with the largest number of cases looked at 72 noncancer pain patients who received intrathecal opioids (morphine or hydromorphone) and 20 controls (patients with noncancer pain of similar intensity with the opioid group but not treated with these agents) (74). The opioid-treated group had lower mean serum IGF-I (138.5 mcg/L ± 64.1) in comparison to the controls (162.0 mcg/L ± 55.3; $P = .045$), as well as lower IGF-I SD score (−0.53 ± 1.45 and 0.57 ± 1.00; $P = .002$). Twelve opioid-treated patients (17%) had an IGF-I SD score below −2 SD, as opposed to no such case in the control group. The peak GH during the ITT was significantly lower ($P = .010$) in the opioid group (n = 62; 14.5 mcg/L ± 12.7) compared to controls (n = 18; 20.9 mcg/L ± 11.5). Nine opioid-treated patients (15%) had a peak GH value consistent with severe GH deficiency (below 3 mcg/L), a finding not demonstrated in any control patient. These results suggest that up to 17% of the patients treated with intrathecal opioids may develop GH deficiency (74). In a study of 40 patients on oral or transdermal opioids for chronic pain (for more than 6 months at an MME dose ≥25 mg) and 25 controls not taking opioids, the opioid users had lower IGF-I (138 mcg/L [99–161] vs 168 mcg/L [138–214]; $P = .004$), although none of them had levels below the lower limit of the reference ranges (116). Another study evaluated 39 noncancer pain patients who received different oral opioids and 20 controls (118); GH stimulation test was not performed but mean serum IGF-I was lower in the opioid-treated group, although statistical significance was not attained. In a report comparing the effects of intrathecal and oral morphine, 18 intrathecal opioids users, 18 oral opioids users, and 18 controls were evaluated (136). Serum IGF-I range was not different between the groups. Serum IGF-I levels below −2 SD were detected in 44% of the oral opioid users in contrast to 28% of the intrathecal opioid users and controls. However, this difference was not statistically significant. Mean peak GH during ITT did not differ between the groups and, although also not statistically significant, peak GH below 3.2 mcg/L was detected in 11% of the intrathecal opioid users (136). In a study of 19 patients with cancer pain treated with several opioids, only measurements of basal serum GH levels were provided; given that this is not the appropriate method to diagnose GH deficiency, conclusions on the effects on the GH axis cannot be drawn (75). Finally, in a report of 22 patients with chronic pain on oral opioids, serum IGF-I levels and glucagon-stimulated peak GH were not different from a control group of 15 subjects on nonopioid analgesia (137).

The GH axis has also been assessed in male heroin addicts (138). ITT was performed in 4 groups: 12 controls (all denied opioid use), 19 methadone-treated patients, 16 heroin-addicted patients, and 12 former heroin addicts. The mean of peak GH was similar in all groups. However, 26% of the methadone-treated group and 31% of the heroin-addicted people exhibited abnormal GH peak on the ITT (138).

Another remarkable aspect of the possible interplay between opioids and GH that deserves attention involves ghrelin, which stimulates GH release via the GH secretagogue receptor type 1a (GHS-R1a). Preclinical studies suggest that ghrelin/GHS-R1a has a significant role in the reinforcing effects of opioids, and in preclinical addiction studies, GHS-R1a antagonism decreased the opioid reward and the symptoms of craving for opioids (139). Ghrelin/GHS-R1a involvement in opioid addiction in humans and the possible benefits of a ghrelin antagonist remain to be elucidated.

Clinical Significance

Taken together, the scarce published literature suggests that long-term use of opioids may compromise the GH axis. Opioid type, dose, and route of administration are potential parameters influencing these effects; more methodologically robust studies would provide definitive conclusions.

Interestingly, in a case report of a 61-year-old man with chronic intercostal neuropathic pain managed with methadone, GH treatment with daily doses up to 0.3 mg led to improvement of cognitive capacity (140). The patient had developed impaired cognitive function as a possible complication of opioid long-term treatment and had been diagnosed with GH deficiency by a GHRH-arginine test.

Overall, currently, there is inadequate evidence to underpin recommendations for monitoring, diagnosis, and management of GH deficiency in long-term opioid users. However, health care professionals prescribing opioids need to be aware of their possible negative effects on the GH axis.

Prolactin

Effects of Opioids

Opioids can cause hyperprolactinemia, most likely by inhibiting the hypothalamic dopamine production (49, 141).

Early studies have shown that acute administration of opioids increases prolactin (PRL) secretion, an effect that is reversed by dopamine agonists (142). These actions have been confirmed in subsequent studies with various types of opioids (143–146).

