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## DIAGNOSIS OF ENDOCRINE DISEASE

**Drug-induced endocrinopathies and diabetes: a combo-endocrinology overview**

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**Abstract**

In the currently overwhelming era of polypharmacy, the balance of the dynamic and delicate endocrine system can easily be disturbed by interfering pharmaceutical agents like medications. Drugs can cause endocrine abnormalities via different mechanisms, including direct alteration of hormone production, changes in the regulation of the feedback axis, on hormonal transport, binding and signaling, as well as similar changes to counter-regulatory hormone systems. Furthermore, drugs can interfere with the hormonal assays, leading to erroneous laboratory results that disorientate clinicians from the right diagnosis. The purpose of this review is to cover a contemporary topic, the drug-induced endocrinopathies, which was presented in the *monothematic annual Combo Endo Course 2018*. This challenging part of endocrinology is constantly expanding particularly during the last decade, with the new oncological therapeutic agents, targeting novel molecular pathways in the process of malignancies. In this new context of drug-induced endocrine disease, clinicians should be aware that drugs can cause endocrine abnormalities via different mechanisms and mimic a variety of clinical scenarios. Therefore, it is extremely important for clinicians not only to promptly recognize drug-induced hormonal and metabolic abnormalities, but also to address the therapeutic issues for timely intervention.

*European Journal of Endocrinology*  
 (2019) **181**, R1–R34

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## Introduction

The endocrine system with its precise interactions through multiple mechanisms maintains homeostasis in every system and organ. In the currently overwhelming era of polypharmacy (1), the balance of the dynamic endocrine system can be disturbed by multiple factors like drugs and medications which can lead to endocrine and metabolic abnormalities.

It is estimated that 10% of the population and 30% of older adults in the United States are taking five or more drugs systematically (2, 3). As a result, drug-related morbidity has been highlighted as a major burden of healthcare systems. In the United States, adverse drug reactions are responsible for four hospitalizations per 1000 people each year (4), with associated annual costs estimated at US\$30 billion (5). Therefore, drugs can be a double-edged sword for our patients' wellbeing and a broadening challenge to our clinical practice.

Drugs can cause endocrine abnormalities via different mechanisms, including direct alteration of hormone production, changes in the regulation of the feedback axis and on hormonal transport, binding, signaling, as well as similar changes to counter-regulatory hormone systems (6). Furthermore, drugs can interfere with the hormonal assays, leading to erroneous laboratory results that disorientate clinicians from the right diagnosis (7).

The purpose of this review is to delineate a 'combo' overview of a contemporary spectrum of drugs, encountered in clinical practice, which induce endocrine and metabolic disorders. In this approach, an effort is made to go beyond a list of adverse effects and via understanding the underlying pathophysiological mechanisms to recognize the drug-induced hormonal and metabolic abnormalities leading to endocrinopathies and diabetes. Conclusively, we aim to raise the clinicians' vigilance in promptly recognizing drug-induced endocrinopathies and diabetes, in order to make it an integral part of clinicians' differential diagnosis, emphasizing the indisputable role of meticulous medical history in order to make the appropriate decision for the therapeutic intervention.

Table 1 summarizes some of the most commonly used drug categories that will be analyzed in the following text, along with their broad spectrum of endocrine side effects.

## Drug-induced pituitary dysfunction

### Drug-induced hypopituitarism

The immune therapies in advanced cancers with immune checkpoint (ICP) inhibitors have led to a great relief and much greater hope in patients and physicians (8). In the past 15 years, ICP inhibitors have emerged as a promising and expanding class of anticancer agents, and their use has resulted in the alteration of the natural history of certain types of cancer (9, 10).

Along with the promising results in the patients who respond to these therapies, the modulation of immune response can result in a number of immune-related adverse events (IRAEs) affecting almost all organ systems. Typically, IRAEs affect the skin, gastrointestinal system, the lung, musculoskeletal, renal and nervous system. Interestingly, endocrine system IRAEs are also commonly involved. The most common of them include hypophysitis and thyroid dysfunction; rare cases of insulin-dependent diabetes mellitus, hypoparathyroidism and primary adrenal insufficiency (adrenalitis) have been reported (11, 12, 13, 14, 15).

#### *Autoimmune hypophysitis related to immune checkpoint (ICP) inhibitors*

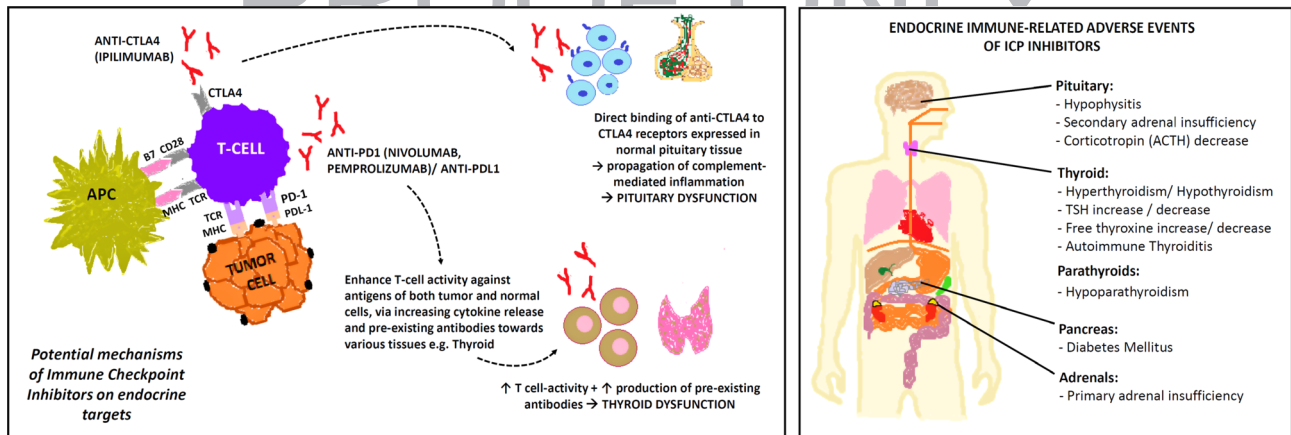
Immune check point signaling pathways are critical in regulating T-cell activation and immune tolerance. Two pathways seem to be important: CTLA4 checkpoint pathway and PD-1/PD-L1 checkpoint pathway (programmed cell death 1/programmed cell death 1 ligand). Immune checkpoint proteins are T-cell surface receptors that serve in maintaining the immune self-tolerance and preventing the development of autoimmune disorders (9, 10). The first signal of the normal T-cell activation involves the binding of a T-cell receptor to the major histocompatibility complex (MHC) presenting an antigen on an antigen-presenting cell (APC). The second signal involves the binding of a T-cell CD28 receptor to the B7 ligand on the APC. CTLA4 receptors on the surface of T cells are able to compete with CD28 for binding to the B7 ligands, thus inhibiting T-cell-mediated immune responses. ICP inhibitors are monoclonal antibodies that block the proteins from binding to the tumor cells and APCs, thereby taking off the brake and allowing the T-cell to recognize and attack the tumor cells (Fig. 1).

The use of CTLA4 and PD1/PDL1 antibodies allows the activation of T lymphocytes who set sight on the endocrine glands causing thyroid dysfunction in 15%, hypophysitis



**Table 1** Commonly used drug categories with broad endocrine side effects.

	Immune checkpoint inhibitors	Opioids	Psychotropics	Antiepileptic drugs	Glucocorticoids	Anabolic androgenic steroids	Oral contraceptives	Aromatase inhibitors	Androgen deprivation therapy	Antihypertensives	Cytotoxic agents
Drug-induced pituitary dysfunction	+	+				+					
Drug-induced SIADH	+	+	+	+						+ (verapamil, methyl dopa)	+
Drug-induced hyperprolactinemia		+	+	+						+ (beta-blockers)	+
Drug-induced thyroid abnormalities	+		+	+						+ (thiazides)	+
Drug-induced calcium and vitamin D deregulation	+		+	+	+					+ (loop diuretics)	+
Drug-induced osteoporosis		+	+	+	+			+			+
Drug-induced obesity		+	+	+	+			+			+
Drug-induced diabetes	+		+	+	+			+		+ (calcium channel blockers, diazoxide, clonidine)	+
Drug-induced dyslipidemia			+		+			+			+
Drug-induced adrenal dysfunction	+	+			+						+
Drug-induced pheo crisis		+	+		+						+
Drug-induced amenorrhea	+	+	+	+	+					+ (beta-blockers)	+
Drug-induced hyperandrogenemia				+	+			+		+ (spironolactone)	+
Drug-induced PCOS				+	+						+
Drug-induced male infertility and sperm abnormalities	+	+	+	+	+				+	+ (beta-blockers, spironolactone)	+

**Figure 1**

Potential mechanisms of CTLA-4 and PD-1/PDL-1 antibodies involved in antitumor immune responses, as well as in major endocrine targets, translated into the main endocrine adverse associated with immunotherapy.

in 9–11%, adrenalitis in 1% and diabetes type 1 in 1% (11, 16, 17, 18). The incidence of hypophysitis after treatment with CTLA-4 antibodies (ipilimumab, tremelimumab) is about 11–12% and is rarer with drugs targeting PD-1 (nivolumab, pembrolizumab) and PDL1 (atezolizumab, durvalumab, avelumab). Recently, the first report on central diabetes insipidus associated with anti-PDL1 treatment has been published (19). ICP inhibitor-induced anterior pituitary hypophysitis presents insidiously with subtle symptoms and with mild-to-moderate pituitary enlargement. Headache and fatigue are the leading symptoms. Most endocrinologists are seeing these patients as a result of referrals from oncologists because of low T4 and TSH. The majority of endocrinopathies are identified with hormonal screening, as most symptoms are typically related to cancer, masking the symptoms of

endocrinopathies. (Fig. 1). Rarely, its clinical presentation may be acute, with headache, vomiting and visual field defects, requiring prompt therapeutic management.

Anterior pituitary hypophysitis is accompanied with hypopituitarism. Not so rarely, isolated adrenocorticotropic hormone (ACTH) deficiency may be observed in these patients. Analogously, isolated interruption of TSH synthesis and secretion can be observed, as well. Apart from immunotherapy, there is a respectable subset of drugs that suppresses TSH either at the level of pituitary or hypothalamus (Table 2). Not all cause clinically significant central hypothyroidism. Glucocorticoids, somatostatin analogs and dopamine agonists suppress TSH but do not cause clinically significant hypothyroidism, while rexinoids (bexarotene) induce clinically significant central hypothyroidism, which requires replacement

**Table 2** Drug-induced suppression of TSH and underlying pathogenetic mechanisms.

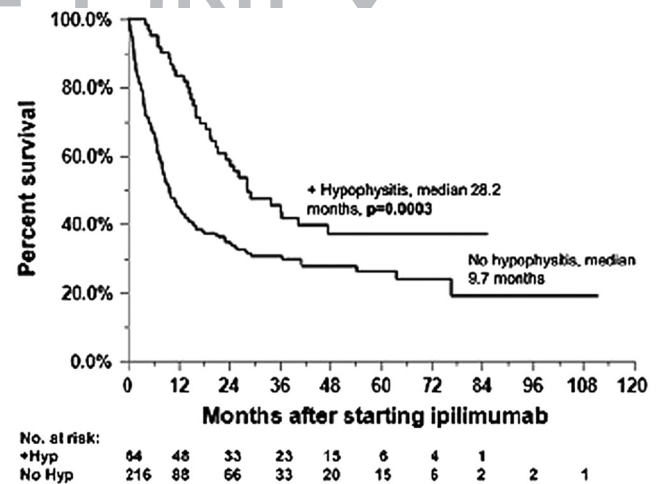
Drug class	Mechanism of action	Clinically significant hypothyroidism
Drug-induced suppression of TSH and underlying pathogenetic mechanisms		
Glucocorticoids	Activation of glucocorticoid receptor. Inhibition of TRH synthesis/secretion.	No
Dopamine agonists	Activation of dopamine receptors (D2) on thyrotropes. Reduced TSH pulse amplitude.	Probably not. May cause hypothyroidism in patients with euthyroid sick syndrome.
Somatostatin analogs	Activation of somatostatin receptors in thyrotropes. Inhibition of TSH secretion.	No
Rexinoids	Probable altered thyroid hormone metabolism. Activation of retinoid X receptor (RXR). Inhibition of TSH $\beta$ transcription in the pituitary. Increased peripheral metabolism of thyroid hormone	Yes

Adapted with permission from Haugen (20).

with levothyroxine (20). Metformin lowers TSH in diabetic patients with concomitant hypothyroidism (21). However, when metformin effect on TSH was studied in patients with subclinical hypothyroidism in a randomized, double-blind, placebo-controlled clinical trial, no significant reduction of TSH was found between the placebo and the metformin group (22).

