Endotext

PHARMACOLOGICAL-CAUSES-OF-HYPERPROLACTINEMIA

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ABSTRACT

Hyperprolactinemia represents a multifaceted endocrine disorder with both physiological and pathological causes. The increased use of anti-psychotic and anti-depressant medications has increased the role pharmaceutical agents play in inducing hyperprolactinemia, being the most frequent cause of hyperprolactinemia in clinical practice. This has particularly impacted females, who demonstrate a higher susceptibility to drug-induced hyperprolactinemia. Of these medications, anti-psychotics, neuroleptic-like medications, anti-depressants, and histamine receptor type 2 antagonists, emerge as the most prominent culprits. Furthermore, opioids, some anti-hypertensive agents, proton pump inhibitors, estrogens, and other less potent hyperprolactinemia-inducing medications are recognized as potential contributors to drug-induced hyperprolactinemia. Many herbal medicines are reported as lactogenic, but their ability to cause hyperprolactinemia remains unclear. This review endeavors to elucidate the intricate mechanisms underlying the induction of hyperprolactinemia by pharmacological agents. We have included available data on the prevalence and extent of drug-induced changes in prolactin levels. We have also included data on herbal agents. We have highlighted where controversial data are identified. Although a detailed exploration of how these medications impact prolactin regulation is beyond the scope of this chapter, this review aims to deepen our understanding of the interplay between pharmacological agents and their effects on prolactin levels, contributing to valuable insights, refined therapeutic approaches, and better patient care.

INTRODUCTION

The most common cause of consistently high prolactin levels is drug-induced hyperprolactinemia. The overall incidence is higher in women compared to men. Drug-induced causes tripled during the 20-year follow-up period, reflecting the increased prevalence of psychoactive drug use (1). Several drugs have been reported to induce hyperprolactinemia, either by inhibiting dopamine receptors or their actions or by directly stimulating prolactin secretion (2).

High levels of prolactin can be attributed to various physiological factors, such as pregnancy and breast-feeding, while minor increases in prolactin levels may also occur during ovulation, after sexual intercourse, during periods of stress, exercise, after food intake, or in association with irritation of the chest wall and breast stimulation. Pathological causes can be related to hypothalamo-pituitary disorders or non-hypothalamo-pituitary disorders. Hypothalamo-pituitary disorders include prolactin-secreting pituitary tumors (including lactotroph tumors, mammo-somatotroph tumors, mature pluri-hormonal PIT1-lineage tumors, immature PIT1-lineage tumors, acidophil stem cell tumors, multi-hormonal pituitary tumors, mixed somatotroph, and lactotroph tumors, and pluri-hormonal tumors) (3); hypothalamic and pituitary stalk compression or damage (non-prolactin-secreting pituitary adenomas, craniopharyngiomas, meningiomas, germinomas, granulomas, metastasis, Rathke cleft cysts, hypophysitis, radiation, surgery, and trauma); infiltrative pituitary disorders; pituitary hyperplasia (McCune-Albright, Carney complex, X-LAG). Other causes include primary hypothyroidism; adrenal insufficiency; systemic diseases such as chronic renal failure and liver cirrhosis; polycystic ovary syndrome; neurogenic causes (chest wall trauma or surgery, herpes zoster); seizures; untreated severe phenylketonuria; pseudocyesis (false pregnancy); autoimmune diseases (lupus, rheumatoid arthritis, multiple sclerosis, systemic sclerosis, Behcet's disease, polymyositis); cancers (breast, ovarian, colon, hepatocellular) (4). During the diagnostic process of hyperprolactinemia, it is crucial to consider the possibility of macroprolactinoma and the 'hook' effect, although the latter is usually not relevant in drug-induced cases (5).

Drug-induced hyperprolactinemia is often characterized by prolactin levels ranging from 25 to 100 ng/mL (530-2130 mIU/L). However, certain medications including metoclopramide, risperidone, amisulpride, and phenothiazines can lead to prolactin levels surpassing 200 ng/mL (4255 mIU/L) (6). On similar doses of prolactin-raising anti-psychotics, women with chronic use are more likely to develop hyperprolactinemia than men, reaching significantly higher prolactin levels, with mean levels of 50 ng/mL (1065 mIU/L) (7,8). Younger age was associated with higher prolactin levels in women, but not in men (8,9). Route of drug administration is important, with prolactin levels returning to normal after cessation of the drug: within 2-3 weeks after stopping oral treatment, but no sooner than 6 months after discontinuation of intramuscular depot administration (10).

This chapter will encompass a comprehensive discussion of all pharmacological causes as well as some alternative factors contributing to changes in prolactin levels especially hyperprolactinemia.

EPIDEMIOLOGY

Drug-induced hyperprolactinemia is the most common cause of consistently high prolactin levels. A retrospective follow-up study conducted in Scotland, involving 32,289 hyperprolactinemic individuals from 1993 to 2013, concluded that within the non-pregnancy-related group, the most prominent cause was drug-induced hyperprolactinemia (45.9%), followed by pituitary disorders (25.6%), macroprolactinoma (7.5%), and hypothyroidism (6.1%). Nevertheless, 15% of cases were deemed idiopathic. The overall incidence was higher in women aged 25-44 years old compared to men (1). Female predominance is reported in other studies with a female: male ratio of 5.9:1 and the mean age at diagnosis of hyperprolactinemia is 40 (range 14–85) years (2,11).The position of hyperprolactinemia as a side effect of medications has been assessed in a French Pharmacovigilance Database from 1985 to 2000, which reported 159 cases of hyperprolactinemia out of 182,836 adverse drug reactions (11). The rates of hyperprolactinemia related to therapeutic drug classes were recorded as 31% associated with anti-

psychotics, 28% with neuroleptic-like drugs (medications with a similar mechanism of actions as neuroleptics, but used for different purposes, for example movement disorders or anti-emetics), 26% with anti-depressants, 5% with histamine receptor type 2 (H2-receptor) antagonists, and 10% with other drugs.