In a systematic review of 6 studies evaluating the long-term effects of opioids on PRL secretion among 346 patients with either cancer pain or noncancer pain, the results were variable (72). In a report of 14 patients on opioids for cancer pain, serum PRL levels were above the reference range in 6 (43%) of them. PRL values seemed to increase with higher opioid doses, but this finding did not reach statistical significance, possibly because of the small sample size (75). In a group of 39 noncancer pain patients on oral opioids, hyperprolactinemia was detected in approximately 40% of them (118). In addition, high PRL levels were found in 2 of 20 (10%) noncancer pain patients on intrathecal morphine (147). In contrast, hyperprolactinemia has not been confirmed in other studies involving noncancer pain patients on intrathecal or oral opioids (74, 136, 148), although in one of them, PRL was higher (but still within normal range) in men in the opioid-treated group, as compared with the controls (148). In a report of 40 patients on oral or transdermal opioids for chronic pain (for more than 6 months on an MME dose ≥25 mg), no difference in the prolactin values was found when compared with 25 controls not taking opioids (116). Finally, similar PRL levels were found between 21 noncancer pain patients on oral opioids and a control group of 15 noncancer pain patients on nonopioid analgesia; hyperprolactinemia was detected only in 1 case of the control group (137).

Higher PRL concentrations (as compared with healthy people) and hyperprolactinemia have been reported in people addicted to heroin and opium smokers (149). In patients on methadone or buprenorphine maintenance treatment, PRL has been found to be reduced, similar, or higher when compared with controls (91, 150, 151).

Overall, based on the published literature, acute administration of opioids increases serum PRL, whereas in patients on long-term opioids, PRL has been found normal or elevated.

Clinical Significance

Diagnostic approach and management

Given that hyperprolactinemia can cause hypogonadism and galactorrhea, health care professionals prescribing opioids need to be aware of this possibility and enquire about these manifestations (152). Serum PRL should be measured only in the context of a suggestive clinical picture, and diagnostic steps should be in accord with published guidelines taking also into account the impact of potential confounding factors (eg, pain, stress) (152).

It has been proposed that if hyperprolactinemia is confirmed, discontinuation or reduction of the opioid dose (or possibly use of an alternative opioid) needs to be considered and PRL levels to be reevaluated (70). If these are not feasible, no other secondary etiology of hyperprolactinemia is identified, or the onset of the signs and symptoms do not coincide with the initiation of the opioid therapy, a magnetic resonance imaging of the sella turcica will be necessary to rule out a prolactinoma or other lesions compressing the pituitary stalk (49).

Therapeutic interventions are not needed in asymptomatic patients or if galactorrhea is not bothersome (49). Symptomatic patients who cannot discontinue or amend their opioid therapy could be treated with a dopamine agonist, usually cabergoline. Alternatively, gonadal hormone replacement could be prescribed for hypogonadism (49).

Hypothalamic-Pituitary-Thyroid Axis

Effects of Opioids

Acute administration of opioids in healthy volunteers has led to increased serum TSH concentrations (153, 154).

Studies with dynamic thyrotropin-releasing hormone test performed in chronic opioid users have demonstrated conflicting results with enhanced (118), blunted (136, 155, 156), or no (74, 157) TSH response. Furthermore, basal TSH values have been reported to be lower (149, 153), unaffected (74, 116, 136, 155–160), or increased (118, 161). Variable results have also been described for the peripheral thyroid hormones; T4 levels were unaffected (74, 118, 136, 159, 160) or decreased (116, 160–162) and T3 levels were increased (74, 159) or unaffected (160) or decreased (161). T3 resin uptake, reflecting thyroid hormone binding globulin, has been reported to be lower (159).

A data mining study from the US Food and Drug Administration Adverse Event Reporting System demonstrated that in patients with OUD, there was positive association with hyperthyroidism (adjusted odds ratio, 1.46; 95% CI, 1.43-1.49) and hypothyroidism (adjusted odds ratio, 1.45; 95% CI, 1.42-1.48) (162). Whether this finding is truly significant, the potential pathophysiological mechanisms and possible links between opioids and autoimmune thyroid disease require further clarification.

Clinical Significance

The data on the impact of opioids on thyroid function in humans are inconsistent. Overall, though, it can be speculated that long-term opioid use does not cause clinically relevant thyroid dysfunction, and, at present, there is no evidence supporting screening of thyroid disorders in these patients.

Arginine Vasopressin

Effects of Opioids

Earlier studies had suggested that morphine induces an antidiuresis in several species, including man, by stimulating the release of arginine vasopressin (AVP) (163, 164). It has also

been shown that IV or epidural morphine administered to children undergoing surgery had led to an increase in AVP levels (165). Fentanyl increased AVP release in both surgical patients (166) and healthy volunteers (167). Accordingly, opioids are mentioned in review articles as inducing the syndrome of inappropriate antidiuresis (168), an effect initially considered to be due to a direct enhancement of AVP release (169). The only opioid, however, that has been associated with hyponatremia in case reports is tramadol, a weak opioid analgesic with the hyponatremia usually occurring within the first 30 days after initiation of this drug (170–173). In a UK population-based cohort study, the use of tramadol was related with a 2-fold increased risk of hospitalization for hyponatremia when compared to codeine; the authors postulated that hyponatremia developed because of stimulation of AVP and/or through inhibition of central reuptake of serotonin, leading to increased AVP release and syndrome of inappropriate antidiuresis (174). According to the Beers criteria for Potentially Inappropriate Medication Use in Older Adults, tramadol should, therefore, be used with caution in older adults and sodium levels need to be monitored when starting this drug or when increasing its dose (175, 176). It should be noted, however, that the results of many of these studies are difficult to be interpreted, as changes in patients' hemodynamic status or side effects of opioids (such as hypotension or nausea), which could secondarily stimulate AVP release, were not controlled.