Recovery from pituitary deficiencies is variable. ACTH deficiency persists in 86–100% of cases, while 13–36% of patients continue to have TSH deficiency and 13–53% a gonadotropin deficiency (18, 23). Features of hypocortisolism may be vague, such as nonspecific tiredness (24). A case of transient ACTH-dependent Cushing syndrome, which appeared after combined ipilimumab and nivolumab therapy, was characterized by spontaneous regression of hypercortisolism and subsequent appearance of severe corticotroph deficiency (25). Morning cortisol should be measured in a patient receiving ICP inhibitors who is unwell. Acute cortisol deficiency may be life-threatening and early recognition and appropriate management is essential. Recent UK guidelines present endocrine assessment and management of acute life-threatening endocrine complications of ICP inhibitor therapies (26). Glucocorticoid replacement is suggested with the usual replacement dose of hydrocortisone (10+5+5 mg) or 7.5 mg prednisolone. Short-term higher doses of glucocorticoids might be beneficial for patients with visual field defects, severe hyponatremia, cranial nerve palsies and in some cases of intractable headache. Newer studies suggest that higher doses of glucocorticoids may negatively affect the antitumor efficacy of ICP inhibitors (27). Hormone deficiencies may improve except for corticotroph function. Immunotherapy can be continued once the patient is clinically stable on appropriate endocrine replacement therapy. Overall survival of patients with ipilimumab-induced hypophysitis is better versus patients without hypophysitis as shown in Fig. 2.

As for the underlying pathophysiology of ICP inhibitor-induced hypophysitis, it has been postulated that pituitary immunogenicity is mediated by CTLA-4 antigen expression by pituitary endocrine cells. This leads to complement activation and infiltration of macrophages (type II hypersensitivity reaction) and autoreactive T lymphocytes (type IV hypersensitivity reaction) (28, 29, 30, 31). The susceptibility of pituitary cells to ICP inhibitors has been recently nicely demonstrated in a patient with pituitary carcinoma resistant to all available treatments including temozolomide but responding robustly to combination ICP inhibitor therapy (32).



**Figure 2**

Overall survival is illustrated after ipilimumab monotherapy in patients who had hypophysitis (1Hyp) versus patients without hypophysitis. Reprinted from Faje *et al.* (27), Copyright (2018) with permission from John Wiley and Sons.

Conclusively, although there is great promise in immunotherapies we must not let excitement of such treatments overshadow the potential problems (33). Early recognition and appropriate management of immune-mediated endocrinopathies, and specifically hypophysitis, is essential. Once the patient is clinically stable on appropriate endocrine replacement therapy, immunotherapy can be safely continued.

### Drug-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH)

SIADH is a common cause of hyponatremia with corresponding hypo-osmolality, absence of volume depletion or of other causes of hyponatremia (normal thyroid and adrenal, no diuretics) (34). Drugs are a common cause of SIADH. Selective serotonin reuptake inhibitors and carbamazepine are the most commonly implicated drugs associated with SIADH. In a retrospective single-center study, which included 198 patients diagnosed with SIADH, five drug classes were found to be implicated in 82.3% of those patients, including antidepressants, anticonvulsants, antipsychotic drugs, cytotoxic agents, pain medications and ecstasy (35). The clinical characteristics of drug-induced SIADH are comparable between different medication classes.

The mechanisms of drug-induced SIADH include inappropriate levels of vasopressin in the state of hypo-osmolality or increased expression of the water channel

aquaporin-2 in renal collecting duct (34). The major predisposing risk factors are the patient's age, as well as the serum levels of the drug. Strategies to improve management are earlier recognition of patients with chronic hyponatremia and subtle neurological symptoms (inability to concentrate, memory problems, mental irritability, drowsiness), better analysis of predisposing factors, monitoring and treatment of hyponatremia with fluid restriction or the use of vasopressin-receptor antagonists (vaptans) (36). No known genetic risk variants for carbamazepine or oxcarbazepine-induced hyponatremia exist, but likely candidate genes are part of the vasopressin water reabsorption pathway (37).

### Drug-induced hyperprolactinemia

For the practicing endocrinologist, hyperprolactinemia is a common laboratory finding and very often it is due to the use of certain medications. Elevation of serum prolactin (PRL) concentrations above 25 µg/L (1 µg/L=21.2 µUI/mL) is very often encountered during the 'hormonal check-up' of a female patient and in most cases is not related to the hypothalamic or pituitary pathology. Therefore, measurement of serum PRL levels should only be performed in patients who have clinical signs of hyperprolactinaemia such as menstrual irregularities, fertility problems, galactorrhea or benign breast disease in women or signs of androgen deficiency (i.e. loss of libido or erectile dysfunction) in men.

When assessing a patient with symptomatic hyperprolactinemia and before performing the magnetic resonance imaging (MRI) of the pituitary one must always exclude the potential effects of medications, which lead to the excessive PRL production. By looking at the mechanisms, which govern the secretion of PRL, it is obvious that all the drugs possessing dopamine D2 receptor antagonistic effects will cause significant hyperprolactinemia (38). Nevertheless, the most frequent cause of a drug-induced hyperprolactinemia is due to the use of estrogen-containing oral contraceptives (OCs) (39, 40). These drugs, which usually contain the potent estrogen ethynylestradiol are very often the cause of a moderate hyperprolactinemia (<100 µg/L). These cases usually do not require treatment but should be re-evaluated after the cessation of the OCs use. Nevertheless, it must be stressed that after the withdrawal of OCs mild elevation of serum PRL levels might also be observed as in the case in women after pregnancy (in the post-partum period) (41).

When the mechanism of drug-induced hyperprolactinemia are due to the inhibition of

dopamine action (dopamine receptor antagonists), serum PRL concentrations are significantly elevated and in some cases can also reach values over 200 µg/L (42). The most common are the typical antipsychotics (i.g. phenothiazines or butyrophenones) and risperidone or its analogs (43, 44). Nevertheless, drugs such as tricyclic antidepressants (i.e. doxepin and amitriptyline), selective serotonin reuptake inhibitors (i.e. fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine), antihypertensives (i.e. verapamil, methyldopa) and opiates (i.e. tramadol, buprenorphine, methadone) can also cause moderate elevations of serum PRL concentrations (45, 46, 47, 48). The drugs are listed in Table 3.

In order to rule out drug-induced hyperprolactinemia, it is recommended to discontinue the medication for at least 3 days or substitute it with an alternative drug and then re-evaluate serum PRL concentrations. If the discontinuation of the drug is not possible or the onset of hyperprolactinemia does not correspond with its initiation, a MRI of the pituitary should be performed in order to rule out the presence of a pituitary or a para-sellar mass (41).

When asymptomatic, drug-induced hyperprolactinaemia usually does not require treatment. If symptomatic (i.e. galactorrhea, amenorrhea, bone loss or androgen deficiency symptoms in men), it is recommended to substitute for a drug with similar action, which does not cause hyperprolactinaemia (i.e. aripiprazole – an antipsychotic drug with both dopamine agonist and antagonist activity) (49). If this is not possible one might consider the cautious administration of a dopamine agonist (i.e. bromocriptine or cabergoline), however, always in consultation with the patient's psychiatrist. Dopamine agonists have been shown to normalize serum PRL concentrations of such patients but on the other hand pose a risk of the exacerbation of the psychotic symptoms (50). When the signs of hypogonadism related to the drug-induced hyperprolactinaemia are evident (i.e. amenorrhea in women or androgen deficiency symptoms in men) or there is an increased risk of bone loss, it is recommended to add estrogen or testosterone replacement therapy (51). Asymptomatic, drug-induced hyperprolactinaemia usually does not require treatment.

### Opiate-induced endocrinopathies

Opioids include the naturally occurring alkaloids of opium or synthetic chemicals that bind to opioid receptors. Their effects are generated after binding to G-protein-coupled receptors and in clinical practice, they are mainly used as

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**Table 3** Drugs inducing moderate or significant hyperprolactinemia.

Drug class	Drugs
Drugs causing moderate hyperprolactinemia (PRL <100 µg/L)	
Estrogens	OCs
Estrogen replacement therapy	
Tricyclic antidepressants	Doxepin, Amitriptyline
Selective serotonin reuptake inhibitors	Fluoxetine, Paroxetine, Sertraline, Citalopram, Fluvoxamine
Antihypertensives	Verapamil, Methyldopa
Opiates	Tramadol, Buprenorphine, Methadone
Drugs causing significant hyperprolactinemia (PRL >200 µg/L)	
Antipsychotic drugs	Phenothiazines (chlorpromazine, levomepromazine, perphenazine, thioridazine)
	Butyrophenones (haloperidol, benperidol)
	Risperidone, Paliperidone
	Promethazine (phenothiazine derivative)
First generation anti-histamines	Domperidone (butyrophenone derivative)
Anti-emetics	Metoclopramide

OCs, oral contraceptives.

analgesic agents. Heroin is used as a recreational drug due to its euphoric effects (illicit use). The use of opioids has risen substantially in the last two decades, between 2000 and 2014, it increased by 216% in USA and 210% globally (52). Exogenous opioids can have various effects on the endocrine system, and we will focus on the most clinically significant ones (hypothalamo–pituitary–gonadal and hypothalamo–pituitary–adrenal axes).

#### *Hypothalamo-pituitary-gonadal axis*

Studies on healthy human volunteers and on patients using opioids for therapeutic purposes or as medication-assisted addiction treatment or as a drug of abuse and dependence have shown their suppressive action on the hypothalamo–pituitary–gonadal (HPG) axis (53, 54). The pathophysiological mechanism involves reduction of the release or disruption of the normal pulsatility of gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, as well as decrease of the release of gonadotrophins from the pituitary gland and of testosterone or estradiol from the gonads (53, 55). Negative effects of opioids on the kisspeptin-induced rise in the luteinizing hormone (LH) pulse amplitude may also be implicated (56). Hyperprolactinemia that has been occasionally found in opioid users, also contribute to the suppressive effects on the HPG axis (53). Direct actions on the gonads have also been reported with reduction in the production of sperm, testicular interstitial fluid and intratesticular testosterone (57).

The reported prevalence of hypogonadism ranges between 21 and 86% (55). The initial studies on this field involved heroin addicts and patients on methadone for

maintenance and had shown decrease in testosterone levels in males, as well as reduction in LH and/or follicle-stimulating hormone (FSH) (58). Amenorrhea and galactorrhea in female heroin addicts have been described in one case series (59), but series systematically assessing this group are not available. Hypogonadism has also been found in patients of both sexes on opioids (oral, transdermal or intrathecal) for cancerous or non-cancerous pain (55). The hormonal changes start as soon as the opioid is taken and they are dose related (60, 61, 62, 63). Clinical manifestations include erectile dysfunction, decreased libido, infertility, fatigue, depression, hot flushes and night sweats in males and reduced libido, amenorrhea or oligomenorrhea with anovulation in premenopausal females. It is of note that chronic use of long-acting opioids is associated with greater odds of androgen deficiency compared to chronic use of short-acting ones (63, 64). Reduction in the dose or cessation of opioid leads to reversal of hypogonadism (65, 66, 67), but the time course of this has not been systematically assessed.

#### *Hypothalamo-pituitary-adrenal axis*

Opioids suppress the hypothalamo–pituitary–adrenal (HPA) axis mainly at the hypothalamic–pituitary level by inhibiting corticotrophin-releasing hormone (CRH) and vasopressin secretion and by reducing their effect on ACTH and cortisol release (55). It has been shown that even single administration of various opioids in normal subjects suppresses ACTH and glucocorticoid secretion, leads to blunted pituitary–adrenal response to CRH and diminished cortisol response to psychosocial or surgical stress (68, 69, 70).

Although several case reports documenting secondary adrenal insufficiency after oral or transdermal opioid administration have been published (66, 67, 71, 72), the accurate prevalence of adrenal insufficiency in these patients has not been clearly defined. Gibb *et al.*, in a series of 48 patients attending chronic tertiary pain clinics and treated with long-term opioid analgesia for at least 6 months and no recent exposure to exogenous glucocorticoids, found failure to respond to synthetic ACTH stimulation in 6% (73). Abs *et al.* in a series of 72 patients on intrathecal administration of morphine or hydromorphone reported peak cortisol <18µg/dL on insulin tolerance test (ITT) in 15% (62).

Factors predicting compromised cortisol stress response have not been as yet established. Nonetheless, given, the widespread use of opioids, a large number of patients are possibly on risk of cortisol deficiency. The altered HPA axis function of opioid users improves or returns to normal after discontinuation or reduction in the dose of the opioid (53, 72, 73), but the interval of this has not been systematically reviewed. Although an evidence-based guidance is not available, patients on opioids should be considered at risk of hypoadrenalism and checking an early morning plasma cortisol (particularly if relevant clinical manifestations are present) is advised. Further dynamic assessment of the HPA axis will depend on the results of the basal cortisol.