PROLACTIN CONTROL MECHANISMS

Prolactin is a polypeptide primarily produced in the anterior pituitary gland, with secondary production occurring in other tissues such as the gonads, mammary gland, endometrium, prostate, lymphocytes, hematopoietic cells, skin, brain, retina, inner ear cochlea, decidua, pancreas, liver, endothelium, and adipose tissue (12–14). In breast and prostate cancer, prolactin has even been proposed as a tumor marker (15,16). Prolactin acts through prolactin receptors (PRLR), which belong to the family of cytokine receptors associated with the non-receptor tyrosine Janus kinase 2. PRLR can activate the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway, MAPK (mitogen-activated protein kinase), PI3 (phosphoinositide 3-kinase), Src kinase, as well as the Nek3 / Vav2 / Rac1 serine / threonine kinase pathway (17). There are different isoforms of this receptor: a long isoform, intermediate isoform, 2 short isoforms S1a and S1b which are formed by alternative splicing and partial deletion of exons 10 and 11, and soluble PRLR (18). These different isoforms are expressed in different tissues, mostly studied in rats. The long isoform is mainly expressed in the adrenal glands, kidneys, mammary glands, small intestine, bile ducts, choroid plexus, and pancreas whereas the short isoform is in the liver and ovaries (19). Prolactin possesses nearly 300 functions apart from lactation including neuroprotection and neurogenesis, offspring recognition by both parents, adipose and weight homeostasis, islet functions, immune regulation, angiogenesis, osmoregulation, and mitogenesis (20).

The secretion of prolactin produced by lactotroph cells in the anterior pituitary gland has a circadian rhythm with higher levels during sleep and lower levels during wakefulness (21). Even though pulsatility frequency does not significantly change over 24 hours, the amplitude of pulses is higher during night and day sleep, while wakefulness is associated with an immediate offset of active secretion. Prolactin is lower during the rapid eye movement stage of sleep (22).

The synthesis and secretion of prolactin is under the complex control of peptides, steroid hormones, and neurotransmitters, which can act as inhibitory or stimulatory factors, either by a direct effect on lactotroph cells or by indirect pathways through inhibition of dopaminergic tracts, and are widely studied in mammals (2). Dopamine plays a crucial role in inhibiting prolactin secretion. Dopamine can bind the five types of dopamine receptors (G-protein coupled receptors): DRD1, DRD2, DRD3, DRD4 and DRD5, while lactotroph cells express mainly D2 receptors. Dopamine can reach the pituitary via three pathways (Figure 1): through the tuberoinfundibular dopaminergic (TIDA) system, the tuberohypophysial tract (THDA), and the periventricular hypophyseal (PHDA) dopaminergic neurons (23). TIDA neurons originate from the rostral arcuate nucleus of the hypothalamus and release dopamine into the perivascular spaces of the medial eminence and through long portal vessels dopamine reaches the anterior pituitary gland. The THDA neurons originate in the rostral arcuate nucleus and project into the medial and posterior pituitary lobes and release dopamine at these sites. From THDA tract dopamine then reaches lactotroph cells through the short portal vessels (24). PHDA neurons originate in the periventricular nucleus and axons terminate in the intermediate lobe and dopamine release follows the same direction as from the THDA neurons. Prolactin-inhibiting neurons are considered to be a functional unit working synchronously (23). The binding of dopamine to D2 receptors on the plasma membrane of lactotroph cells inhibits prolactin protein, PRL gene

transcription, as well as lactotroph proliferation (24). The release of prolactin through exocytosis of prolactin secretory granules is influenced by dopamine through various pathways. Specifically, D2 receptors are coupled with pertussis toxin-sensitive G proteins, which subsequently inhibit adenylate cyclase activity, resulting in decreased levels of cyclic adenosine monophosphate (cAMP) (25).

Additionally, the activation of potassium (K+) channels occurs, leading to a reduction in voltage-gated calcium (Ca2+) currents and inhibition of inositol phosphate production. Collectively, these intracellular signaling events culminate in a decrease in the concentration of free calcium ions (Ca2+) resulting in membrane hyperpolarization, ultimately inhibiting the exocytosis of prolactin from its granules (26). The inhibition of PRL gene transcription occurs when D2 receptors are activated, leading to the inhibition of MAPK or protein kinase C pathways. This activation results in a reduction of phosphorylation events on Ets family transcription factors. These transcription factors play a crucial role in the stimulatory responses of thyrotropin-releasing hormone (TRH), insulin, and epidermal growth factor (EGF) on prolactin expression. Moreover, the Ets family transcription factors interact with the PIT1 protein, which is essential for cAMP-mediated PRL gene expression (27). Dopamine exerts anti-mitogenic effects by activating D2 receptors through multiple pathways. These include the inhibition of MAPK (mitogen-activated protein kinase) signaling, protein kinase A signaling, and stimulation of phospholipase D activity. Additionally, dopamine engages a pertussis toxin-insensitive pathway, activates the extracellular signal-regulated kinases 1 and 2 (ERK1/2) pathway, and inhibits the AKT/protein kinase B pathway (28–31).

In addition to the dopaminergic inhibitory system, the γ-aminobutyric acid (GABA)-ergic tuberoinfundibular system, culminating in the median eminence, exhibits inhibitory properties, albeit of lesser potency compared to the dopaminergic system, while also having a role in prolactin modulation. GABA-B receptors are discernible both within the anterior pituitary gland, contributing to the maintenance of low prolactin levels, and in TIDA neurons which can be powerfully inhibited by GABA via hyperpolarization, consequently contributing to an elevation in prolactin levels (32,33).

Prolactin itself has two negative feedback effects: through ``short-loop feedback regulation`` it enhances the activity of TIDA neurons, where both long and short forms of the PRLR are expressed, with the long isoform being predominant in the arcuate and periventricular nuclei, regulating tyrosine hydroxylase (a rate-limiting enzyme in dopamine synthesis) leading to increase of dopamine release, which inhibits prolactin, as well as autocrine inhibition (34,35). Several other local factors influence prolactin release within pituitary gland as shown in Figure 1.