In contrast to these hypothesis, others have proposed that the primary effect of opioids is to suppress rather than stimulate AVP release. DAMME, a long-acting analogue of met-enkephalin, produced water diuresis in dehydrated or in hypertonic saline-loaded subjects by inhibiting AVP release (177); in this study, the effect of opioids on AVP seemed to be dependent on the hydration status, as DAMME infused into water-deprived healthy volunteers produced diuresis that was attenuated by naloxone, whereas when subjects were hydrated, there was no change in water excretion (177). The inhibiting effect of DAMME on AVP has been confirmed in further reports (178, 179). It has also been shown that acute administration of the kappa-opioid receptor agonist asimadoline in normal subjects at doses 1, 5, and 10 mg reduced plasma AVP during 2.5% saline infusion in 6 of 8 participants receiving the highest dose of 10 mg, compared to placebo (180). Finally, opiate-dependent patients on diacetylmorphine (heroin) maintenance treatment had reduced AVP levels compared with controls (181). Thus, it may be speculated that the antidiuretic effect of opioids observed in some studies, as well as the occurrence of hyponatremia may not be mediated via AVP. Indeed, in a case report of a 19-year-old female with complete AVP deficiency since the age of 6 years, the patient developed hyponatremia on treatment with hydrocodone offered after the extraction of her wisdom teeth (182). In this case, an increase of AVP levels could not explain the hyponatremia because she was not able to produce AVP due to her AVP deficiency.

It is also worth looking at data on copeptin, a 39 amino acid long glycosylated peptide with a leucine-rich core region, which derives from the precursor protein Pre-Pro-Vasopressin together with AVP and Neurophysin II (183). In recent years, copeptin has emerged as a surrogate marker for AVP because, in contrast to AVP, it can be measured reliably in clinical routine by commercially available assays with high-standard technical performance. A strong correlation between plasma AVP (when measured with a well-established radio-immunoassay) and copeptin levels has been demonstrated in healthy volunteers (184), and, therefore, copeptin measurement could be an alternative marker to elucidate the effects of opioids on AVP. However, only very limited data on the effect of exogenous opioids on copeptin are available to date. A recent study measured copeptin levels before, during, and after electrophysiological stimulation in healthy volunteers, initially before and then during opioid delivery; after administration of opioids, there was no visible effect on copeptin values (185).

Clinical Significance

Based on the published literature, the effects of exogenous opioids on AVP secretion in humans are inconclusive and their clinical significance is unclear. The conflicting results might be due to discrepancies in fluid/hydration status, as well as from side effects of opioids leading to nonosmotically stimulated AVP. Given the finding that some opioids such as DAMME inhibit AVP release and induce diuresis in dehydrated subjects, careful hydration of patients receiving opioids may need to be considered. Furthermore, sodium monitoring is of importance in patients on tramadol, especially during the first 30 days of this treatment, and this agent should be used with caution in older adults.

Oxytocin

Effects of Opioids

Oxytocin receptors are present in the uterus, consistent with their known role in parturition, and in diverse other tissues. Oxytocin has a key role in the regulation of socioemotional functioning, including attachment and pair bonding, fear extinction, emotion recognition, and empathy (186–189). In line with this, it may act as a stress-buffering hormone and influence the hypothalamic-pituitary-adrenal axis because there was a trend toward attenuated cortisol levels by oxytocin (190). Besides the release from axonal terminals, there is dendritic release of oxytocin into the central extracellular space with local action and direct projection to other brain regions, including the amygdala, hippocampus, and brainstem, where it acts as a neurotransmitter (191). Specifically, over the past decades, it has been hypothesized that the prosocial effect of oxytocin might be secondary to an anxiolytic effect that involves modulation of amygdala responsivity (eg, to threatening stimuli of different social valence [faces and scenes]) (192).