## Drug-induced thyroid abnormalities

### Thyroid dysfunction secondary to cancer immunotherapy

In patients treated with ICP inhibitors, thyroid dysfunction can be primary or secondary (related to hypophysitis), and it is therefore important for the clinician to distinguish between the two entities. It is possible that disruption of immune tolerance via PD1/PDL1 is responsible for the development of thyroid IRAEs; however, the exact mechanisms remain unclear. It has been hypothesized that polymorphisms in the *CTLA-4*, *PDI* or *PDL1* genes may lead to a higher incidence of autoimmune thyroid disorders and hypophysitis (15, 74, 75, 76). Whether the presence of thyroid auto-antibodies has a pathogenetic role is also unclear, although an increase in thyroid antibodies has been reported in patients with pembrolizumab-induced thyroiditis (77). In another report, pembrolizumab-induced thyroiditis was

thought to be mediated by circulating CD56, CD16 and NK cells (15).

Primary thyroid dysfunction is usually related to painless thyroiditis presenting with an initial phase of thyrotoxicosis due to the release of thyroid hormone as a result of thyroid gland inflammation, followed by a hypothyroid phase. As the thyrotoxic phase is commonly asymptomatic, it may be missed and the patient may present with primary hypothyroidism (i.e. with an elevated TSH and low or normal free T4). The diagnosis of secondary (central) hypothyroidism is on other hand suspected when the free T4 level is low and TSH is low or low-normal. Graves' orbitopathy with or without associated hyperthyroidism may rarely occur (78, 79, 80).

The incidence of primary hypothyroidism with CTLA4 antibody treatment (ipilimumab) ranges from 5.2 to 5.9%, with 'thyroiditis' been reported in 3.2%, whereas secondary hypothyroidism due to hypophysitis is more common (7.6%) (10, 11, 14, 17). With PD1/PDL1 inhibitor use, primary hypothyroidism is observed in 5.9/4.3% and primary hyperthyroidism in 3.3% of cases (10). When both classes of ICIs are used in combination, thyroid dysfunction (of any cause) is even more common, with a mean incidence of 13.9% for hypothyroidism and 8.0% for hyperthyroidism, in earlier studies (81, 82, 83, 84). More recent studies report rates of primary thyroid dysfunction as high as 14–20% with combination ICP inhibitors treatment (74). The natural history of ICP-related thyroiditis was studied in a recent large retrospective study from MD Anderson Cancer Center (85); 657 patients with normal baseline thyroid function who developed thyrotoxicosis due to ICP inhibitors use were included. Overall, 84% of patients developed hypothyroidism and only 9% eventually recovered from transient hypothyroidism. The median time to thyrotoxicosis was 5.3 weeks (0.6–19.6) and the median time to hypothyroidism was 10.4 weeks (3.4–48.7). The majority of patients in this study were asymptomatic during the thyrotoxic phase and no patient had to discontinue ICI treatment (85). In an analogous study by Lee *et al.*, it was confirmed that thyroiditis is the most common thyroid disorder induced by ICP inhibitors use. The time to onset of thyrotoxicosis after treatment initiation and evolution of thyrotoxicosis to hypothyroidism was short, emphasizing the importance of close monitoring of thyroid function in these patients (86).

Recent oncology guidelines provide detailed guidance on appropriate screening and management of endocrine IRAEs; regular thyroid function testing is recommended

every 4–6 weeks (87, 88). Endocrine consultation is advised for patients who develop thyroiditis or hypophysitis. During the thyrotoxic phase, before progression to hypothyroidism, no specific treatment is usually required. In patients with symptoms such as tachycardia or tremor, symptomatic treatment with  $\beta$ -blockers may be used. Glucocorticoids are not routinely recommended. Thyroid replacement with levothyroxine is indicated for patients who develop hypothyroidism. The median dose of levothyroxine in one recent study, was 1.2  $\mu\text{g}/\text{kg}$  (as compared to the usual dose of 1.6  $\mu\text{g}/\text{kg}$  in other forms of primary hypothyroidism) (85). Lower starting doses (25–50  $\mu\text{g}$  daily) should be used in elderly or fragile patients. Adrenal dysfunction should always be replaced before thyroid therapy is initiated to prevent Addisonian crisis. Importantly, cancer immunotherapy does not usually need to be discontinued, unless the patient's symptoms are severe and the event is CTCAE (Common Terminology Criteria for Adverse Events) grade  $\geq 3$ , in which case ICI therapy can be withheld and restarted when the grade has improved to  $< 1$ . For persistent hyperthyroidism or when there is clinical suspicion, measurement of thyroid-stimulating immunoglobulin (TSI) or TSH receptor antibodies (TRAbs) and thyroid scintigraphy may be arranged to rule out Graves' disease. When secondary hypothyroidism develops as a result of hypophysitis, recovery is possible (in 6–64% of cases), whereas secondary adrenal insufficiency is usually permanent.

Apart from cancer immunotherapy, alemtuzumab, a monoclonal antibody used in multiple sclerosis (MS) has also been associated with thyroid dysfunction. Specifically, TRAb-positive hyperthyroidism is reported with a frequency of 20–30% in these patients, with its management being similar to 'wild-type' Graves' disease (89).

### Tyrosine kinase inhibitors-induced thyroid disorders

Tyrosine kinase inhibitors (TKIs) have been established as a crucial therapeutic stepping stone in anticancer therapy. Via targeting different receptors, they manage to attenuate cancer cell survival and growth, invasiveness and angiogenesis in multiple cancer entities. One of the most common side effect of TKIs is thyroid dysfunction, accompanied by an important prognostic value, as median progression-free survival and overall survival has been shown to be much better in patients who developed hypothyroidism on TKI therapy, as compared to patients who remained euthyroid (90).

Many mechanisms with respect to this adverse effect have been proposed including their induction of thyroiditis, capillary regression in the thyroid gland, antithyroid peroxidase antibody production and their ability to decrease iodine uptake by the thyroid gland (91). Thus, TKI therapy should be accompanied by a thyroid hormonal evaluation before their initiation, as well as monitor thyroid function during and after the end of treatment (92).

### Psychotropics-induced thyroid abnormalities

Despite their potent effect in various psychiatric disorders, psychotropic drugs, particularly antidepressants and antiepileptics may induce thyroid dysfunction. In a study looking into the risk of hypothyroidism over 4 years of treatment, the cumulative risk of hypothyroidism for lithium (8.8%) was 1.39-fold that of the therapy presenting the lowest risk with oxcarbazepine (6.3%) (93). Lithium conferred a higher degree of risk for hypothyroidism when compared with other treatments (lamotrigine, valproate, oxcarbazepine or carbamazepine) or antipsychotics (aripiprazole, olanzapine, risperidone or quetiapine) (93). Lithium is usually effective either as monotherapy or as combined treatment. However, the drug may rapidly, within 3–4 weeks, induce goiter by inhibiting thyroid hormone secretion and increasing TSH, particularly in females and also dependent on dose and duration of treatment (94, 95). It was shown in different cell lines that lithium activates canonical Wnt signaling and inhibits GSK-3 $\beta$ , suggesting a crucial role of Wnt/ $\beta$ -catenin signaling in lithium-dependent thyrocyte proliferation (96).

Furthermore, a recent cross-sectional study including 298 patients with epilepsy, 52 (17.4%) showed low fT4 with older age ( $P=0.004$ ), female sex ( $P=0.014$ ), longer duration of epilepsy ( $P=0.001$ ) and intractable epilepsy ( $P=0.009$ ), which is strongly associated with low fT4 (97). The drugs carbamazepine (30.1%), topiramate (28.6%) and levetiracetam (24.3%) or a combination of more than three drugs was significantly associated with decreased thyroid function. Based on these findings and other studies, it is recommended that patients under antiepileptics should be monitored for thyroid dysfunction.

In the event of undiagnosed hypothyroidism, even of a mild degree, a higher risk of serotonin syndrome or of neuroleptic malignant syndrome (NMS) may be documented (98). Serotonin syndrome is caused by drugs that inhibit the release or the reuptake of serotonin, serotonin-norepinephrine reuptake inhibitors (SNRIs),

selective serotonin reuptake inhibitors (SSRIs), as well as monoamine oxidase inhibitors (MOI), which retards the catabolism of 5-HT by inhibiting the catalytic enzyme monoamine oxidase (97). Given that reduced 5-HT responsiveness and increased 5-HT turnover in the brainstem have been reported in hypothyroid patients, it is conjectured that severe hypothyroidism may impair the degradation of 5-HT (99). Simultaneously, while primary hypothyroidism is thought to predispose to NMS by altering dopamine activity in central tracts susceptible to neuroleptics blockade (98), thyroid hormone administration could completely reverse the clinical picture. It is thus recommended that patients under psychotropic drug treatment and whose clinical picture is unclear should have their thyroid function assessed.

**Table 4** Amiodarone basic characteristics and properties.

#### Amiodarone characteristics

- Amiodarone is derived from Amphiphilic Benzofurane, with a long plasma half life, ranging from 30 to 100 days.
- Iodine comprises 37% of its molecular weight, 8–17% of which is released as free iodide.
- Highly lipophilic, concentrates in adipose tissue, muscles, liver, lungs, cornea & thyroid gland mainly.
- Inhibits type 1 5'-deiodinase enzyme activity, thereby decreasing the peripheral conversion of T4 to triiodothyronine (T3) and reducing the clearance of both T4 and reverse T3 (rT3). Consequently, the serum levels of T4 and rT3 increase and the serum levels of T3 decrease by 20–25%.
- Inhibits entry of T4 and T3 into the peripheral tissue, via inhibiting thyroid hormone transport across the plasma membrane, and via directly binding to the thyroid hormone receptors. Serum T4 levels increase by an average of 40% above pretreatment levels after 1–4 months of treatment with amiodarone.
- Inhibition of type 2 5'-deiodinase enzyme activity in the pituitary due to feedback mechanism is observed in the first 1–3 months and leads to an increase in thyroid-stimulating hormone (TSH) levels. This is not an indication for T4 replacement in these patients. Serum TSH levels return to normal in 2–3 months as T4 concentrations rise sufficiently to overcome the partial block in T3 production.
- The response of TSH to TRH may be reduced.
- Amiodarone and its metabolites may have a direct cytotoxic effect on the thyroid follicular cells, which causes a destructive thyroiditis.
- Amiodarone and its metabolite, desethylamiodarone, can act as a competitive antagonist of T3 on cardiomyocytes.

#### Amiodarone properties

- A. Antiadrenergic properties
  1. Alpha-blocking (vasodilation)
  2. Beta-blocking (bradycardia)
- B. Cytotoxic effects by
  1. Lysis
  2. Oxidative stress
  3. Antigen release
- C. Immunomodulatory properties
  1. Emergence of sensitized lymphocyte subsets

### Amiodarone-induced thyroid disorders: therapeutic particularities

Amiodarone is a potent antiarrhythmic drug with a number of side effects, including thyroid dysfunction. Thyroid abnormalities have been noted in up to 14–18% of patients receiving long-term amiodarone therapy. However, a meta-analysis suggested that with the lower doses of amiodarone (150–330 mg) the incidence of thyroid dysfunction is 3.7%. The effects range from abnormal thyroid function tests to overt thyroid dysfunction, which may be either amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH) (100, 101, 102). Both pathologies can develop in apparently normal thyroid glands or in glands with preexisting abnormalities. Pathophysiologically, amiodarone effects in the thyroid gland and its metabolism are both unique and quite complex and occur via a number of differing mechanisms. Thyroid dysfunction linked to amiodarone is not only related to iodine overload, secondary to the exposure of increased iodine levels from amiodarone, but also to the intrinsic effects of amiodarone to the thyroid hormone metabolism (102) (Tables 4 and 5).

### Drug-induced bone and calcium metabolism deregulation

#### Drug-induced deregulation of calcium and vitamin D metabolism

More and more drugs have been found to interact with vitamin D and calcium metabolism affecting bone health of patients and making this topic of increasing interest. Most of these drugs act through the pregnane X receptor (PXR) to mediate their effects on vitamin D metabolism.

PXR is a nuclear receptor, which is expressed in various tissues among them the gastrointestinal tract, kidneys and liver and shows 63% homology with the vitamin D receptor in the DNA-binding domain. Thus, it can bind to vitamin D-responsive elements (VDREs) at the promoter of genes that are normally regulated by vitamin D, such as those encoding enzymes which are implicated in the metabolism of vitamin D. A long list of drugs can affect vitamin D metabolism acting mainly as PXR ligands among them, antiepileptic, antiretroviral, antineoplastic (taxol, cyclophosphamide), antihypertensive (nifedipine) and antibiotics (cotrimoxazole, rifampicin) (103). It is of interest that herbal medicine such as St John's wort can also activate PXR (103).