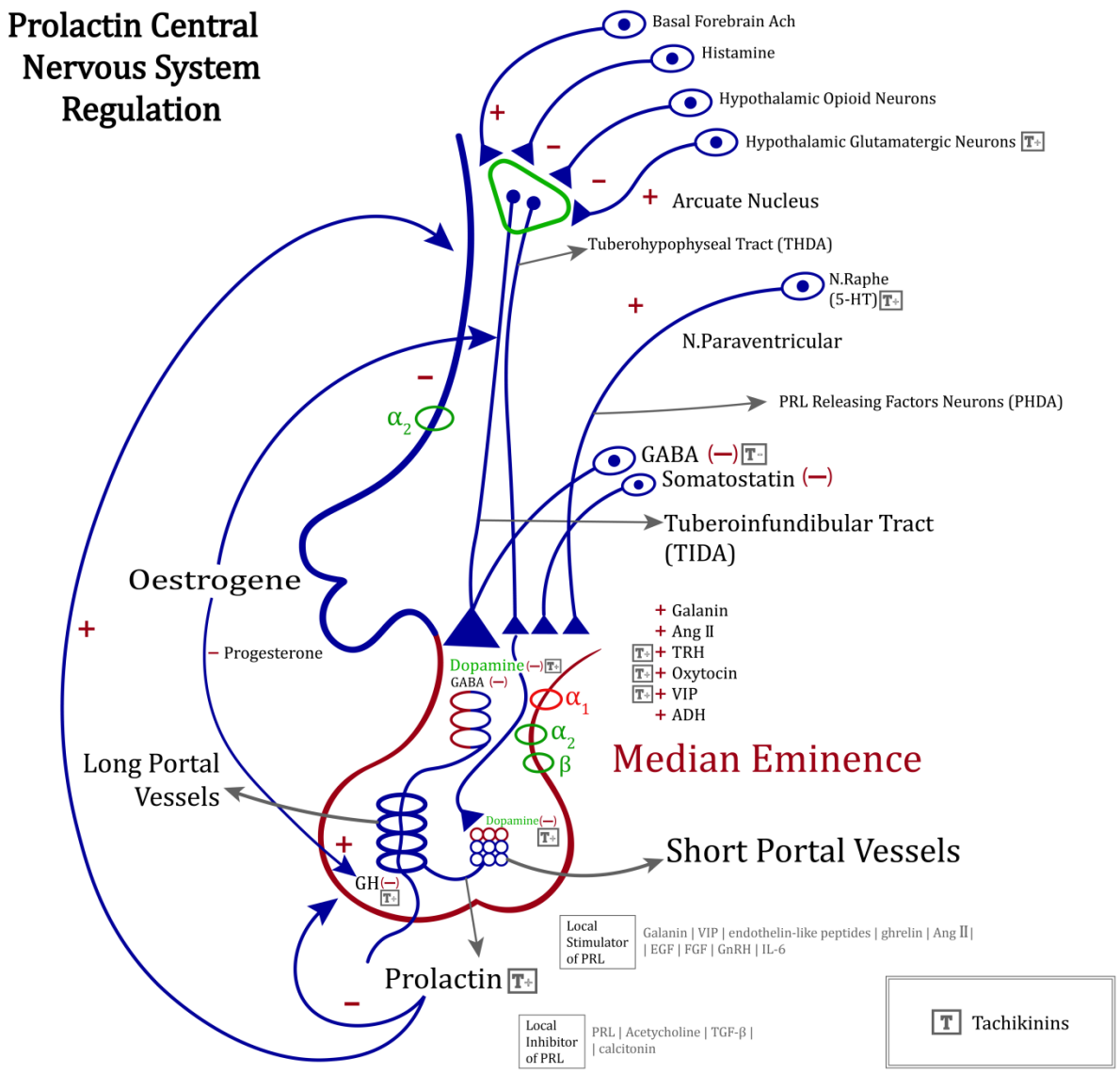

Figure 1. Prolactin – Central Nervous System Regulation.

Other prolactin inhibitory factors include somatostatin, acetylcholine, endothelins, gastrin, and growth hormone, while stimulatory factors include thyrotropin-releasing hormone (TRH) (as seen in primary hypothyroidism), angiotensin II, vasopressin, oxytocin, VIP, galanin, and estrogen.

Experiments conducted on rats to elucidate the relationship between the adrenergic system and the regulation of prolactin secretion have focused on stimulating or inhibiting α and β adrenergic receptors. Functional hyperprolactinemia is a complex hormonal interplay of stress-induced neuroendocrine changes involving the dopamine, serotonin and adrenergic systems (36,37). Evidence suggests that the mediobasal hypothalamus and preoptic-anterior hypothalamus harbor the primary adrenoreceptors (38,39). Injecting the α2 agonist clonidine into the mediobasal hypothalamus resulted in a dose-dependent increase in prolactin secretion. This effect

was counteracted by the blockade of idazoxan (α2 antagonist). Similarly, the stimulation of prolactin release was induced by isoprenaline (β agonist) and notably attenuated by the β antagonist propranolol. The β2 agonist salbutamol also exhibited efficacy in stimulating prolactin secretion. Conversely, adrenergic agonists such as noradrenaline (mixed α and β), phenylephrine (α1), and tyramine (sympathomimetic) in the mediobasal hypothalamus, failed to elicit an effect on prolactin secretion.

Within the preoptic anterior hypothalamus, noradrenaline and adrenaline were found to stimulate prolactin secretion (40). However, the administration of the α1 agonist phenylephrine failed to stimulate prolactin, indirectly suggesting that the stimulatory effect of noradrenaline in the preoptic anterior hypothalamus is likely due to its action at α2 sites. α2 agonism has been shown to reduce the function of tuberoinfundibular dopaminergic neurons leading to increase prolactin production and secretion (41). Consequently, it was inferred that the activation of α2 and β adrenoceptors in the mediobasal hypothalamus and α2 adrenoceptors in the preoptic-anterior hypothalamus, proximal to prolactin-regulating neurons, leads to heightened prolactin secretion, while the action of α1 in the mediobasal hypothalamus may be inhibitory (42).

Cholinergic activation may have opposite roles in rodents and humans. Cholinergic agonists suppress prolactin release induced by morphine in rats, suggesting that the central cholinergic system has an inhibitory effect on the prolactin release triggered by morphine or β-endorphine, but this cholinergic inhibition does not occur through catecholaminergic neurons (43). Conversely, in humans, cholinomimetic drugs can increase prolactin levels associated with raised plasma β-endorphin, suggesting a stimulatory interplay of cholinergic factors and endogenous opioids on prolactin levels (44), although circulating opioids may not directly relate to central levels.

TIDA neurons express estradiol and progesterone receptors. Estradiol action leads to reduced secretion of dopamine into the portal blood system and mediates a prolactin surge. Progesterone, in addition, suppresses dopamine release being responsible for the plateau phase of the surge (23). Estrogen specifically affects prolactin synthesis by influencing lactotroph cell sensitivity, expression of pituitary dopamine receptor downregulation, and the expression of the prolactin receptor gene (2,34). Ghrelin, a hormone involved in metabolic balance, directly stimulates prolactin secretion at the pituitary level (45).