Studies on the effects of opioids on oxytocin in humans have primarily focused on women, particularly investigating the effect of analgesics during pregnancy and labor. It has been shown that morphine and naloxone have no impact on oxytocin levels during pregnancy (193) and that morphine administration to the mother has no effect on fetal oxytocin levels (194). However, during the first stage of labor, morphine inhibited plasma oxytocin levels, whereas naloxone had no effect (195). Furthermore, after delivery, morphine inhibited the rise in oxytocin secretion in breast-feeding women but the amount of breast milk was not measured in this study (196). Similarly, other opioid analgesics, such as fentanyl, did not suppress oxytocin levels during pregnancy, but inhibited them during the onset of labor (197, 198). Systemic opioids have a long tradition in analgesia during labor; in line with the inhibiting effect of opioids on oxytocin, in a

nonrandomized study, women offered opioid analgesia had longer labor and more need for oxytocin augmentation compared to controls not on labor analgesia (199). Women treated with IV opioids did not show oxytocin augmentation compared to those on epidural analgesia (200).

An intriguing aspect in the interplay between opioids and oxytocin is the effect of this hormone on opioid addiction and withdrawal. A randomized, double-blind clinical trial in heroin-dependent subjects showed that acute oxytocin treatment reduced craving and withdrawal scores, without, however, a significant effect on anxiety (201). It has been proposed that social attachment (the emotional bond or connection that individuals form with others, typically within social groups such as families, friends, or communities) seems to protect against addiction (202). It has therefore been postulated that oxytocin, through interaction with the central dopaminergic, serotonergic, and endogenous opioid system, could increase resilience against addiction by facilitating the process of social bonding (203).

Clinical Significance

Data on the impact of opioids on oxytocin in humans outside pregnancy or labor are lacking. The clinical relevance of the finding that administration of opioids during labor might lead to higher need for oxytocin augmentation (to facilitate labor and birth) requires further investigation and should also be correlated with labor outcomes (eg, offering cesarean section, time to delivery, and risk of adverse perinatal outcomes). The proposed benefits of oxytocin treatment on opioid addiction and withdrawal are promising but they necessitate further validation before they are applied in clinical practice.

Bones

Effects of Opioids

Exogenous opioids exert detrimental effects on bone homeostasis and metabolism and are associated with low bone mineral density (BMD) and an increased fracture risk. There are three main hypotheses that could explain the augmented fracture risk in chronic opioid users: bone loss caused by direct opioid effects on bone remodeling; increased risk of falls because of CNS effects; and chronic opioid-induced hypogonadism and its impact on bone metabolism (204).

Opioids and bone remodeling/bone healing

Data deriving from in vitro experiments on animal and human cells, as well as in animal models indicate that opioids can reduce BMD by directly influencing osteoblast activity (205–210). Pivotal experiments from two decades ago confirmed the expression of three types of opioid receptors, namely MOR, delta-opioid receptors, and kappa-opioid receptors in the human osteoblast-like cell line MG-63 via reverse transcription-polymerase chain reaction and immunohistochemistry (208). Treatment with high concentrations of the MOR agonist morphine significantly inhibited the expression of osteocalcin, a marker of osteoblast activity, without influencing the secretion of alkaline phosphatase (208). In addition, treatment with the opioid antagonist naloxone reversed the effect of morphine with regards to osteocalcin expression (208). These results were replicated in a murine model, in which treatment with morphine inhibited mineral nodule formation (207), and in human bone marrow-derived mesenchymal stem cells, where morphine altered the ability of mesenchymal stem cells to differentiate into adipocytes or osteoblasts (206). Conversely, naltrexone, an antagonist of canonical opioid receptors and opioid growth factor receptor, administered daily intraperitoneally to mice for 28 days increased their femoral bone mass, bone formation ratio, and osteoblast number/bone surface values when compared with control animals (210). Two additional experimental studies indicated a pro-osteogenic effect of naltrexone in a murine model of osteoporosis induced by liver cirrhosis (211, 212). Thus, the findings of these preclinical studies suggest a pro-osteogenic role of opioid receptors antagonists, although this will need to be validated in humans. Moreover, maternal consumption of morphine in rats led to impairment of longitudinal bone growth, as well inhibition of protein expression of chondrogenic and osteogenic markers in their offspring (209). A recent murine study using continuous morphine delivery via subcutaneous osmotic minipumps for 25 days indicated a sex difference in the bone outcome, where male mice treated with morphine had reduced trabecular bone volume and trabecular BMD in the distal femur compared with vehicle, whereas bone microarchitecture had not changed in females after morphine treatment (205). Of interest, this study also identified potential mediating miRNAs in the suppression of bone formation in male mice (205). Pregnant women addicted to heroin and cocaine displayed low serum levels of osteocalcin, a finding also corroborated in the umbilical arteries of their newborns, which also suggests toxic effects of these drugs on osteoblasts (213). Although potent opioid agonists exert negative effects on osteogenesis, the impact of opioids with lower affinity for the classic opioid receptors on bone appears to be less potent. For example, chronic use of tramadol, which has a lower affinity for MOR, led to a less pronounced osteoporotic phenotype in adult female rats compared to morphine or fentanyl (214). Furthermore, some interesting data have emerged on remifentanil, an ultra-short-acting opioid mainly used in the setting of perioperative anaesthesia or analgesia in the intensive care unit (215). Under hypoxia-reoxygenation conditions, remifentanil preconditioning enhanced the cell viability and maturation of human fetal osteoblasts (216), whereas in the pre-osteoblast C2C12 murine cell line, it increased osteoblast differentiation by upregulation of the expression of two key osteogenic transcription factors Runt-related transcription factor 2 and osterix (217).