**Table 5** Amiodarone-induced thyroid dysfunction: classification, pathophysiology and management.

#### A. Amiodarone-induced hypothyroidism (AIH)

##### Characteristics

- Affects 4–22% of the treated population.
- The most likely mechanisms of AIH are an enhanced susceptibility to the inhibitory effect of iodine on thyroid hormone synthesis and the inability of the thyroid gland to escape from the Wolff–Chaikoff effect after an iodine load in patients with preexisting Hashimoto thyroiditis. In addition, iodine-induced damage to the thyroid follicles may accelerate the natural trend of Hashimoto thyroiditis toward hypothyroidism.
- Patients without underlying thyroid abnormalities are postulated to have subtle defects in iodine organification that lead to decreased thyroid hormone synthesis, peripheral downregulation of thyroid hormone receptors and subsequent hypothyroidism.

##### Management

LT-4 therapy, with gradual introduction. It improves quality of life and regulates lipid levels. Thyroid panel monitoring is strongly advised.

#### B. Amiodarone-induced thyrotoxicosis (AIT)

##### Characteristics

Type 1: usually affects patients with latent or preexisting thyroid disorders and is more common in areas of low iodine intake. It is caused by iodine-induced excess thyroid hormone synthesis and release (JodBasedow phenomenon).

Type 2: occurs in patients with a previously normal thyroid gland and is caused by a destructive thyroiditis that leads to the release of preformed thyroid hormones from the damaged thyroid follicular cells.

Mixed forms of AIT may occur in an abnormal thyroid gland, with features of destructive processes and iodine excess.

##### Management

Depends on the type of AIT. Type 1 AIT is treated with high doses of antithyroid drugs to block thyroid hormone synthesis, while type 2 AIT is treated with a relatively long course of glucocorticoids. When the mechanism of hyperthyroidism is uncertain, a combination of glucocorticoids and thionamides is used as initial therapy. Thyroid panel monitoring is strongly advised.

#### Antiretroviral therapy

Antiretroviral therapy (ART) is mainly responsible for the alterations in vitamin D metabolism, acting as PXR ligands, although there are slight differences in their mode of action. They induce cytochrome P450 altering thus the activity of several enzymes in this family. These include CYP24A1 which acts mainly at the liver and converts both 25(OH)D and its active form calcitriol (1,25(OH)<sub>2</sub>D), to their inactive metabolites. They can also induce other cytochrome P450 enzymes involved in the biotransformation of active substances (e.g. CYP3A4).

Additionally to the aforementioned mechanisms, protease inhibitors (PIs), have been shown to suppress CYP2R1 and CYP27B (encoding for 25-hydroxylase and 1- $\alpha$ -hydroxylase respectively) in a dose-dependent manner, resulting thus in a decrease of 1,25(OH)<sub>2</sub>D levels (104, 105). Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), is the antiretroviral drug most involved in lowering vitamin D levels.

Cross-sectional and longitudinal studies have showed that efavirenz is associated with low 25(OH)D levels (106, 107, 108). Nylen *et al.* showed that the prevalence of vitamin D deficiency (<10 ng/mL) increased from 27 to 43% at 48 weeks in patients initiating EFV-based ART (108). Apart from efavirenz, another ART regimen, zidovudine, a nucleotide reverse transcriptase inhibitor (NRTI), was associated with vitamin D deficiency, as MONET trial showed (109). In the same study, participants who changed from efavirenz or zidovudine to regimen with boosted PI (darunavir) achieved the greatest increase in vitamin D levels (109).

According to the latest version of the European AIDS Clinical Society Guidelines, vitamin D screening in patients receiving ARTs associated with low vitamin D levels is recommended (110). Recent studies in participants receiving EFV or TDF-cART showed that a dosage supplement of 50,000–60,000 IU per month was enough to reach the goal of 25(OH)D  $\geq$ 30 ng/mL after 6 months (111, 112).

#### Antiepileptic drugs

Among the conventional AEDs, early reports have focused on inducers of cytochrome P450 (CYP) enzyme such as carbamazepine, phenobarbital, phenytoin and primidone that can activate the PXR, increasing vitamin D metabolism and eventually leading to hypocalcemia and secondary hyperparathyroidism (113). In a total of 600 patients receiving AEDs, 45% had 25(OH)D level <20 ng/mL while deficiency was present in 54% of enzyme-inducing and 37% of non-enzyme-inducing antiepileptic drug groups (114). Interestingly, Tombini *et al.* found that patients taking multiple AEDs had lower levels of 25(OH)D than patients taking single therapy, with 25(OH)D levels depending on treatment duration (115).

To date, there is lack of robust clinical studies to evaluate the effects of conventional and newer AEDs on vitamin D levels, in order to suggest the appropriate use of vitamin D supplementation. According to the Endocrine Society Clinical Practice Guideline, patients on medications affecting vitamin D metabolism are suggested

to receive a higher dose (two to three times higher; at least 6000–10,000IU/day) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/mL, followed by maintenance therapy of 3000–6000IU/day (116).

#### *Antiresorptive drugs for osteoporosis and hypocalcemia*

The risk of symptomatic hypocalcemia in patients with osteoporosis receiving antiresorptive drugs is small. Case reports and retrospective analyses have identified a number of risk factors associated with the development of hypocalcemia in those receiving inhibitors of bone resorption; these include malnutrition, malabsorption, renal insufficiency, hypomagnesemia, vitamin D deficiency and bone metastasis usually treated with higher dosage of bisphosphonates and denosumab (117).

Body *et al.* reported that the type of cancer (with small-cell lung cancer and prostate being the most common), creatinine clearance <60 mL/min, higher alkaline phosphatase levels, emerge as factors that are significantly associated with the risk of developing hypocalcemia among denosumab-treated patients participating in three identically designed phase 3 trials of denosumab 120 mg s.c. (118). Moreover, hypocalcemia occurs more frequently in patients receiving denosumab than in those receiving zoledronic acid and during the initial stages of therapy, but 'stabilizes' thereafter, irrespective of the duration of exposure (119).

#### *Calcimimetics*

Cinacalcet is a known allosteric activator of the calcium-sensing receptor which can decrease parathyroid hormone (PTH) secretion by the parathyroid glands.

A recent meta-analysis of 24 RCTs (including 10,031 dialysis patients) confirmed the significant higher risk of hypocalcemia (120). Moreover, a post hoc analysis of the randomized, double-blind, placebo-controlled Evaluation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events (EVOLVE) trial showed an increased incidence of at least one episode of hypocalcemia developed within 16 weeks after the first administered dose in patients randomized to cinacalcet compared to those randomized to placebo (58.3 vs 14.9%, respectively) (121).

#### *Glucocorticoids*

It is well known that glucocorticoids reduce 1,25-(OH)<sub>2</sub>D<sub>3</sub> levels via disturbing its biosynthetic and catabolic enzymes. In particular, glucocorticoids decrease the CYP27B1, while enhance the expressions of CYP3A1, CYP24A1 the dominant enzymes for vitamin D degeneration, resulting in vitamin D depletion and consequently in reduced intestinal calcium absorption. Moreover, independently of 1,25(OH)<sub>2</sub>D<sub>3</sub>, glucocorticoids can decrease the transcellular pathway of intestinal absorption via reducing duodenal transient receptor potential vanilloid subfamily member 6 (TRPV6), Calbindin-9k (CB9k) and plasma membrane calcium ATPase 1b (PMCA1b) expression (122). According to the Endocrine Society Clinical Practice Guideline, glucocorticoids are included in the medications affecting vitamin D metabolism, thereby patients taking glucocorticoids are suggested to receive a higher dose (two to three times higher) to maintain vitamin D sufficiency (116).

#### *Antineoplastic drugs*

Rare cases of hypocalcemia due to drug-induced either reversible/functional or irreversible hypoparathyroidism include novel drugs such as immune check point inhibitors (123) antineoplastic drugs (adriamycin, doxorubicin, cytarabine, vinblastin) (124).

### **Medication-induced osteoporosis: When to screen and treat**

Most harm concerning bone health is done by glucocorticoids, aromatase inhibitors and androgen deprivation treatment by GnRH agonists (125) (Table 6).

#### *Glucocorticoid-induced osteoporosis (GIO)*

Significant bone loss starts immediately after introducing glucocorticoid (GC) therapy. Skeletal fractures may occur within 3–6 months of starting GCs, and up to 30–50% of patients on long-term GC treatment will suffer an osteoporotic fracture (126, 127). Both high daily and high cumulative GC doses increase the risk of fracture, particularly vertebral fracture, due to the greater effects of GCs on trabecular bone than on cortical bone (128). Daily prednisolone doses of 7.5 mg or higher (or equivalent doses of other GCs) are associated with the greatest risk. However, a significantly increased fracture risk was seen even in patients with median prednisolone doses as

**Table 6** List of drugs inducing bone loss.

Hormones and drugs with actions on the endocrine system
Glucocorticoids
Thyroid hormones
Sex hormones lowering agents
Aromatase inhibitors
Medroxyprogesterone acetate
GnRH agonists
PPAR-gamma inhibitors (thiazolidinediones)
Drugs with actions on the CNS
Antidepressants (SSRI)
Anticonvulsants
Drugs with actions on the immune system
Immunosuppressants (calcineurin inhibitors)
Antiretroviral therapy
Anticoagulants
Heparin
Diuretics
Loop diuretics
Drugs with actions on the gastrointestinal tract
Proton pump inhibitors

Adapted from Mirza and Canalis (125).

GnRH, gonadotropin-releasing hormone; PPAR-gamma, peroxisome proliferator-activated receptor gamma; SSRI, selective serotonin reuptake inhibitors.

low as 2.5 mg daily. Decreased bone mass and increased fracture risk has also been demonstrated with inhaled and alternate day treatment regimens with GCs (128).

GCs adversely affect all phases of bone remodeling. Bone resorption is initially increased through various mechanisms, including decreased production of osteoprotegerin, an endogenous inhibitor of bone resorption, increased formation of RANK ligand that stimulates osteoclastogenesis and an increase in osteoclast survival. GCs also promote apoptosis of osteocytes, the mechanosensors that normally maintain bone strength by coordinating bone remodeling. Finally, as skeletal exposure to GCs continues, bone formation is suppressed by apoptosis of existing osteoblasts and decreased recruitment of new osteoblasts and a state of decreased bone remodeling ensues long term (126).

As GCs rapidly increase fracture risk, it is important to identify patients at moderate and high risk who would benefit from appropriate preventative treatment, soon after introducing GCs, during the first 6 months latest (128).

All guidelines recommend that patients treated with GCs for  $\geq 3$  months should have an optimized intake of calcium and vitamin D, together with appropriate lifestyle modifications, such as a well-balanced diet, regular weight-bearing physical activity and avoidance of alcohol and smoking. Patients with moderate and high fracture risk

should receive an oral bisphosphonate. If this treatment is inappropriate, an intravenous bisphosphonate formulation should be considered, and teriparatide if a bisphosphonate is not appropriate. Bisphosphonates are the most commonly used treatment for GIO and are generally well tolerated. The medication doses equal those used in postmenopausal osteoporosis. As the main long-lasting pathogenetic mechanism in GIO is reduced bone formation, in patients with very high fracture risk or prevalent fractures teriparatide therapy stimulating bone formation should be introduced. Teriparatide has been shown to produce superior BMD increases compared to oral bisphosphonates (129). GC treatment is a potentially reversible risk factor for osteoporosis; when GC treatment is terminated, BMD increases and fracture risk declines (127, 128, 130). Pharmacological anti-osteoporotic therapy could be stopped upon withdrawal of GC unless the patient remains at increased risk of fracture.

#### *Aromatase inhibitors in women with breast cancer and bone loss*

Aromatase inhibitors (AIs) lower aromatase activity and reduce estrogen levels by 98% (131). As oestrogens play a crucial role in bone tissue homeostasis (132) reducing oestrogens adversely affects bone quantity and quality. In contrast to GCs, AIs predominantly affect cortical bone that composes 80% of bone tissue and mostly determines bone strength. AI-associated bone loss (AIBL) leads to a marked increase of bone resorption, with a 2- to 4-fold increased bone loss compared to physiologic postmenopausal BMD loss (133). Fractures occur at younger ages and higher BMD than expected for patients in this age group without breast cancer. Even hip fracture incidence is higher and occurs earlier in postmenopausal women on AIs (134).