Tachykinins (substance P, neurokinins A, and B, neuropeptide K, neuropeptide Y) can act directly on the lactotroph cell and indirectly within the hypothalamus or posterior pituitary. They have a multifaceted impact on prolactin secretion, with both stimulatory and inhibitory effects. They can stimulate prolactin secretion by stimulating and potentiating the release of oxytocin, vasopressin, TRH, VIP, serotonin and glutamate, and by inhibiting GABA. Tachykinins through paracrine actions can directly increase prolactin within the anterior pituitary. They can also increase dopamine but the overall effect is prolactin elevation. Under specific circumstances, the stimulation of dopamine release can be prominent leading to a decrease in prolactin (46). Endogenous opioids are involved in regulating prolactin secretion, particularly during stressful situations, by reducing the activity of tuberoinfundibular dopaminergic neurons mediated by μ-, κ-, and δ- opioid receptors, resulting in increased prolactin release (47). Prolonged nicotine exposure has been associated with desensitization of dopamine receptors, diminished dopamine turnover, and a decrease in their abundance within the nigrostriatal pathways (48). These alterations have been suggested to contribute to a diminished prolactin response to opiate blockade observed in individuals who smoke. Similar to opioids, histamine has been shown to induce prolactin production predominantly

through inhibiting dopaminergic and stimulating serotoninergic and vasopressin-ergic neurons (49).

Serotoninergic pathways originating from the dorsal raphe nucleus play a physiological role in mediating nocturnal surges and suckling-induced prolactin rises through a serotonin interaction via serotonin type 1 and 2 receptors (5-hydroxytryptamine receptors, 5HT1, and 5HT2). 5-HT could either release a PRL-releasing factor or inhibit dopamine release. The paraventricular nucleus, where serotoninergic pathways terminate, contains postsynaptic serotonin 5-HT1A, 5-HT2, and 5-HT2C receptor subtypes, and possibly 5-HT3 receptors (50). It was shown that the prolactin-releasing effect of serotonin probably occurs mostly via 5-HT1C / 2 receptors because ritanserin (an elective 5-HT1C / 2 receptor antagonist) opposed this effect (51). Serotonin stimulation of prolactin–releasing factor (PRF) neurons in the paraventricular nucleus leads to PRF release (like VIP and oxytocin) mediating hyperprolactinemia. Moreover, serotoninergic stimulation of GABAergic neurons in the tuberoinfundibular-GABA system has been shown to inhibit TIDA cells which contain 5-HT1A receptors, therefore inhibiting dopamine synthesis/release resulting in increased prolactin secretion (52).

Oxytocin, through the posterior pituitary and vasoactive intestinal peptide (VIP) in the anterior pituitary, play significant roles in enhancing PRL gene transcription and modulating dopamine inhibition. Animal studies suggest a potential mediation of VIP by oxytocin to stimulate prolactin secretion (53).

The extensive hormonal regulation of prolactin renders it susceptible to various disturbances caused by different classes of medications.

CLINICAL CHARACTERISTICS

Persistent hyperprolactinemia is associated with disturbances of the gonadal axis leading to interruptions of gonadotrophin-releasing hormone pulsatility and inhibition of luteinizing hormone and follicle-stimulating hormone release (54). Clinical manifestations attributed to hyperprolactinemia predominantly stem from the suppression of the gonadal axis. In premenopausal women, a spectrum of menstrual cycle dysfunctions is observed, spanning from luteal phase shortening to complete amenorrhea, often correlating with elevated prolactin levels. Secondary amenorrhea can be due to hyperprolactinemia in up 30% of patients, and up to 75% of patients with amenorrhea and galactorrhea (55). Beyond these effects, an array of hypoestrogenic indicators may manifest, including symptoms like vaginal dryness, diminished libido, and decreased energy levels. Galactorrhea can be present in up to 80% of females (55,56). In men, the impact of hyperprolactinemia is manifested through a decrease in libido, ranging from diminished sexual desire to oligospermia or even azoospermia attributed to hypogonadotropic hypogonadism. Notably, erectile dysfunction may arise, primarily attributed to the direct inhibitory influence of dopamine, and can be potentially reversed through the administration of dopamine agonists (57). Gynecomastia, on the contrary, is a manifestation of secondary hypogonadism rather than elevated prolactin levels, whereas galactorrhea is rare in men (21).

In both genders infertility can be observed, with diminished bone mineral density. In females, bone mineral density is significantly decreased in women with amenorrhea and increases during treatment and menstrual cycle restoration (58). Additionally, in cases where hyperprolactinemia is attributed to a mass, accompanying clinical indications may encompass headaches, visual field disturbances, cranial nerve palsies, and hypopituitarism. Notably, these manifestations may be the only clinical features in post-menopausal women (21,59).

PSYCHOTROPIC MEDICATIONS

Anti-psychotics and neuroleptic-like drugs are psychotropic medications which primarily exert their

anti-psychotic effects through the blockade of DRD2 and D4 receptors in the mesolimbic area. Newer classes of anti-psychotics block 5HT2 and sometimes noradrenergic α1 or α2 receptors (4,35,60). Blockade of D2 receptors in the hypothalamic tuberoinfundibular system and lactotroph cells *results in disinhibition of prolactin secretion* leading to hyperprolactinemia, being the most common drugs known to induce hyperprolactinemia (61) (Figure 2). On the contrary, strong binding to D2 receptors can extend the half-life of dopamine by approximately 50%. This effect is achieved through two primary mechanisms: direct blockade of the dopamine transporter (DAT) and antagonism of D2 autoreceptors. These processes collectively result in reduced reuptake of dopamine, prolonging its presence in the synaptic area and further stimulating an upregulation of receptors. However, it is important to note that chronic use of anti-psychotics can lead to the reversal of upregulation of DAT (mRNA and protein), potentially contributing to treatment resistance and potentially lower prolactin elevations in the long term. Nonetheless, it is worth mentioning that anti-psychotics typically exhibit a lower affinity for dopamine transporter blockade compared to selective DAT blockers such as nomifensine (62).