The effects of opioids on osteoclasts are less well described. A number of studies have reported indirect effects on osteoclastogenesis and osteoclast function through modulation of osteoblast-derived factors. For example, tramadol was shown to enhance osteoprotegerin synthesis in osteoblasts, thus indirectly suppressing the formation and function of osteoclasts (218, 219). On the other hand, some evidence of direct effects of opioids on osteoclasts exists. In this vein, remifentanil promoted the differentiation of murine pre-osteoclasts and induced their maturation in one experimental setting (220), although the exact opposite effects, namely reduction of the number and size of osteoclasts and the formation of tartrate-resistant acid phosphatase-positive multinuclear osteoclasts by remifentanil, have also been described (221). In humans, higher serum concentrations of the bone resorption marker β C-terminal telopeptide were reported in male heroin users compared to healthy volunteers (222), a finding replicated in men receiving opioid substitution therapy (223). Conversely, no up-regulation of C-terminal telopeptide was

found in another cohort of men on methadone substitution therapy (224).

Traditional opioids have been found to impair bone healing in some animal models of bone trauma (225). In a rat fracture model, morphine administration inhibited callus strength at 8 weeks (226), whereas fentanyl caused immature spinal fusion in a rabbit model (227). In contrast, low doses of naloxone enhanced bone mineralization and callus formation of a cortical defect induced in a sheep model (228).

In conclusion, data on the impact of opioids on bone remodeling and bone healing are discordant (225). Potential limitations for preclinical experiments appear to be different doses and duration of opioid application. Nonetheless, it appears that different opioid categories, also depending on their affinity for the respective opioid receptors, exert differential effects on bone cells. Moreover, most studies suggest differential effects on humans and preclinical models.

Clinical Significance

Opioid prescription in the elderly population and bone health

Pain is common in elderly patients, being reported in up to 50% of the elderly population and up to 80% of care facility inhabitants (229). Chronic pain is a limiting factor in daily activities and is linked to deconditioning, frailty, increased risk of accidents, and polypharmacy (229). As the population ages, next to the burden to the individual, pain is bound to have considerable economical and societal impact (230). Thus, the associations between current comorbidities, clinical presentation and analgetic prescribing in elderly patients is a subject of interest.

In a large cohort of elderly patients admitted in a tertiary care hospital in Australia, analgesics were prescribed in 69% of them (more commonly in women), whereas opioids were prescribed in 34% of analgesic users (231). Female sex was associated with an increased likelihood of opioid prescription, with oxycodone being the most prescribed opioid (56%) (231). Another study investigating the prevalence and indications for daily opioid use among home care clients reported prevalence of 9.3% in opioid use for long periods (median duration of use was 357 days before study entry, and opioids were mostly continued during the follow-up year) (232). Most common indications for prescription were musculoskeletal disorders (ie, vertebral osteoporotic fractures, degenerative spinal disorders, and osteoarthritis), with only 3.2% of the study population using an opioid for cancer-related pain (232). Similarly, a population-based cohort study of opioid-naive community-dwelling US citizens reported continuous opioid use in 6.4% of patients one year after sustaining an index hip fracture (233). Of interest, a study assessing opioid use in the immediate 14-day period post-hip fracture in older nursing home residents found that opioid use in that period was associated with a lower likelihood of death and functional decline (234). Regarding vertebral fractures, which are often associated with severe pain, vertebral augmentation procedures, such as balloon kyphoplasty and vertebroplasty, were associated with decreased or discontinued opioid prescription fills in a significant proportion of 8845 patients undergoing these procedures (235). In this vein, a second smaller study in a tertiary academic center confirmed decrease in pain scores, daily morphine consumption and improvement in functional status after kyphoplasty (236).

Bone mass in patients on opioids

Long-term opioid therapy is a risk factor for low BMD, as has been shown in various groups of patients.

A prospective longitudinal nationwide study of mid-life women assessed the impact of different analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids] on bone mass and reported a more pronounced BMD decline over 5 years in opioid users (237). In contrast, an older Danish cohort study with a 10-year follow-up period had failed to identify such a trend, albeit the number of opioid users in that study was very small (238). In a small observational study comprising 20 males receiving long-term intrathecal opioid treatment for nonmalignant bone pain, 17 patients displayed biochemical hypogonadism, whereas 10 of hypogonadal patients had osteopenia or osteoporosis (147). Of interest, in a study evaluating the effect of testosterone substitution in a small cohort of male patients developing hypogonadism under intrathecal opioid treatment, restoration of gonadal status and BMD after two years of testosterone therapy was reported (239). Another study including 12 men and 14 premenopausal women treated with oral opioids for chronic pain for at least one year found high prevalence of hypogonadism in men (75%), whereas only 21% of the women reported oligo- or amenorrhea indicating hypogonadism; osteopenia was detected in 50% of men and 21% of women, suggesting a potential sexual dimorphism in long-term effects of opioids regarding gonadal status and bone health (158). Last, in a cross-sectional analysis of Third National Health and Nutrition Examination Survey, opioids were associated with significantly reduced BMD after adjustment for several common causes of secondary osteoporosis (240).