It is recommended that all women starting adjuvant therapy with AIs should be carefully assessed for baseline risk of osteoporotic fractures (DXA measurement; clinical risk factors) (135, 136). All patients initiating or receiving AI therapy with any two of the following risk factors should receive antiresorptive therapy: T-score  $< -1.5$ , age  $> 65$  years, low BMI ( $< 20 \text{ kg/m}^2$ ), family history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use of  $> 6$  months and current or history of smoking (135).

Several antiresorptive agents can prevent and treat AIBL including oral and i.v. bisphosphonates. Overall, the evidence for fracture prevention is strongest for denosumab 60 mg s.c. every 6 months (135, 137). Additionally, recent

studies as well as an individual patient data meta-analysis of all available randomized trial data support additional anticancer benefits from adjuvant bisphosphonate treatment in postmenopausal women with a 34% relative risk reduction in bone metastasis and 17% relative risk decrease in breast cancer mortality that needs to be taken into account when advising on management of AIBL (138).

#### *Androgen deprivation therapy in patients with prostate cancer and bone loss*

Androgen deprivation therapy (ADT) dramatically reduces testosterone and oestrogen concentrations, induces a high bone turnover with rapid bone loss similar to that in early menopause and results in an increased risk of fracture (139).

The extent of bone loss observed under ADT for prostate cancer in men receiving GnRH analogs is 4% BMD loss per year (140). Patients with untreated prostate cancer already have a high prevalence of osteoporosis (4–38%) (141). This increases to 53% in patients with prostate cancer receiving ADT (142). In a large meta-analysis of 14 trials, men who had ADT had an increased risk of overall fracture of 23% compared with men with prostate cancer who did not receive ADT (143). The fracture risk is directly correlated with the number of GnRH agonist doses given (144).

Before introducing ADT, men should be assessed for BMD, fracture risk by FRAX® tool and other secondary causes of osteoporosis. An initial low BMD (T-score <−2.5 or <−1, with other risk factors) indicates a high risk of subsequent nonmetastatic fracture. General measures for bone health should be followed. Bisphosphonates have all been shown to prevent loss of BMD in patients with prostate cancer (145). Of antiresorptive medications, 6–12 monthly zoledronic acid and 6-monthly denosumab are considered the most convenient and reliable treatments. In a placebo-controlled trial of denosumab in 1468 men receiving ADT for nonmetastatic prostate cancer, 36 months of denosumab treatment was associated with a 62% relative reduction in new vertebral fractures (1.5% with denosumab versus 3.9% with placebo) (146).

## **Drug-induced diabetes, obesity and its metabolic complications**

### **Drug-induced obesity and its metabolic consequences: focus on mechanisms and possible therapeutic options**

Modern pharmacological treatments for various medical conditions like diabetes, mental health disorders and cardiovascular disease can contribute to weight gain both in patients with and without this predisposition. It is vital that this is recognized by the medical community so that healthcare professionals warn the patient of this potential side effect.

#### *Glucose-lowering medications*

Insulin is very effective in controlling glycaemia rapidly but is also well recognized in inducing a mean of approximately 4 kg weight gain in a dose-dependent manner (147). This takes place during the first year of treatment and then tends to plateau unless further increases in dose are made. Long-acting insulin use alone tends to be more weight friendly than basal bolus regimens and there is some evidence that specific types of long-acting insulins may be better than others in this respect (e.g. detemir) (148). The mechanism appears to be multifactorial and includes the stimulation of hunger, the ‘retention’ of calories, the anabolic effects of insulin as well as snacking in order to prevent or treat hypoglycemia. Sulphonylureas and meglitinides appear to be working in similar ways, while in the thiazolidinediones group, the weight gain is via fluid retention and increase of subcutaneous fat, being dose dependent, ranging from 2 to 4 kg (149).

#### *Psychotropic medication*

Psychotropic medication may be effective for the treatment of the underlying psychopathology but can have deleterious effects on metabolic control. The weight gain happens rapidly, and a 5% increase of body weight within the first 4 weeks of initiation is a poor prognostic sign. Patients on psychotropic medication tend to overeat but also have a preference for energy-dense foods (150). The medications interfere with central neurotransmission of dopamine, serotonin, histamine and endocannabinoids in selective and non-selective ways making it challenging to be certain about the precise mechanism underlying weight gain. Antidepressants of the tricyclic/ tetracyclic

class e.g. amitriptyline, mirtazapine tend to induce more weight gain than selective serotonin reuptake inhibitors e.g. fluoxetine and citalopram (151). Antipsychotics are the most potent weight inducers among the class of psychotropic medications with patients often exceeding their ideal body weight by 20% (152).

#### *Epilepsy medications*

Drugs for epilepsy are also associated with weight gain due to their interference with central neurotransmitters and cytokines. Valproate, carbamazepine, pregabalin and gabapentin tend to cause more weight gain than lamotrigine and levetiracetam, while agents like topiramate are associated with weight loss (153).

#### *Glucocorticoids*

GCs, almost invariably associated with weight gain and possibly metabolic complications (154), also induce hepatic and peripheral insulin resistance, often resulting in the metabolic syndrome and diabetes (155).

#### *Principles of treatment*

By far the most effective treatment is discontinuation of the therapy, but this can be challenging specifically in patients who have benefited from the drug and their disease stability. If this is not feasible, then the standard principles of weight loss apply. Indeed, these could be introduced upon initiation of the relevant medication. Lifestyle modification should be performed in a supportive way, and one should consider the strong biological triggers of the weight gain. Obesity pharmacotherapy should be considered in all cases. The use of GLP-1 analogs is probably the safest option for the majority of patients and has been applied successfully in patients with mental health disorders as part of a randomized controlled trial (156). The use of centrally acting non-hormonal treatments e.g. bupropion/naltrexone, topiramate/phentermine and lorcaserin should be considered, but with caution and frequent monitoring especially in patients with mental health disease. Obesity surgery is by far the most effective treatment both for weight loss and metabolic control (157). It should certainly be considered in all patients and even those with severe mental illness as long as this is stable and there is appropriate psychological support available.

#### **Antipsychotic drugs induced diabetes (SGAs)**

In patients with preexisting diabetes, the initiation of antipsychotic drugs (SGAs) has been associated with worsening hyperglycemia (158), and in non-diabetics with weight gain, obesity, hypertriglyceridemia (159, 160, 161). A prospective randomized study, CATIE, showed that chronic treatment with different antipsychotic agents was associated with differential weight gain and changes in glucose levels (162) (Table 7). Nicol *et al.* (163) used gold-standard measures of adiposity (dual-energy X-ray absorptiometry and MRI) and insulin sensitivity (a hyperinsulinemic-euglycemic clamp) and found that 12 weeks of treatment with low-dose olanzapine, risperidone or aripiprazole in youths who were antipsychotic-naïve, produced rapid-onset adverse changes in adiposity and insulin, with larger increases in those who used olanzapine compared with those that used risperidone and aripiprazole.

Other proposed mechanisms may be more relevant to mechanisms underlying treatment-related ketoacidosis. Blockade of pancreatic beta-cell 5HT-1A receptors might contribute to hyperglycemia and pancreatitis reported with SGAs (164, 165). Alpha 2 adrenergic inhibition of insulin release has also been suggested as a possible mechanism of antipsychotic-induced hyperglycemia (166).

Tricyclic antidepressants (TCAs) have been associated with weight gain and worsening glycemia in diabetic patients (167). However, SSRIs and other antidepressants are largely weight neutral; some have been associated with weight loss and improved insulin sensitivity (168). The effect of SSRIs upon weight depends upon the specific medication prescribed and the length of treatment.

In addition, weight gain during SSRI treatment is significantly related to poor appetite at the beginning of treatment (169). Until the exact mechanisms are elucidated, it is prudent to screen for diabetes at baseline and monitor blood glucose levels at reasonable intervals during treatment with all antidepressants (170).

#### **New insights in steroid diabetes**

Hyperglycemia is one of the most important adverse effects of glucocorticoid administration (171, 172). Real estimations of the risk for steroid-induced hyperglycemia (SIH) and diabetes (SIDM) are quite difficult, as steroid formulations, treatment duration, dosing regimens and individual susceptibility may vary greatly. A large recent meta-analysis of 13 studies has shown the overall event

**Table 7** Weight and HbA1C changes, during treatment with antipsychotic agents Lieberman *et al.* (162).

Antipsychotics	Change in HbA1C (%)	Change in weight (lb)
Weight and HbA1C changes, during treatment with antipsychotic agents Lieberman <i>et al.</i> (162)		
Olanzapine	0.40 ± 0.07	9.4 ± 0.9
Quetiapine	0.04 ± 0.08	1.1 ± 0.9
Risperidone	0.07 ± 0.08	0.8 ± 0.9
Ziprasidone	0.11 ± 0.09	-1.6 ± 1.1
Perphenazine	0.09 ± 0.09	-2.01 ± 1.1

rate of hyperglycemia and diabetes among patients treated with GCs was 32.3 and 18.6%, respectively (173). Moreover, GCs approximately double the risk of developing diabetes in patients without a prior history of hyperglycemia (174).

The mechanism by which GCs cause diabetes predominantly involves insulin resistance, but  $\beta$ -cell function and insulin secretion are also impaired particularly at higher doses (175). Thus, GCs increase hepatic gluconeogenesis and glucose output, while they also inhibit glucose uptake in muscle and adipose tissue, primarily by inhibiting glucose transporter type 4. During chronic therapy, promotion of weight gain and visceral fat expansion may further contribute to their diabetogenic effects.

The initial steps to prevent development of postprandial hyperglycemia and improve glycemic control should provide dietary counseling for restriction of carbohydrates and advice for increased physical activity. Especially for temporary steroid therapy in patients without a history of diabetes or with adequately controlled diabetes, diet and lifestyle may be sufficient to achieve therapeutic goals. In the more severe cases, choice of therapy should take into account pharmacokinetics and pharmacodynamics of the used steroid compounds, as well as preexisting glycemic status and the presence of comorbidities.

In the cases where glycemia is relatively mild (<200mg/dL), together with or after lifestyle measures, hypoglycemic drugs with insulin sensitizing actions are indicated as the first choice (172, 175). Metformin can represent an attractive option given acceptable liver and renal function, because it directly counteracts glucocorticoid effects by enhancing insulin sensitivity and reducing gluconeogenesis. Thiazolidinediones (TZDs) may also improve glycemia by antagonizing the pathways of steroid-induced insulin resistance and by neutralizing their adverse effects on  $\beta$ -cell function. Their usefulness, however, is limited because of the risk of edema and bone fractures, which they share with GCs (175, 176). Second choice drugs or insulin therapy can be considered, taking

into account their profile of action, tolerance, cost, and risk of hypoglycemia.

Basal insulin should be used with high doses of glucocorticoids, mainly in patients with existing diabetes, with a starting dose of 0.1U/kg before bedtime (177). Another possibility, especially for those receiving a single morning steroid dose, is to opt for basal insulin in the morning in order to blunt the late afternoon peak of intermediate-acting GCs. In case of multiple steroid doses or longer-acting GCs (dexamethasone), basal insulin should be reduced to 30% of daily insulin requirements with the remaining 70% divided between meals (177, 178).

Conclusively, is clear that guidelines for the management of SIDM and SIH (179) should be developed and universally shared in order to harmonize the treatment of these conditions overtaking empirical therapeutic strategies.

### Hyperglycemia and diabetes secondary to treatment with commonly used drugs

Apart from corticosteroids and antipsychotics, there is a broad spectrum of commonly prescribed drugs that can potentially have an effect on glucose metabolism. Diuretics and beta-blockers have been historically implicated with drug-induced hyperglycemia. Specifically, long-term use of beta-blockers or thiazide diuretics increased new onset diabetes with a relative risk of 1.20–1.32 in prospective cohorts (180). Another drug class, commonly used in patients with cardiovascular disease that may also have diabetogenic potential, is statins. Statins interfere with many glucoregulatory pathways resulting in decreased insulin secretion and action, with diabetes risk being associated with dose and duration of their use and other diabetes risk factors (181).

Somatostatin analogs (SA), primarily used for acromegaly and Cushing's disease by endocrinologists, are characterized by an increased risk for developing diabetes, via inhibiting insulin and glucagon secretion. Particularly, pasireotide, the newer and more potent SA,

almost tripled new onset diabetes and has been associated with hyperglycemia and diabetes in up to 30% of patients, compared to octreotide or lanreotide (182). Finally, the anticancer agents, mechanistic target of rapamycin (mTOR) inhibitors, temsirolimus and everolimus, have been associated with 5.3% incidence of high grade hyperglycemia (blood sugars >250mg/dL) (183).