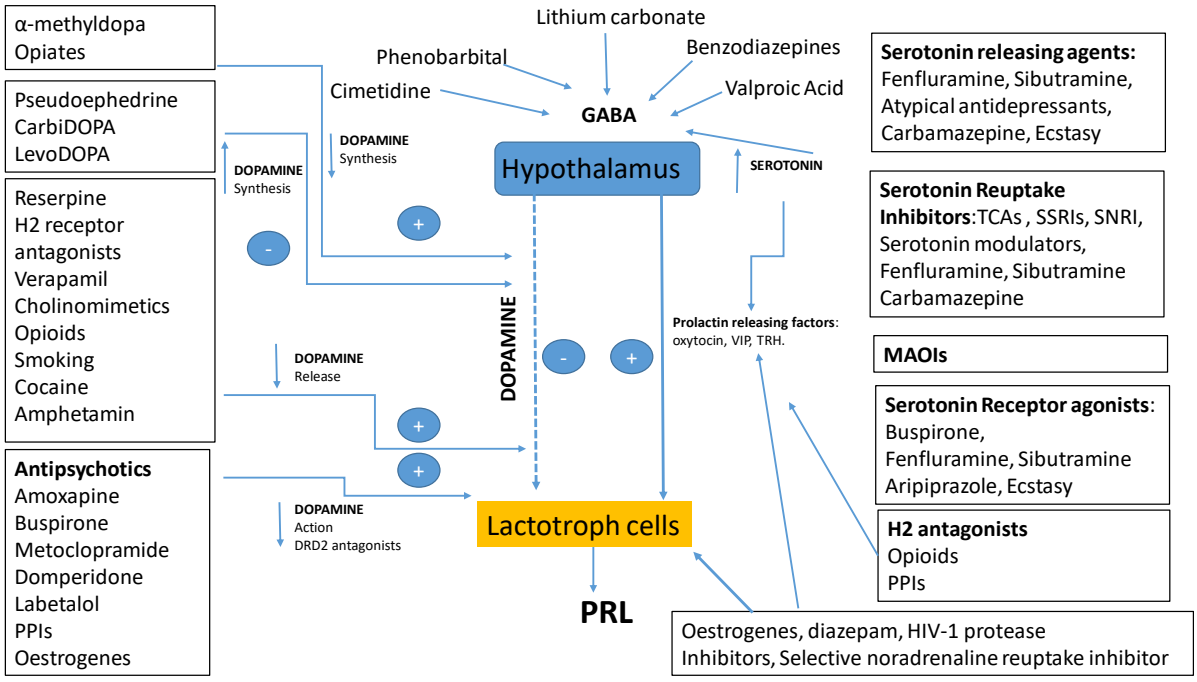

Figure 2. Mechanisms of drug-induced hyperprolactinemia with selected examples (adopted from La Torre et al. (2). In addition to opiates, cholinomimetics, PPIs and smoking indirectly also stimulate the opioid receptors. PPIs, Protein pump inhibitors; TCAs, tricyclic anti-depressants; MAO, monoamine oxidase; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-noradrenaline reuptake inhibitors.

The potency of anti-psychotics and neuroleptic-like medications to induce a rise in prolactin levels varies (Table 1). The level of prolactin increase depends on the anti-psychotic drug (different affinity and selectivity for dopamine receptors; blood-brain barrier penetrating capability, degree of serotoninergic inhibition), the dose administered, and the patient's age and sex (34,35). Lastly, polymorphisms in genes related to dopamine receptors (such as DRD1, DRD2, DRD3) (63), dopamine transporters (SLC6A3), and

dopamine-metabolizing enzymes (such as monoamine oxidase and catechol-O-methyltransferase) have been associated with individual variations in response to anti-psychotic treatment and the development of side effects, including hyperprolactinemia (64).

Although direct evidence establishing the involvement of adrenergic receptors in hyperprolactinemia caused by antipsychotic and antidepressant medications remains unproven, indirect indications, as elucidated in Figure 1, suggest the potential implication of these receptors. It is plausible that adrenergic receptors might play a partial role in the hyperprolactinemia induced by these medications.

Table 1. Medications and Their Ability to Cause Hyperprolactinemia

Cluster Name	Subclass mechanism of action	Medications	Prolactin increment	Frequency of prolactin increment (61,65)
Anti-psychotics				
First generation anti-psychotics	Antagonize/block dopamine receptors, especially D2 receptors. Can block α1 adrenergic receptors.	Butaperazine	UP to 2-3-fold normal range with dozes 60 mg/daily. Higher in women (66)	High
		Chlorpromazine	Up to 3-fold with initiation of treatment, up to 2-fold in long-term treatment) (67)	Moderate/ High
		Flupenthixol	Up to 2-3-fold during the first month, and normalization in the next few months (68)	High
		Fluphenazine	Up to 3-fold with initiation of treatment, up to 2-fold in long-term treatment (67). Up to 40-foldof the upper end of the normal range (69)	High
		Haloperidol	Up to 9-fold at the beginning of treatment (3-fold in long-term treatment) (70)	High
		Loxapine	Up to 3-foldof the upper end of the normal range in women (66)	Moderate
		Perphenazine	Up to 40-fold of the upper end of the normal range (69)	Moderate
		Pimozide	?	Moderate

		Prochlorperazine	?	?
		Promazine	Up to 4-fold of the upper end of the normal range (69)	
		Thiordiazine	Up to 3-fold with initiation of treatment, up to 2-fold in long-term treatment) (67)	High
		Thiothixene	Up to 3-fold with initiation of treatment, up to 2-fold in long-term treatment (71)	Moderate/ High
		Trifluoperazine	?	Moderate
		Veralipride	Up to 10 time increment, transient (72)	High
		Zuclopenthixole	?	?
Second generation anti-psychotics	Dopamine receptors blockade especially D2 receptors, serotonin (5-HT) receptor blockade, glutamate modulation, can antagonize α1 or α2 adrenergic receptors and histamine receptors.	Amisulpiride	Up to 10-fold at the beginning of treatment and remained elevated during treatment but lower levels (68)	Case reports
		Aripiprazole	Reduce prolactin levels (73)	Case reports / No effect/ Reduced prolactin
		Asenapine	Up to 2-fold increment and rarely with higher doses up to 4-fold (35)	Low, Moderate
		Brexpiprazole	Mild increment (74)	Low
		Clozapine	Mild (up to 2-fold) and transient (75)	Case reports or No effect
		Iloperidone	Mild increment, transient (76)	Case reports or No effect
		Levosulpiride	Up to 15-fold normal range (77)	Case reports / Moderate for galactorrhea (78)
		Lurasidone	Up to 10-fold normal range (79)/ no effect (80)	Case reports or No effect
		Molindone	?	Moderate
		Olanzapine	Mild (up to 2-fold) and transient (75)	Low

		Paliperidone	2-10-fold for depot formulations (81)	High
		Perospirone	None (82)	None/ Case reports
		Quetiapine	Mild and transient (75)	Low
		Risperidone	2-10-fold	High (83)
		Sertindole	Mild and transient (75)	?
		Sulpiride	Up to 6-7-fold from baseline, dose dependent effect (84)	High
		Thiethylperazine	?	?
		Ziprasidone	Up to 4-fold from baseline and transient (35,75)	Low
Neuroleptic-like medications				
	Block D2 receptors	Domperidone	Up to 10-fold (85,86)	High
		Droperidol	Significant increment after 10 minutes of administration, with peak at 20 minutes (87)	?
		Metoclopramide	Up to 15-fold (2)	High
Anti-depressants				
TCAs	Block the reuptake of both serotonin and noradrenaline.	Amitriptyline	2-fold increment on dosage 200/300mg (88)	Low
		Amoxapine	3,5-fold to baseline (89)	High
		Clomipramine	Up to 3-fold increment from baseline (90)	High
		Desipramine	Just above the normal limit with 100 mg oral administration (91)	Low, Controversial
		Imipramine	Up to 4-fold normal range (69)	Controversial
		Nortriptyline	2-fold in the first 2 weeks in one patient (88)	None or Low
SSRI	Block the reuptake of serotonin.	Citalopram/ Escitalopram	Up to 3-fold increment (52)	None or Low (rare reports), Controversial data
		Fluoxetine		
		Fluvoxamine		
		Paroxetine		
		Sertraline		