A number of studies have investigated bone health of patients on opioid substitution therapy from either previous addiction or chronic pain. A Swiss cross-sectional study including 144 men receiving opioid substitution therapy with either methadone (69%) or morphine (25%) or buprenorphine (6%) reported a decreased BMD compared to compared to age- and BMI-matched healthy controls, predominantly on the axial skeleton in 73% of participants (223). In all age groups, BMD was significantly lower than in age- and BMI-matched controls, whereas free testosterone was shown to be an independent predictor of bone mass (223). Of note, another cross-sectional study including 83 patients (48 men, 35 women) on methadone maintenance therapy (MMT) for a median of 11 years confirmed lower testosterone levels in men on MMT compared to controls and reported mean BMD values at each skeletal site approximately 10% below the population mean in men, albeit not in women (224). Furthermore, a small case-control study including young women on MMT compared with age- and BMI-matched controls found only marginally lower BMD at the hip of these subjects with no differences in other skeletal sites, despite a largely unhealthy lifestyle in patients (high alcohol and nicotine intake) (241). A previous cross-sectional study in a mixed population (36% men) had described decreased BMD (compared to a gender and race/ethnicity-matched, young adult reference population) in 83% of people enrolled in a MMT program and identified male gender, low BMI, heavy alcohol use, and HIV infection as significant predictors of low BMD; however, sex steroids were not evaluated in this study (242). In this vein, a prospective study aiming to investigate the combined effects of HIV infection and MMT in a sample of

middle-aged women reported similar rates of decline in BMD between HIV-infected and HIV-uninfected women, but also indicated that MMT was associated with bone loss (243). A recent systematic review assessing all of these studies on patients on opioid substitution therapy concluded that this population should be screened for low bone mass and that risk factors significantly associated with low BMD were male gender, low BMI, low testosterone levels, methadone or heroin use, and longer duration of heavy alcohol use (244).

In conclusion, low BMD is a long-term side effect of opioids, and especially in male patients, it appears to be pathophysiologically connected to hypogonadism.

Fracture risk in patients on opioids

Use of exogenous opioids has been associated with an increased risk of fractures in several meta-analyses (245–248). Using mostly cohort and case-controls studies, these meta-analyses have reported an increased risk for hip fractures (245), falls (247), and major osteoporotic fractures (246, 248) in opioid-treated patients.

As previously stated, the increased fracture risk among individuals with chronic opioid use is attributed to three main reasons: reduced BMD caused by direct opioid effects on bone metabolism, chronic opioid-induced hypogonadism, and increased risk of falls caused by CNS side effects, including sedation, gait disorders, and lack of concentration. The first two mechanisms have been elaborated above. Regarding CNS side effects, it has been shown that the rates of hospital visits for falls and fractures is disproportionally high at the initiation phase of opioid treatment, a trend not seen with other analgesics, such as nonsteroidal anti-inflammatory drugs (249). Of note, such an increase in falls and fractures is accentuated in new opioid users with cognitive impairment, as seen in a study of patients with Alzheimer disease (250). Conversely, some data including time-to-event analyses, highlight a high incidence of falls and fractures in long-time opioid users, as reported for example in non-tramadol opioid users with osteoarthritis experiencing fractures in a median time of 14 months after opioid initiation (251). Thus, it appears that patients with continuous opioid use remain at high risk for falls and fracture.

Diagnostic approach and management

Acknowledging that majority of data on skeletal effects of opioids derives from observational studies characterized by considerable heterogeneity, various confounders (eg, poor global nutrition, acidosis, low calcium and vitamin D intake, low body weight, weight loss, smoking, alcohol, use of additional drugs, seizures, reduced muscle mass, inactivity, chronic medical condition/malignancy) and different follow-up periods, it appears indisputable that opioid use is associated with detrimental skeletal consequences. Thus, measurement of BMD by dual-energy X-ray absorptiometry and evaluation of additional osteoporosis risk factors is indicated in long-time opioid users, especially in the presence of hypogonadism. Careful assessment of the necessity of chronic opioid treatment and de-escalation/discontinuation of their use is of major importance. In case of osteopenia/osteoporosis, management should be tailored to current osteoporosis guidelines. Scarce data exist on the effects of sex hormone substitution on bone health in hypogonadal patients on opioids. A small observational study of male hypogonadal patients on intrathecal opioids for noncancer pain who received testosterone substitution corrected the decreased testosterone levels and improved BMD (239). Regular exercise has effects on bone density, size, and shape, resulting in substantial improvements in mechanical strength (252), but data on the effect of exercise interventions on the bone quality of opioid-dependent individuals are limited. An 8-month aerobic gymnastics training program in young opioid-addicted women failed to show any effects on bone quality, as assessed by quantitative ultrasound (253). Additional large well-designed studies investigating such approaches in individuals on chronic opioid use will underpin further guidance.