In all the above drug classes, surveillance for diabetes is recommended and once noted, lifestyle modification and/or antidiabetic medications are recommended for treatment. In the majority of patients, hyperglycemia is mild and usually reversible upon discontinuation of the responsible agent. However, the benefit of continuing the drug often outweighs the risk of discontinuation, particularly if hyperglycemia can be treatable (184).

### Drug-induced dyslipidemias associated with endocrinopathies

Several drugs can affect either positively or negatively principal lipoproteins. The ones most commonly used affecting lipoprotein profile are steroid hormone-based drugs and antidiabetic medications.

#### *Steroid hormones based drugs*

**Estrogens** Estrogen administration raises high-density lipoprotein cholesterol (HDLc) levels by 5–20% (particularly the HDL<sub>2</sub> cardioprotective subfraction) and lowers, in a dose-dependent manner, total cholesterol (TC) and low-density lipoprotein cholesterol (LDLc) by 2–10% and by 5–20% respectively (185). These estrogenic effects are due in part to the induction in LDL receptors, the increase in apolipoprotein (apoA<sub>1</sub>) production and the decrease in apolipoprotein B (apoB) levels. Additionally, a decrease in lipoprotein (a) [Lp(a)] concentration, which is an independent cardiovascular risk factor, by 20–25% has also been observed (185, 186). However, estrogens can also increase triglyceride (TG) levels by 30–40% mainly in patients with genetic background of hypertriglyceridemia and this can lead to gross hyperchylomicronemia and risk of acute pancreatitis. The increase in TG levels arises from the hepatic overproduction of very low-density lipoproteins (VLDL) by oral estrogens as well as by the reduced lipoprotein lipase (LPL) and hepatic lipase (HL) activities resulting in a reduction of TG clearance (185, 187). Several factors can modulate estrogenic effects on lipid profile such as route of administration, type of preparations, dosing regimen, genetic background and baseline lipid abnormalities (185).

**Progestogens** The effect of progestogens on lipid metabolism is complex. In general they antagonize the estrogen-induced lipid changes, raising LDLc and decreasing, sometimes intensely, HDLc levels by 15–30% (188). The decline in HDLc is due to increased catabolism of this particle induced principally by an increase in HL lipase activity. These effects depend on the androgenic potency of each molecule. Progestogens with strong ‘androgenicity’ such as norethisterone, norgestrel and levonorgestrel can reduce HDLc levels as low as 10mg/dL. Less androgenic progestogens like desogestrel and natural progesterone induce milder lipid changes. The third-generation compounds (desogestrel, gestodene) are less androgenic and have neutral or even favorable effects on LDLc and HDLc levels but may cause hypertriglyceridemia (185, 187).

Estrogens and progestogens are used frequently in combined preparations for oral contraception or menopausal hormone therapy (HRT). In general, when combining both steroids, the estrogen-induced HDLc elevation is blunted but the reduction in LDLc is not affected (185). Triglycerides, however, should be measured and taken into account before considering any hormonal therapy containing estrogens (187).

**Androgens** Androgen replacement therapy with testosterone in early clinical studies showed small decreases in TC and LDLc levels and more profound decrease in HDLc concentrations (189), although more recent meta-analyses find no changes or small reduction in TC and TG levels and no change in HDLc (190). Interestingly, transdermal testosterone regimen has less influence on HDLc levels than intramuscular administration or oral preparations. Mechanisms for the decrease in HDL concentrations include increases of the scavenger receptor class B type I (SRBI) in the liver and increase in HL activity. Studies of the testosterone treatment impact on CV disease and atherosclerosis have shown conflicting results with some studies reporting an increased risk and others no risk (191, 192).

**Corticosteroids** In the Third National Health and Nutrition Examination Survey (NHANES) with 15.000 subjects over age 60 years, oral and inhaled GCs were associated with higher HDLc and ApoA<sub>1</sub> levels without adverse LDL or TG profile (193). It seems that these drugs sometimes increase TC (+10–15%), more often TG (until +40%), but more constantly increase HDL levels up to 20–40%. The

dose of GCs, sex, duration of treatment, route of administration, preexisting obesity or metabolic syndrome are important modulating variables.

#### Antidiabetic drugs

**DPP-4 inhibitors** The DPP-4 inhibitors exert direct hypolipidemic properties. In short-term studies with sitagliptin, vildagliptin and alogliptin a decrease in postprandial chylomicron TG and apoB48 it was shown, while the effect on fasting TG was less notable (194).

**GLP-1 receptor agonists** Most studies investigating the impact on lipid profile were performed with either liraglutide or exenatide in healthy subjects and in patients with T2DM and showed significant reduction of fasting and postprandial chylomicron TG levels, modest decreases in TC and LDLc and small or no significant change in HDLc levels (195). In the case of liraglutide, it seems that there is direct effect of the drug on the expression of genes involved in the biosynthesis of chylomicron and a reduction of APOB48 pool (194, 196).

**SGLT-2 inhibitors** Concerning lipid profile, these agents mediate small increase in HDLc, decrease or have no effect on TG and increase LDLc levels from 3 to 8% (187, 197). While the favorable effects observed in HDLc and TG concentrations could be explained by body weight reduction, the mechanism behind the small increase in LDLc remains unclear. One explanation could be that these drugs cause a switch from carbohydrate to lipid utilization, thereby increasing hepatic fatty acids levels to induce ketone and hepatic TC production. Empagliflozin was also associated

to a lower LDL receptor expression and LDLc catabolism (198).

Drug-induced effects on serum lipid levels and CV risk are summarized in Table 8.

## Drug-induced adrenal dysfunction

### Glucocorticoid-induced adrenal suppression and Cushing syndrome: A delicate balance

GCs when administered exogenously to suppress adrenal function, as in the case of congenital adrenal hyperplasia (CAH), can inhibit HPA axis activity and lead to suppression of adrenocortical glucocorticoids and androgens secretion. In CAH, their administration aims to replace the lack of endogenous cortisol and prevent the consequences of androgen excess, while avoiding glucocorticoid overtreatment and development of Cushing syndrome. Because this goal is not easily attainable, non-optimized treatment of CAH contributes to the poor health status of adults with CAH.

To control the overnight HPA-driven increase in adrenal androgens, a variety of glucocorticoid treatment regimens have been used (199). Regarding, biochemical monitoring, optimal treatment with glucocorticoids is achieved when serum levels of 17-OH progesterone (17OHP) are found above normal range (between slightly above the upper limit and three times the upper limit of normal range). Circulating concentrations of androstenedione should be within normal range. Excess glucocorticoid exposure is suspected when 17OHP concentrations are within or below normal range and androstenedione concentrations are low. Patients receiving hydrocortisone during the day will inevitably demonstrate high concentrations of 17OHP before taking their morning hydrocortisone dose;

**Table 8** Effect of endocrine-based drugs on serum lipid levels and CV risk.

Drug	TC	LDLc	TG	HDLc	Lp(a)	CV risk
Steroid hormone						
Estrogen	↓	↓	↑ or ↑↑	↑	↓	↑ ↔ or ↓
Progestogen	↔ or ↑	↔ or ↑	↔ or ↓	↓	↔ or ↓	↔ or ↑
Androgen	↔ or ↓	↔ or ↓	↔ or ↓	↓	↓	↔ or ↑
Corticosteroids	↔ or ↑	↔ or ↑	↑	↑	NA/I	NA/I
Antidiabetic drug						
DPP-4 inhibitor	↔	↔	↓ (pp)	↔	NA/I	↔
GLP-1R agonist	↓	↓	↓	↔ or ↑	NA/I	↓
SGLT-2 inhibitor	↔ or ↑	↑	↓	↑	NA/I	↓

↑ increase, ↓ decrease, ↔ no change, NA/I, data not available or insufficient, pp, post-prandial, TC, total cholesterol, LDLc, low-density lipoprotein cholesterol, HDLc, high-density lipoprotein cholesterol, TG, triglycerides, LP(a), lipoprotein(a), CV, cardiovascular, DPP-4, dipeptidyl peptidase-4, GLP-1R, glucagon like peptide-1 receptor, SGLT-2, sodium glucose co-transporter-2.

then these concentrations fall after taking the treatment. By contrast, patients treated with a night-time dose of prednisolone or dexamethasone might have normal or low concentrations of androgens on waking. Good control is important for fertility. Hypertension is common, so mineralocorticoid replacement therapy should avoid suppressing plasma concentrations of renin below normal range (as evaluated by measurement of plasma rennin activity), and blood pressure should be monitored regularly in adults with CAH (200). Trying to normalize androgen concentrations can lead to overtreatment with deleterious outcomes (i.e. cushingoid appearance, psychological effects, short stature, obesity, hypertension, osteoporosis, muscle atrophy and myopathy, insulin resistance and adverse metabolic profile. Furthermore, glucocorticoid overtreatment inhibits GnRH secretion leading to hypogonadotropic hypogonadism (201).

Optimal management of adults with 21OHD is far from being achieved. These patients present with many unmet medical needs, and additional research in the natural history of the disease as well as optimal therapeutic interventions are urgently needed to improve outcomes.

### Adrenolytic agents induce adrenal suppression: an unavoidable necessity

Several compounds, including ketoconazole, metyrapone, etomidate, and mitotane, have been commonly used in the therapeutic management of severe hypercortisolism for any etiology of endogenous Cushing's syndrome or control of excess steroid production in adrenocortical carcinoma. Acting via interfering with one or more of the enzymes in the steroidogenic pathway, they can cause subsequent decrease in cortisol secretion and adrenal insufficiency. Thus, adrenal function should be monitored closely to these patients, as hydrocortisone replacement may be mandatory (202, 203).

### Drug-induced phaeo crisis

Phaeochromocytoma crisis is a life-threatening condition, characterized by hemodynamic instability induced by a surge of catecholamines, manifested with a complexity of symptoms. (204).

Crises can occur spontaneously or can be precipitated by exercise, abdominal palpation, urination or by drugs (205). However, apart from anesthesia and beta-blockers, which are the most known precipitating factors in acute pheochromocytoma crisis, there are also other medications, commonly used in clinical practice, able to trigger this

life-threatening condition (Table 9) (205). For example, the gastroprokinetic agent *metoclopramide*, a worldwide medication used very often to treat nausea and vomiting, is known to stimulate catecholamine secretion from pheochromocytomas. The mechanism of metoclopramide-evoked hypertensive crisis in these patients likely involves an increase in norepinephrine release via presynaptic D2 receptor blockade, an inhibition of the vasodilatory effect of dopamine leading to potentiation of the hypertensive action of norepinephrine and epinephrine, and a direct stimulatory effect of the drug on pheochromocytoma cells. However, recently it was shown that serotonin receptors are also involved. Metoclopramide is able to act as a partial agonist at the serotonin (5-HT<sub>4</sub>) receptor type 4. Recently, Guillemot J. *et al.* have discovered that pheochromocytomas actually express functional 5-HT<sub>4</sub> receptors that are responsible for the stimulatory action of metoclopramide on catecholamine- and granin-derived peptide secretion (206).

Interestingly, glucocorticoids are actively involved in catecholamine metabolism, production, and release not only in healthy adrenal medulla but also in pheochromocytoma cells (205). In fact, they can exert inducing effects in crucial catecholamine biosynthetic enzymes such as phenylethanolamine N-methyltransferase that converts norepinephrine to epinephrine tyrosine hydroxylase, a rate-limiting enzyme in catecholamine metabolism, and proopiomelanocortin, an ACTH precursor (207). While in normal medulla catecholamine production and release is not affected by glucocorticoid administration, the anatomical and functional alterations in pheochromocytomas may increase the susceptibility of chromaffin cells to glucocorticoids. Dexamethasone and betamethasone, which have high glucocorticoid potency and long duration of action, are more likely to induce a pheochromocytoma crisis.

Thus, in patients with adrenal incidentalomas, glucocorticoids should be avoided or administered cautiously especially if the suspicion for pheochromocytoma is high (208). However, if dexamethasone suppression test is considered necessary before ruling out pheochromocytoma, the endocrinologist should preferably proceed with the overnight dexamethasone suppression protocol, as no cases of pheochromocytoma crisis have been reported, as yet, with this dose (209).

**Table 9** Medications that are implicated in adverse reactions in patients with pheochromocytoma and that can precipitate a crisis (205).

**Medications that are implicated in adverse reactions in patients with pheochromocytoma and that can precipitate a crisis**

Dopamine D2 receptor antagonists (including some antiemetic agents and antipsychotics)	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
Beta-adrenergic receptor blockers	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Opioid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Amitriptyline, imipramine
Serotonin reuptake inhibitors (rarely reported)	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids	Dexamethasone, prednisone, hydrocortisone, betamethasone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

## Drug-induced gonadal dysfunction

### Drug-induced amenorrhea: Differential diagnosis and clinical workup

During women's reproductive lives, from menarche to menopause, the HPG axis is active and functioning. Medications can have profound effects on all components of the HPG axis and the outflow tract

#### *Hypothalamic-pituitary axis*

Medications can affect this axis in one of three ways:

#### 1. **Alter the production or action of GnRH:**

*Opioids:* Opioids decrease GnRH production and release and may cause amenorrhea in young women as outlined in the section on opioids.