SNRI	Block the reuptake of both serotonin and noradrenaline.	Duloxetine	Up to 2-fold normal range (92)	Case reports
		Milnacipran	Not increased risk of hyperprolactinemia (93)	None
		Venlafaxine	Up to 2-fold normal range, dose related (94)	Case reports
MAO inhibitors	Inhibit the enzyme. Monoamine oxidase, which breaks down serotonin, noradrenaline, and dopamine, though increasing their levels.	Clorgyline	Up to 2-fold from baseline (95)	Low
		Pargyline	Up to 3-fold from baseline (95)	Low
		Phenelzine	Unclear elevation, galactorrhea (96)	Low/ Case reports
Atypical anti-depressants	Inhibit noradrenaline and dopamine reuptake.	Bupropion	No significant change (80)	Case reports
	Increases the release of both serotonin and noradrenaline.	Mirtazapine	No significant change (80)	Case reports
Serotonin modulators	Modulate serotonin receptors in the brain to enhance serotonin transmission.	Indoramine	(97)	Case report
		Nefazodone	Mild increment from baseline only at acute administration (98)	None/ Case reports
		Trazodone	Up to1.5-fold from baseline (99)	None, Low
		Vortioxetine	Up to 2-fold elevation (100)	Case reports
Selective noradrenaline reuptake inhibitor	Inhibit reuptake of norephinephrine.	Reboxetine	Up to 2-fold from baseline (101)	Case reports
NMDA receptor antagonist	Block NMDA receptors though influencing glutamate neurotransmission.	Esketamine	?	None
Gastric acid reducers				
H2 receptor antagonists	H2 receptor antagonists.	Cimetidine	Up to 3-fold after 400 mg IV infusion (102)	Low
		Ranitidine	Mild increment only in high IV doses (103)	Low
		Esomeprazole	?	

Protein pump inhibitors (PPIs)	Inhibit the activity of the proton pump (H+/K+ ATPase) in the stomach's parietal cells.	Lansoprazole	4-fold increment from baseline (104)	Case reports or No effect
		Omeprazole	No significant change (105)	
		Pantoprazole	No significant change (106)	
		Rabeprazole	No significant change (107)	
Opioids				
	They activate opioid receptors. Main types of opioid receptors: mu (μ), delta (δ), and kappa (κ).	Apomorphine	By acting as dopamine agonist it lowers prolactin (108)	None
		Heroin	Elevated in addiction (within normal range) compared to healthy control or during abstinence (109)	Moderate in addicted patients that have values over 25 ng/mL
		Methadone	Mild increment, transient increases for several hours following the administration (110)	?
		Morphine	Up to 2-fold increment from baseline (111)	High
Antihypertensives				
	It decreases the release of noradrenaline.	Methyldopa	3-4-fold (65) up to 40-fold normal range (69)	Moderate
	Inhibit the storage of neurotransmitters like noradrenaline and serotonin in nerve cells, though decreasing their release.	Reserpine	2.5-fold increment from baseline (112) Up to 40-fold normal range (69)	High
	Block calcium channels in cardiac and smooth muscle cells.	Verapamil	2-fold (113)	Low
Estrogens				
	By using as contraceptives they suppress sexual axis.	Estradiol infusion	3-4-fold, dose-dependent, way of administration is important (oral and IV) (114)	Low

		Estradiol withdrawal	?	
Gonadotropins and GNRH agonists				
	Same as endogenous components, used for fertility induction.	hCG	Up to 4-fold increment, transient (115)	High
		hMG	Up to 2.7-fold increment from baseline, transient (116)	High, Transient
	GnRH agonist.	Leuprolide acetate	1.5-fold higher prolactin in compared to hMG alone, transient (117)	High
Other drugs				
Benzodiazepines	Enhances the effects of GABA in the brain.	Diazepam	Mild, dose-dependent (118)	Controversial
Anxiolytics	Serotonin receptor agonist.	Buspirone	2-fold (119)	Case report or No effect
	α-2 adrenergic agonist.	Clonidine	?	Case reports
Anticonvulsant	Block sodium channels in nerve cells.	Carbamazepine	Less than 2-fold in sleep entrained (120,121)	?
		Phenytoin	Controversial, it can also lower prolactin levels (122)	?
	Enhances the effects of GABA in the brain.	Phenobarbital	Controversial (123)	
		Valproic Acid	Controversial, it can also lower prolactin (124)	Case reports
Mood stabilizer	Decrease dopamine release and glutamate, increase GABA inhibition.	Lithium Carbonate	Controversial, no effect (183)	None
Antimigraine medication	Calcium channel blocker.	Flunarizine	Mild increment, up to 1.5-fold from baseline (125)	Case reports
Weight loss medications	Increase the release of serotonin and inhibit its reuptake.	Fenfluramine	Mild increment within normal range in previews non-hyperprolactinemic patients (126)	High
	Inhibit the reuptake of serotonin,	Sibutramine	4-fold (2,127)	Case report

	noradrenaline, and dopamine.			
Anticholinesterase inhibitors	Reversible acetylcholinesterase inhibitor.	Physostigmine salicylate	Less than 100 ng/mL (44).	Low
Prokinetic medication	Stimulate serotonin receptors in the gut.	Cisapride	High increment (up to 200 ng/dL) but in co-administration of other drug inducing hyperprolactinemia (128)	Case reports
Antihistaminic with sedative and antiemetic properties	Block histamine receptors.	Promethazine	?	?
Central Nervous System Stimulants	Increase the release and reduce the reuptake of noradrenaline and dopamine in the brain.	Amphetamine	Mild, only during withdrawal (129)	?
		Methylphenidate	No effect (130)	Case reports/ No effect
ADHD medication	α -2 adrenergic agonist.	Guanfascine	Controversial, it can also lower prolactin (131)	Case reports
Decongestant	Sympathomimetic amine, predominantly α-1 agonist	Pseudoephedrine	Lower prolactin levels (132)	Case reports
Rheumatoid arthritis medications	Reduce inflammation, modify immune response.	Bucillamine	Mild increment within normal range (133)	Case report
		Penicillamine	?	Case reports
Osteoporosis medication	Monoclonal antibody that inhibit the receptor activator of nuclear factor kappa-B ligand (RANKL).	Denosumab	?	Case reports
Substance of abuse	Blocks the reuptake of noradrenaline, dopamine, and serotonin in the brain.	Cocaine	Decrease prolactin levels (134) Mild increment only during withdrawal (129)	Case reports
	Increases the release and inhibits the reuptake of serotonin and to	Ecstasy	Mild or no effect (135)	?