Summary of Key Points on Actions of Exogenous Opioids on Endocrine System in Humans

- Opioids inhibit the hypothalamic-pituitary-gonadal axis and can cause hypogonadism.
- Opioids inhibit the hypothalamic-pituitary-adrenal axis; low basal morning cortisol levels and inadequate response of cortisol on dynamic testing have been reported; the significance of these effects and the occurrence of clinically relevant adrenal insufficiency is not fully elucidated.
- Acute administration of opioids has a stimulatory effect on GH secretion; data on the impact of long-term use of opioids on the GH axis are not consistent but cases with compromised response of GH on dynamic testing have been reported.
- Acute administration of opioids increases prolactin secretion. Chronic use of opioids can lead to hyperprolactinemia.
- Opioids have variable and inconsistent effects on the hypothalamic-pituitary-thyroid axis.
- Data on the effects of opioids on AVP secretion are inconclusive.
- Evidence of opioid actions on oxytocin derived from studies of women in labor suggests an inhibitory effect (opioids can inhibit plasma oxytocin levels during labor).
- Opioid use can have negative impact on bone homeostasis and metabolism; reduced BMD and increased risk of fracture have been reported; proposed implicated mechanisms for these negative sequelae include direct effects on bone remodeling, increased risk of falls, and hypogonadism.

Gaps in Knowledge

Despite the global opioid crisis, the gaps in knowledge around the actions of opioids on the endocrine systems, their clinical significance and their optimal management are wide. In Table 3, we summarize the most pertinent ones on the areas this Statement has covered that require careful consideration.

Conclusions/Future Directions

This Scientific Statement presents an overview of the landscape of research relating to the effects of exogenous opioids on various components of the human endocrine system. It specifically describes clinically relevant data on the actions of opioids on the hypothalamic-pituitary system and on bone health. It also identifies areas requiring further research that will enhance our understanding on the consequences of the

Table 3. Gaps in knowledge on the effects of exogenous opioids in humans on the endocrine systems covered in the Statement

Hypothalamic-pituitary-gonadal axis
Data on type, route of administration, and regimens of opioids associated with higher risk of hypogonadism in both males and females derived from studies adjusting for confounding factors. Impact of partial agonists (eg, buprenorphine).
Impact of opioids on fertility in males and females.
Time frame of recovery of the hypothalamic-pituitary-gonadal axis after opioid discontinuation to inform management protocols.
Benefits and risks of gonadal hormone replacement in premenopausal females and in males with hypogonadism attributed to opioids from prospective adequately powered and of appropriate duration randomized trials; this also includes impact on pain sensitivity and on the effects on recovery of people on methadone maintenance therapy.
Hypothalamic-pituitary-adrenal axis
Standardization and validation of diagnostic tests and criteria for opioid-induced adrenal insufficiency.
Prevalence of hypoadrenalism with different opioids, doses, and routes of administration.
Individual susceptibility to the inhibitory effects of opioids (could differences in opioid metabolism combined with a possible opioid concentration threshold which inhibits the axis explain why some individuals are more susceptible to these effects?).
Patients at risk of developing adrenal insufficiency while on opioids.
Clinical significance and optimal management approach of opioid-induced adrenal insufficiency (need for daily physiological glucocorticoid replacement or cover with glucocorticoids in case of stress?).
Time course of the reversal of the changes in the axis following withdrawal or reduction of opioid dose to inform management protocols.
GH axis
Clear understanding of the effects of chronic use of opioids on the GH axis (with different opioids, doses, and routes of administration).
Clinical significance of compromised GH axis in patients on opioids for cancer or noncancer pain and in people with opioid use disorder and potential benefits/risks of treatment with GH replacement.
PRL
Types, doses, and route of administration of opioids etiologically related with clinically significant hyperprolactinemia.
Benefits and risks of dopamine agonist treatment in patients with opioid-induced hyperprolactinemia.
Consequences of untreated long-term opioid-induced hyperprolactinemia.
Hypothalamic-pituitary-thyroid axis
True effects of opioids on thyroid function and their clinical relevance.
Implications of opioids in the development of autoimmune thyroid disease.
Arginine vasopressin
True impact of different opioids on AVP release after adjusting for confounding factors and considering hydration status of the patients.
Effects of opioids on copeptin as a surrogate marker of AVP secretion.
Mechanisms leading to hyponatremia in patients treated with opioids (AVP-dependent or AVP-independent?).
Oxytocin
Effects of opioids on oxytocin in males and in nonpregnant women.
Clinically relevant impact of opioids offered as analgesics on labor outcomes.
Role of oxytocin in the treatment of opioid addiction and withdrawal.
Bone health
Differential effects of various opioid agonists on bone homeostasis and factors related with them.
Role of opioid antagonists in increasing BMD and possible treatment for osteoporosis.
Sexual dimorphism of opioid effects in bone homeostasis and its significance.
Impact of gonadal hormone replacement on improving/reversing reduced BMD and on risk of fracture in long-term opioid users.