*Hypothalamic-pituitary-adrenal axis (HPA):* There is cross-talk between the HPA axis and the HPG axis which promotes amenorrhea as the functional adaptation to stress (210). Corticotropin releasing hormone infusion in women decreases gonadotropins, an effect prevented by GnRH administration. In addition, women given supraphysiological doses of prednisolone have decreased LH response to GnRH, suggesting a pituitary effect (210).

*GnRH agonists:* As GnRH effect is short lived, GnRH long-acting agonists, such as leuprolide, were developed to prolong its effect. However, while these agonists stimulate LH release for 5–12 days, thereafter LH concentrations plummet and a hypogonadotropic state ensues in both men and women. This effect appears to relate to GnRH receptor downregulation. This 'medical hypophysectomy' (as regards gonadotropins) induced by GnRH agonists has proved

useful in the treatment of central precocious puberty, endometriosis, hormone dependent cancers as well as in assisted reproduction to prevent premature LH surges during ovarian stimulation.

#### 2. **Induce hyperprolactinemia:**

Discussed in the section on drug-induced hyperprolactinemia and categorized in Table 2. If the medication cannot be discontinued, for example in the case of antipsychotics, the medication can be changed to one that does not elevate prolactin, such as quetiapine, or aripiprazole, which has both dopamine agonistic and antagonistic properties, can be added. These changes can only be considered in conjunction with the treating psychiatrist.

#### 3. **Induce pituitary inflammation causing hypophysitis:**

Discussed in the section on hypophysitis. Amenorrhea may occur in young women.

#### *Ovary*

The effect of chemotherapeutic agents on the ovary can be profound. Most anticancer medications affect dividing cells, such as granulosa and theca cells. Thus many women of reproductive age develop amenorrhea during chemotherapy, with high FSH and LH and low estradiol but menstrual function may return months later. The effect of such drugs on the oocytes/primordial follicles is variable and agent dependent. In addition, as the number of primordial follicles decrease with age, the effect of these drugs is also age dependent. For example, 5 g of cumulative cyclophosphamide may cause permanent amenorrhea in a woman in her 40s but 10 g or more are needed to do the same in younger women. Alkylating agents are

the most damaging, affecting both resting (oocytes) and dividing cells. These include cyclophosphamide, chlorambucil, melphalan, procarbazine, dacarbazine and busulfan. Agents such as vinca alkaloids, antimetabolites, heavy metals and TKIs may also cause amenorrhea. These include vinblastine, cytosine arabinoside, cis-platinum and imatinib. Antimetabolites such as methotrexate, fluorouracil, 6-mercaptopurine and vincristine have a low probability of causing amenorrhea. Information is available for certain drug regimen: for example, MOPP (mechlorethamine, vincristine, procarbazine and prednisone) may lead to permanent ovarian failure in 12–46%, whereas newer regimen such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) appear to have less toxicity. In a report of over 2000 childhood cancer survivors greater than 18 years of age, 8% had ovarian failure, versus 0.8% of siblings (211). Even in those whose menses return after chemotherapy, earlier menopause may be anticipated.

#### *Outflow tract*

Progestin-releasing intrauterine contraceptive devices and implants are often associated with amenorrhea, which for many women may be a desirable effect, lasting only during their use. However, the effect of intramuscular depot medroxyprogesterone acetate, given every 3 months, may last longer and 25% of women can remain amenorrhic up to a year after the last injection. This may relate to the accumulation of the drug within adipose tissue. If the drug cannot be discontinued, there is no suitable substitute or the drug has had a permanent effect, as in the use of chemotherapeutic agents, estradiol and progestin replacement must be given to hypoestrogenic women to preserve bone and cardiovascular health, if not contraindicated.

### **Anabolic steroids on the reproductive system of females**

Anabolic-androgenic steroids (AASs), often shortened to ‘anabolic steroids’, are synthetic steroidal androgens, which promote the growth of skeletal muscle (anabolic effects) and the development of male sexual characteristics (androgenic effects) in both males and females (212). These compounds, which are structurally related to testosterone, exert their action by binding to androgen receptor and exhibit both masculinizing as well as anabolic effects to a varying degree.

Nowadays, AASs are the most widely misused appearance and performance drugs (APEDs) and their use has become a serious global public health problem. A variety of adverse effects of AASs use on several organ systems have been described, including cardiovascular, hematologic, psychiatric, hormonal and metabolic effects (213) (Table 10). In females, AASs use can be associated with menstrual irregularity and infertility due to a negative feedback in the regulation of the hypothalamic–pituitary–gonadal axis, and subsequent suppression of pituitary LH and FSH secretion. It is known, however, that chronic strenuous exercise can often lead to the same symptoms due to disruption of the GnRH pulse generator, making it difficult to distinguish the effects of intensive exercise and AASs use (214). In females, anabolic steroids can also cause masculinization. Acne, hirsutism alopecia, mammary atrophy, clitoris hypertrophy and irreversible deepening of the voice are further consequences of AASs use. No well-documented case reports or studies concerning possible irreversible clitoris hypertrophy as a result of AASs use in women are available (215). Finally, there seems to be no connection between the administration of AASs in young female athletes and breast cancer (215).

Animal studies in female rats and mice have collectively shown that administration of nandrolone decanoate, the most commonly used injectable steroid by athletes and non-athletes, not only results in decreased serum levels of LH, FSH, progesterone and estrogen due to an increase in circulating androgen levels, but also causes irreversible damage to the ovarian tissue (216). Previous studies described that both folliculogenesis and luteogenesis have been severely affected by nandrolone decanoate in a dose- and time-dependent manner, resulting in follicular apoptosis, ovarian degeneration and atrophy (217, 218).

Accumulating evidence shows that about 32% of people who misuse AASs develop dependence syndrome via at least three separate pathways: the anabolic, androgenic and hedonic mechanisms (219, 220). Data show that anabolic steroid use in women is accompanied by extreme dissatisfaction with body image and a body dysmorphic syndrome analogous to anorexia (221). Symptoms of dependence can include tolerance or withdrawal once AASs use stops. Withdrawal symptoms can include fatigue, restlessness, loss of appetite, insomnia, reduced libido and the most dangerous of all, depression.

Although testing procedures are now in place to detect steroid use, novel compounds put athletes who use these substances, one step ahead of testing efforts. We can suspect AASs abuse in someone who exhibits a change

**Table 10** Adverse effects of anabolic-androgenic steroids (AASs) use.

Cardiovascular system
Dyslipidemia
Atherosclerosis
Cardiomyopathy
Cardiac conduction abnormalities
Polycythemia
Hypertension
Endocrine (males)
HPT suppression
Gynecomastia
Hypogonadism
Prostatic hypertrophy/cancer
Endocrine (females)
HPO suppression
Mammary atrophy
Menstrual irregularities
Masculinization effects
Psychiatric
Mood disorders: mania/depression
Aggression
AAS dependence
Cognitive defects
Musculoskeletal
Premature epiphyseal closure (in adolescent)
Tendon rupture
Hepatic
Inflammatory and clolestatic effects
Peliosis hepatis
Neoplasms (rare)
Kidney
Renal failure secondary to rhabdomyolysis
Focal segmental glomerulosclerosis

Adopted from: Pope Jr *et al.* (213).

in behavior, such as depression, irritability or aggression or in a woman who develops irregular menstrual cycles, hirsutism, acne, breast atrophy, temporal hair recession, deepening of the voice, clitoromegaly, increased muscle mass and decreased body fat. In blood tests, these patients usually develop high hematocrit, low-to undetectable LH levels and low SHBG levels. The approach to the patient taking exogenous AASs is really challenging as individuals are very reluctant to discuss this with their physicians, with one study reporting that 56% of users had never told their physicians about their use (222).

Special attention should also be paid on 'dietary/nutritional supplements' that are claimed to be 'thermogenic', 'non-anabolic', 'non-androgenic' supplements, such as vitamins, minerals, herbs, plants and aminoacids. These supplements could be contaminated, intentionally or unintentionally, with banned substances, mostly prohormones in low concentrations and/or active ingredients could be misrepresented on the label. The

health risk is high, especially for pregnant women, women and children due to gender differences in sex-steroid hormone synthesis. Professionals in many disciplines should inform their patients that supplements are drugs and that consultation is needed before and during their use.

### Drug-induced hyperandrogenemia

Hyperandrogenemia is suspected in a female of any age in the presence of hyperandrogenic signs such as hirsutism, hypertrichosis, acne, clitoromegaly and deepening of the voice. Specifically, if a patient exhibits terminal hair (long, thick and pigmented) located in scalp, eyebrows, eyelashes, face and pubis then the diagnosis of drug-induced hypertrichosis is not substantiated. On the other hand, the presence of vellus hair (short, fine, non-pigmented) located anywhere else from the above-mentioned areas of the body, strengthens the possibility of drug-induced hypertrichosis (223). However, it should be differentiated from hirsutism because it is independent of androgen stimulation. Drugs usually associated with this phenomenon are cyclosporine, acitretin, azelaic acid, cetirizine, citalopram, topical corticosteroids, diazoxide, penicillamine, phenytoin, streptomycin and minoxidil (224). Nevertheless, in the presence of a female with hirsutism the diagnosis of drug-induced hyperandrogenemia is a diagnosis of exclusion and several causes such as PCOS, non-classical CAH, ovarian hyperthecosis and ovarian/adrenocortical carcinoma must be ruled out by appropriate testing. Additionally, a thorough and detailed review of medical and drug history will guide the diagnosis.

Regarding the presence of increased androgen levels in the blood of a female, the first drug that should be excluded is testosterone. The gradual decrease of testosterone during menopause has been associated with the loss of sexual desire in a significant proportion of postmenopausal women, given the principal role of testosterone in female sexuality. Based on this notion, several experiments of testosterone administration have shown a significant improvement on different aspects of sexual function such as sexual fantasies, desire and engagement and these actions are directly related to increased levels of bioavailable testosterone levels (225). This approach has led to the enormous number of two million prescriptions for off-label compounded formulations of testosterone for women in 2006–2007 in USA. Since women are prescribed testosterone at various dosages and different formulations, an unknown

percentage might be receiving more than the suggested dose of just 300 µg daily with unknown effects.

The widespread use of supplements is another important and common cause of hyperandrogenemia in women. Of note the gold stone in this market is DHEA supplements. Although beneficial effects of DHEA supplementation has not been demonstrated universally, the oral consumption of a moderate dose of 50 mg DHEA for 12 months has doubled circulating testosterone levels in postmenopausal women (226).

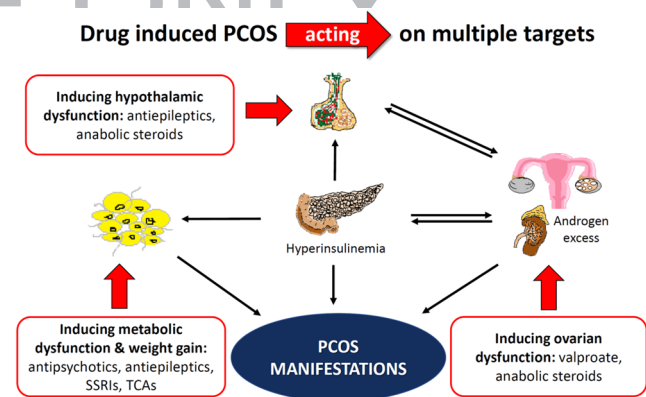
A common disorder associated with drug-induced hyperandrogenemia is epilepsy. This observation should be attributed to two different facts. First, epilepsy *per se* is a state associated with dysregulation of GnRH pulse generator due to neuronal paroxysmal discharges (227). Second, the use of valproate, an effective antiepileptic drug is linked to several aspects of androgen production. Namely, valproate induces centrally mediated modification of GABA-ergic neurotransmission leading to reduced serum gonadotropin levels. Additionally, valproate exerts direct effect on follicular steroidogenesis in the ovary leading to increased  $\Delta 4A$  levels (228). Finally, the induction of CYP17 and CYP11A genes by valproate leads to higher androgens levels. The total effects of valproate in circulating androgen levels can be summarized as follows: increased total testosterone levels, free androgen index, SHBG,  $\Delta 4A$  and decreased estradiol levels (229). Regarding the others classes of drugs used in the treatment of epilepsy such as phenobarbital, phenytoin, carbamazepine the induction of hepatic microsomal enzymes, leads to increased SHBG production and reduction of free, circulating androgen and estrogen concentrations.