	some extent, dopamine and noradrenaline.			
	Stimulates nicotinic acetylcholine receptors, leading to the release of neurotransmitters like dopamine and noradrenaline.	Smoking	Mild increment, transient (136)	Moderate
Anti-HIV medications	Protease inhibitors that prevent the cleavage of viral proteins and thereby inhibiting viral replication.	Ritonavir / Saquinavir	Mild (137)	Case reports
Radiotherapy	Use of high-energy radiation to damage the DNA within the targeted cells.	Intracranial radiotherapy	?	Moderate (138)

*Frequency of increase to abnormal prolactin levels with chronic use: high: >50%; moderate: 25 to 50%; low: <25%; none or low: case reports. The effect may be dose-dependent. Drugs marked with blue have controversial data or decrease prolactin levels as explained in the table. Where we could not identify reliable data for the parameters in the table we added a question mark. *First-generation anti-psychotics, non-selective dopamine receptors antagonists. **Second-generation anti-psychotics.*

Anti-Psychotics

Anti-psychotics are traditionally classified as first- and second-generation, but more recently a new classification taxonomy has been developed by McCutcheon et al. to express different receptor affinity of different anti-psychotics. Due to the impossibility to include in this new classification all drugs that cause hyperprolactinemia, we have used the old classification (Table 1) (139,140).

The first-generation anti-psychotics are typically associated with more severe hyperprolactinemia (2-3-fold increment), whereas second-generation drugs have lower D2 affinity and stronger blockade of 5HT2A receptors leading to milder prolactin elevations (1-2-fold), except risperidone, paliperidone, and amisulpiride. Amisulpiride has the greatest potential to cause hyperprolactinemia of all anti-psychotics (4).

The first-generation anti-psychotics, such as fluphenazine and haloperidol, act as non-selective dopamine receptors antagonists (2,10). The therapeutic effects on psychotic symptoms occur through D2 and D4 receptor binding in the mesolimbic area, while side effects are mediated by D2 blockade in the striatal area (linked to extrapyramidal effects) and in the hypothalamic infundibular system (linked to hyperprolactinemia) in more than 50% of patients. A clinical trial involving 69 patients examined the effects of various anti-psychotic medications on prolactin levels, including chlorpromazine, depot haloperidol, fluphenazine, zuclopenthixol, sulpiride, pimozide, droperidol, and flupenthixol. The study found a significant elevation in prolactin levels only in females, with a mean level of 1106 mIU/L (52 ng/mL) compared to the normal range of <480 mIU/L (22.6 ng/mL). In

males, the mean prolactin levels were within the normal range, which may be attributed to the significantly lower total daily dose of chlorpromazine used in males (199.0-220.1 mg/day) compared to females (384.4-302.48 mg/day, P<0.05) (7).

Second-generation anti-psychotics with lower D2 affinity led to milder prolactin elevations (1-2-fold), except for paliperidone, risperidone, and amisulpiride whose effect on prolactin is similar to the first-generation neuroleptics. Chlorpromazine, loxapine, olanzapine and quetiapine have variable effects on prolactin secretion, while aripiprazole, clozapine, iloperidone, lurasidone have little or no effect on prolactin secretion (35).

An important factor contributing to variations in the induction of hyperprolactinemia by different anti-psychotic medications is the blood-brain barrier. Permeability glycoprotein transporter (P-gp), coded by the ABCB1 gene, is expressed in various tissues including in the cells of the blood-brain barrier. P-gp plays a role in actively transporting hydrophobic drugs with a molecular weight greater than 400 Da out of the brain, thus protecting the brain from these medications; therefore, this protein can change drug bioavailability (141,142).

The affinity of risperidone, paliperidone, and amisulpiride (prolactin rises up to 10-fold with these drugs) for P-gp is approximately twice that of olanzapine and chlorpromazine (prolactin rise is up to 3-fold with these drugs), and four times greater than haloperidol and clozapine (prolactin rise can be high initially but usually reduces with time) (143). The higher affinity of risperidone, paliperidone, and amisulpiride to P-gp could, among other mechanisms, partly explain the greater induction of hyperprolactinemia by these drugs, as P-gp does not allow them to enter the brain via the blood-brain barrier. Therefore, the portal circulation of the anterior pituitary delivers a somewhat higher concentration of these drugs to the lactotrophs, which are located outside the blood-brain barrier, to inhibit the D2 receptors (144).

Aripiprazole can act as a partial agonist at D2 receptors and display partial agonist activity at 5HT1A receptors, while also acting as an antagonist at 5HT2A receptors. Antagonism at these receptors can help to normalize prolactin levels since 5HT2A receptor activation has been associated with increased prolactin release. That is why it is considered a prolactin secretion modulator (145). Its role in prolactin levels has been investigated in a study involving both retrospective and prospective components (146). The retrospective part of the study included 30 patients undergoing risperidone treatment, when it was observed that after 6 months of treatment, prolactin levels remained high although somewhat lower than at the start of observation. In the prospective part of the study, 30 other patients were divided into two groups: one group receiving risperidone alone at a daily dosage of 2-4 mg and the other group receiving a combination of risperidone and aripiprazole at a daily dosage of 5-10 mg. The group receiving adjunctive aripiprazole exhibited significantly lower serum prolactin levels compared to the risperidone-only group at weeks1 (914±743 vs 1567±1009 mU/L), 2 (750±705 vs 1317±836 mUI/L) and 6 (658±590 vs 1557±882 mUI/L). Notably, during aripiprazole treatment, prolactin levels at weeks 1, 2, and 6 were significantly lower than at baseline (P< 0.05) (at baseline patients were treated with risperidone as monotherapy), suggesting that aripiprazole may effectively alleviate risperidone-induced hyperprolactinemia. Similar findings supporting the role of aripiprazole in reducing prolactin levels have been reported in other studies (147). Combination therapy presents a promising therapeutic approach for adjunctive treatment or for transitioning from risperidone to mitigate hyperprolactinemia (146).