Abbreviations: AVP, arginine vasopressin; BMD, bone mineral density; PRL, prolactin.

available opioids and will provide evidence guiding the optimal diagnostic approach and management of their endocrine adverse sequelae. These are additionally mandated by the opioid pandemic we are witnessing and will open perspectives for exciting and impactful future research.

The true prevalence and the risk of opioid-induced hypogonadism in both males and females in various patient cohorts needs to be clarified in methodologically sound studies with adjustment for confounding factors (eg, pain, chronic stress, comorbidities). Of particular importance is the identification of the types and doses of opioids associated with high potential of causing hypogonadism and the time frame for restoration of the hypothalamic-pituitary-gonadal axis after their cessation or dose reduction. Randomized, controlled, adequately powered and long-duration trials are required to assess the effects of gonadal hormone replacement not only on known manifestations/consequences of hypogonadism but also on aspects related to pain management and recovery of people on methadone maintenance therapy. The paucity of data on females highlights the need for studies in women that also look at fertility outcomes.

Research is needed to establish consensus diagnostic criteria for adrenal insufficiency in patients on opioids. Without them, future studies will not be directly comparable. Increasing use of liquid chromatography-tandem mass spectrometry for the measurement of cortisol should largely eliminate the cutoff

variability observed using immunoassay technology, both for basal morning cortisol concentrations and for stimulation tests. More detailed pharmacokinetic, pharmacodynamic, and pharmacogenomic studies need to be undertaken to improve our understanding of relationship between opioid dose, plasma concentration, and causation of secondary adrenal insufficiency (and also of other opioid-related endocrine effects), aiming to identify people who might potentially be at increased risk of developing opioid-induced adrenal insufficiency. The evidence behind recommendations to routinely treat all patients diagnosed with opioid-induced secondary adrenal insufficiency using standard physiological glucocorticoid replacement doses is weak and a well powered, double-blind randomized control trial comparing hydrocortisone with placebo is required to definitively answer the question. In addition, the time course of hypothalamic-pituitary-adrenal axis recovery during the process of opioid withdrawal requires more detailed documentation in a longitudinal manner, as does whether administration of full replacement glucocorticoid doses during this process impedes or promotes recovery—symptomatically and functionally.

The scarce published literature suggests that long-term opioid use could possibly impact negatively on the GH axis in humans. Nonetheless, the existing evidence is not sufficient to elucidate this area and clinical recommendations are not possible. Methodologically robust studies, adequately powered and with appropriate controls, are needed to reveal the true impact of various opioids and its clinical significance, as well as the benefits of testing the integrity of the GH axis and offering GH replacement in cases with biochemically confirmed GH deficiency and no contraindications for this treatment.

Long-term use of opioids has been associated with hyperprolactinemia, the true prevalence of which is not clear, necessitating studies to clarify its frequency depending on the opioid, dose, and route of administration. The optimal management approach for the hyperprolactinemia including the use of dopamine agonists requires further research.

The effect of opioids on the hypothalamic-pituitary-thyroid axis require longitudinal studies looking at biochemical measures and clinical parameters reflecting thyroid dysfunction, acknowledging the baseline risk to encounter thyroid disease in general.

The effects of opioids on AVP in humans are inconclusive and their clinical significance is not well defined. Further studies providing insights on the interplay between opioids, AVP/copeptin secretion, and water balance, as well as the role of hydration status on the effects of these agents are needed. Other confounding factors will need to be considered in the design of these studies (eg, influence of pain and nausea on nonosmotic AVP secretion).

The clinical relevance of the inhibitory action of opioids during labor necessitates further investigation. Additional studies are also needed to clarify the effects of opioids on oxytocin in males and in nonpregnant women and to explore and validate potential benefits of oxytocin in the treatment of opioid addiction and withdrawal.

Further research is needed to illuminate the different effects of various opioids on bone metabolism and whether these are characterized by sexual dimorphism. In addition, well-designed prospective studies accounting for confounding factors and of appropriate follow-up will elucidate the long-term benefits of hormonal replacement on BMD and facilitate the development of safe and cost-effective guidelines on the bone health of chronic opioid users.

Finally, studies investigating the awareness of clinicians (and particularly those prescribing opioids) and of patients on the endocrine consequences of these agents will identify gaps in the provision of care in these groups of patients and will offer additional insights into the implications of the opioid crisis on the health care system.

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