### Drug-induced PCOS

PCOS is a clinical entity that in fact a plethora of drugs can act on multiple levels of its multifactorial etiology, including reproductive and metabolic axes (Fig. 3). Drug-induced PCOS can be defined as the manifestation of PCOS symptoms and signs, originating from drugs that can either unravel an underlying, preexisting PCOS or induce hormonal/metabolic signs and symptoms imitating PCOS. Analogously to the intrinsic diagnostic difficulties of the syndrome, drug-induced PCOS may be equally diagnostically challenging.

#### Drugs that can unravel preexisting PCOS

Multiple drug categories that can promote weight gain and obesity, including tricyclic antidepressants,



**Figure 3**

Pathophysiological mechanisms underlying drug-induced PCOS.

SSRIs, atypical antipsychotics, lithium, anticonvulsants and antidiabetic agents, can lead a PCOS prone background to metabolic dysfunction, insulin resistance and compensatory hyperinsulinemia, which may further potentiate androgen excess, contributing to unraveling a clinically silent and occult PCOS (230). In this context, a meticulous history and clinical examination, along with high clinical suspicion, are paramount in order to reveal pharmaceutical causes that can trigger the clinical manifestation of PCOS components and prevent a possible PCOS misdiagnosis.

#### Drugs inducing the complete spectrum of PCOS syndrome

In 1993, Isojärvi and coworkers published the first scientific data that in reproductive-aged women treated with valproate (VPA) for epilepsy, most of them had cardinal features of PCOS, including increased testosterone blood levels and polycystic ovarian morphology (231). A decade later, Nelson-DeGrave *et al.* provided analogous biochemical data, in which long-term cultures of theca cells isolated from follicles of women treated with VPA for 72 hours displayed increased steroidogenesis, in comparison with normal ovulating women. The observed increment of stimulated steroidogenesis was attributed to changes in chromatin modifications (histone acetylation) that augment transcription of steroidogenic genes. Interestingly, the most pronounced effect of VPA on androgen biosynthesis was observed in the dose range of 300–3000 microm, which represents the therapeutic levels in the treatment of epilepsy and bipolar disorder (232). Furthermore, the same research group showed that VPA can also induce a PCOS-like genomic phenotype, via

the observation that VPA- and PCOS-induced changes in gene expression (enhanced Akt/PKB signal transduction) in human theca cells were similar (233).

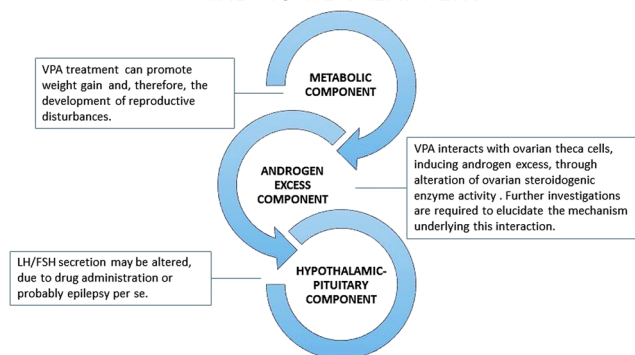
Apart from the effects in androgen biosynthesis, VPA can also disrupt normal hypothalamic signaling, leading not only to LH/FSH altered secretion but also to increased appetite and, thereby, weight gain. The observed deregulation in multiple pathways of female metabolic and reproductive axes represents a pathophysiological process very similar to that of PCOS and leads to a clinical phenotype mimicking this syndrome (Fig. 4) (234).

Although epilepsy *per se* has been associated with various reproductive endocrine disorders, including PCOS (via perturbing the hypothalamic–pituitary axis), all the above experimental and clinical data have consistently proved that VPA treatment is associated with PCOS manifestation. A meta-analysis by Hu *et al.*, involving 11 studies and 556 women with epilepsy treated with VPA, 593 women treated with other antiepileptic drugs (AEDs), 120 women with untreated epilepsy and 329 healthy controls, has also verified this close association. The raw incidence of PCOS in VPA-treated epileptic women was significantly higher (approximately 1.95-fold) with respect to nontreated patients, although some differences in the results were detected according to different definitions or diagnostic criteria of PCOS (235).

### Drug-induced male infertility and sperm abnormalities

Studying the reproductive effects of a drug may be challenging, since a compound may affect male fertility

#### VALPROATE TREATMENT

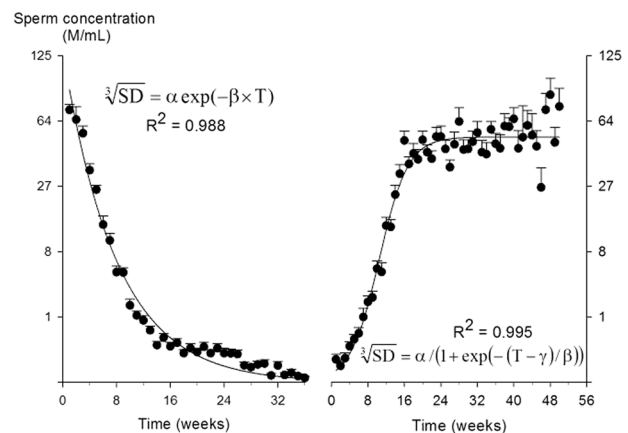


#### DEREGULATION IN MULTIPLE PATHWAYS, EXACTLY LIKE PCOS.

#### Figure 4

Valproate induces deregulations in multiple pathways of female metabolic and reproductive axes, creating a pathophysiological process very similar to that of PCOS.

#### Suppression and Recovery of Human Sperm Output: WHO Studies



#### Figure 5

Suppression of sperm output after testosterone (T) administration for contraception (A) and recovery after T discontinuation (B), using pooled data from the WHO contraceptive studies. Data points represent sperm concentration mean and SE (error bar) of semen samples grouped within weeks. Sperm concentration fell in the majority of samples below 1 million/mL in 12 weeks after T administration, whereas almost all individuals were expected to recover by 24 months after discontinuation. Note cube-root scale on the y-axis. Reprinted with permission by Ly *et al.* (237).

in many ways: either by causing sexual dysfunction (including erectile or/and ejaculation dysfunction) or by disrupting spermatogenesis; the latter as a result of insults targeting the HPG axis, the seminiferous epithelium, semen transition and maturation or combinations of the above (236).

The detrimental effects of exogenous androgen administration on male fertility are well established. Landmark studies supported by WHO have shown that exogenous testosterone (T) with or without progestins leads up to 95% of men to severe oligospermia ( $<10^6$  sperm/mL) by suppressing the HPG axis and diminishing intratesticular T levels. These effects on sperm parameters are generally reversible within 3–12 months after stopping T and the recovery time depends on age, testosterone dose, route of administration and duration of treatment (Fig. 5) (237).

On the other hand, spermatogenesis may be affected by drugs that diminish or hamper the action of T (e.g. anti-androgens). Cyproterone acetate is a progestin with anti-androgenic properties used in the palliative treatment for prostate cancer, which is associated with a reversible

decrease in sperm parameters and is accompanied by symptoms of androgen deprivation such as loss of erectile function and libido (238). Similarly GnRH agonists or antagonists desensitize or block the GnRH pituitary receptors respectively, resulting in 'chemical' castration. A relevant class of drugs, frequently prescribed for benign prostate hyperplasia are 5 $\alpha$ -reductase inhibitors (5-ARI), such as finasteride and dutasteride, which block the conversion of T to its drastic metabolite Dihydrotestosterone. These drugs have well-documented negative effects on libido and erectile function, which may persist several months after discontinuation ('Post Finasteride Syndrome') (239). 5-ARIs can also significantly decrease sperm count and mobility; however, this effect is insufficient to reduce fertility in men with normal semen prior to treatment. The above side effects are generally less common among men treated with lower doses of 5-ARIs for male-pattern baldness (240).

Psychotropic drugs also have profound negative effects on male fertility and include antidepressants, antipsychotics and recreational drugs, such as opioids and cannabis. This may be attributed to a central action of elevated serotonin on the hypothalamus, moderate elevation of PRL and possibly a direct action on smooth muscle cells. One should consider that ejaculatory dysfunction is also prevalent among untreated men with depression as well (240).

The most popular and studied antidepressants with respect to male fertility are SSRIs which may increase ejaculatory latency up to 50–65%, while in 5.6% of patients they cause retrograde ejaculation. Treatment with SSRIs may negatively affect sperm quality - especially sperm DNA fragmentation, an effect seen as soon as 4 weeks after the initiation of therapy, which is possibly a result of abnormal epididymal sperm transit rather than a defect of spermatogenesis (241). Non-SSRI antidepressants such as Norepinephrine/dopamine reuptake inhibitors (NDRIs) and Serotonin Antagonists & Reuptake Inhibitors (SARIs) have minimal sexual side effects and could be used as alternatives to SSRIs in men with sexual dysfunction, while their effects on semen quality have not been assessed so far (242).

Regarding chemotherapy, many chemotherapeutic drugs cross the blood-testis barrier and cause irreversible damage of the germ-cells and the seminiferous epithelium. Alkylating agents and especially mustine are associated with almost 100% permanent azoospermia, while platin-based regimens show long-term spermatogenesis recovery. Various cytoprotective strategies have been applied to minimize these side effects, such as

prophylactic downregulation of the HPG axis with GnRH agonists/ testosterone; however, pretreatment sperm cryopreservation represents the most rational option (243).

Some of these cytotoxic agents such as cyclophosphamide have been used in lower doses as immunosuppressants for the treatment of severe, chronic inflammatory diseases (e.g. SLE). Similarly the risk of sustained azoospermia or oligozoospermia reaches 90% and cryopreservation prior to therapy should be recommended. Other immunosuppressant drugs that impact negatively fertility are purine metabolism disruptors (azathioprine, methotrexate). Regarding methotrexate, there is evidence from animal models of gonadotoxic and probably teratogenic action, whereas evidence in men is limited (244). On the contrary data on azathioprine/mercaptopurine has shown no significant changes in semen quality during treatment or congenital anomalies in the offspring, representing alternative options in men who seek fertility (245).

Antihypertensives are also well known to cause sexual dysfunction, including both erectile and ejaculatory dysfunction, whereas there is insufficient evidence to link their use with testicular dysfunction. Their negative impact is generally related to the decrease of pressure and the net hydraulic effects that it may have on erection, while specific actions are mediated by receptor binding. Peripheral  $\beta$ 1-adrenergic antagonists and especially atenolol are associated with erectile dysfunction (ED), an effect seen less often with 'cardioselective' beta-blockers such as nebivolol (246). Mineralcorticoid receptor antagonists, such as spironolactone disrupt androgen action by exerting a peripheral anti-androgen effect due to cross-reactivity with the androgen receptor, effects that can be ameliorated by the use of the more selective blocker eplerenone.

Miscellaneous drugs used in everyday practice have been implicated in derangement of male reproductive function. Metoclopramide is an antagonist of the dopamine receptor 2, used for nausea and vomiting and is well known to increase PRL levels; however, there are no data on detrimental effects on the HPG axis or on semen parameters (247). Interestingly paracetamol, possibly the most frequently consumed painkiller, has been shown to cause sperm abnormalities, including DNA fragmentation, and to increase time to pregnancy, effects that are reversible and dose related (248). A possible mechanism for this effect is the ability of paracetamol to decrease prostaglandins, which are relevant to the fertilization capacity of spermatozoa (249). Statins finally

are thought to cause a possible decrease in T levels due to depletion of the substrates of steroidogenesis as well as disruption of sperm membranes which are particularly rich in cholesterol. Nevertheless, low level of evidence exists only for Simvastatin and Pravastatin (250).

## Conclusions

In the era of polypharmacy, this review aimed to cover a contemporary topic, the drug-induced endocrinopathies, which was presented in the *monothematic annual Combo Endo Course 2018*. This challenging part of endocrinology is constantly expanding particularly during the last decade, with the new oncological therapeutic agents, targeting novel molecular pathways in the process of malignancies. In this new era of drug-induced endocrine disease, clinicians should be aware that drugs can cause endocrine abnormalities via different mechanisms and mimic a variety of clinical scenarios. In the context of the delicate balance of the endocrine system, even imperceptible drug-induced deregulations can lead to a clinical expressed endocrinopathy. Therefore, clinicians should not only promptly recognize drug-induced hormonal and metabolic abnormalities, but more importantly proceed on time therapeutically.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

### Funding

V Popovic: This study was supported by a grant from the Ministry of Science of Republic of Serbia (Project 175033). The rest of the authors did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 3 March 2019

Revised version received 25 April 2019

Accepted 3 June 2019

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*JOB NUMBER:* 190154

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