More recently, a new medication SEP-363856, a trace amine-associated receptor 1 (TAAR1) and 5HT1A agonist, has been developed to treat schizophrenia.

Its mechanism of action is not based on D2 antagonism, and has a favorable effectiveness and tolerability profile, without causing hyperprolactinemia (148). This category of medication serves as compelling evidence for the significant involvement of dopamine receptors in drug-induced hyperprolactinemia, and it is a future viable therapeutic choice for patients experiencing adverse effects associated with hyperprolactinemia.

DRUG-INDUCED HYPERPROLACTINEMIA IN PEDIATRIC PATIENTS

Anti-psychotic medications have been found to induce hyperprolactinemia in the pediatric population as well as in adults. In a trial involving 35 children and adolescents with early-onset psychosis, primarily diagnosed with childhood-onset schizophrenia or psychotic disorder not otherwise specified, prolactin levels were measured after a 3-week washout period, as well as after 6 weeks of treatment with haloperidol, olanzapine, and clozapine (149). Following the 6-week treatment period, haloperidol (9 of 10 patients – mean age 13.4 years) and olanzapine (7 of 10 patients– mean age 15.9 years) resulted in prolactin levels above the upper limit of normal. The mean increase was 5.2-fold for haloperidol and 2.4-fold for olanzapine. The prolactin response did not show statistically significant differences between females and males treated with haloperidol and olanzapine. Clozapine (22 patients, mean age 14.7) caused a small but significant rise in females (1.2-fold) but levels remained in the normal range for all patients. There was no rise in males. Why this difference between females and males is only on clozapine remains unclear and difficult to explain. However, in a study involving 36 girls aged 8-17 years, mean prolactin levels were higher in girls compared to boys, with the most significant increase occurring around the age of 13y, correlating with menarche. A highly significant correlation was found between increases in plasma prolactin and estradiol levels between the ages of 11 and 13 years. Girls with long menstrual cycles (>28 days) between the ages of 14 and 16 years had higher prolactin levels ($p<0.05$) (150). Even though the mean age of patients on clozapine was above 13 years, we do not possess information on the duration of the menstrual cycle of those girls, as if it is longer, the physiologic estrogenization because of the longer menstrual cycle can impact the range of prolactin elevation. In any case, the population sample size was relatively small to draw definitive conclusions and to provide answers why this happens only in clozapine patients (149).The authors concluded that the prolactin response in male children and adolescents treated with haloperidol or olanzapine was significantly higher than that observed in adult males. However, the prolactin response in female children and adolescents after haloperidol treatment did not differ significantly from that of adult females in similar studies, possibly due to the adult similarity of estrogen status seen in female adolescents (149). Aripiprazole in another study showed a lesser prolactin increase than olanzapine, quetiapine, and risperidone, similar to the adult population (151).

In another clinical trial involving 396 children and adolescents (aged 14.0 ± 3.1 years), the impact of anti-psychotic medications on prolactin levels was studied. The medications involved risperidone, olanzapine, quetiapine, and aripiprazole. Risperidone caused the highest incidence of hyperprolactinemia (93.5%) and had the highest peak prolactin levels (median = 56.1 ng/mL) followed in order by olanzapine, quetiapine, and aripiprazole. Menstrual disturbances were the most prevalent side effect (28.0%), particularly with risperidone (35.4%). Notably, severe hyperprolactinemia was associated with decreased libido, erectile dysfunction, and galactorrhea (152).

In conclusion, a comprehensive meta-analysis comprising 32 randomized controlled trials with a total of 4643 participants, with an average age of 13 years, has demonstrated that risperidone, paliperidone, and olanzapine are associated with a significant increase

in prolactin levels among children and adolescents. Conversely, aripiprazole is linked to a notable decrease in prolactin levels in this age group. It is worth noting that haloperidol was not included in these studies, resulting in an absence of evidence regarding its prolactin-related effects in this population (153).

These findings underscore that haloperidol, risperidone, paliperidone and olanzapine are potent inducers of hyperprolactinemia in children and adolescents, mirroring observations in the adult population. A comprehensive listing of medications associated with hyperprolactinemia in children can be found in Table2.

Table 2. Drugs Reported to Induce Hyperprolactinemia in Children and Adolescents

Medication class	High >50 percent of patients	Moderate 25-50 percent of patients	Low <25 percent of patients	Case reports
Anti-psychotics, first-generation 'typical'	Fluphenazine (154) Haloperidol (149,155)	Chlorpromazine (156) Loxapine (157) Pimozide (158,159)		
Anti-psychotics, second-generation 'atypical'	Paliperidone (160,161) Risperidone (152,155,162–164)	Asenapine (165) Molindone (166) Olanzapine (149,152) Lurasidone (167,168)	Ziprasidone (169) Quetiapine (152,162)	Clozapine (149) Aripiprazole* (152,170) Amisulpride (171) Brexpiprazole (172)
Anti-depressants	Clomipramine (173)		Desipramine (174)	Bupropion (175) Citalopram (176) Escitalopram (177) Fluoxetine (178) Sertraline (179) Duloxetine (177) Paroxetine (180) Venlafaxine (181)
Anti-emetics and gastrointestinal medications	Metoclopramide (182–184) Domperidone (185,186)			Omeprazole (187) Lansoprazole (187) Cisapride
Others	Fenfluramine (188)		Estrogens (189) Triptorelin (190)	Clonidine (191) Methylphenidate (181) Guanfacine (181) Valproic acid (181) Penicillamine (181)

**Aripiprazole is a partial agonist at the type 2 dopamine receptor and display partial agonist activity at the type 1A serotonin receptor (5HT1A) and antagonist at 5HT2A receptor. It can be used in combination with other psychotropic medications to reduce prolactin levels. Aripiprazole itself can sometimes cause mild hyperprolactinemia (192).*

CLINICAL MANAGEMENT OF ANTI-PSYCHOTIC-INDUCED HYPERPROLACTINEMIA

Drug-induced hyperprolactinemia should be considered in the differential diagnosis of elevations of prolactin levels, sometimes greater than 200 µg/L (4260 mIU/L). Particularly when serum prolactin levels exceed 80-100 µg/L (1700-2130 mIU/L), pituitary magnetic resonance imaging (MRI) should be performed to rule out the presence of any underlying pituitary or hypothalamic masses that may contribute to hyperprolactinemia (193). According to the guidelines from the Endocrine Society, in symptomatic patients suspected of having drug-induced hyperprolactinemia, it is recommended the first test to diagnose drug-induced hyperprolactinemia is the discontinuation of the medication for 3 days or switch to an alternative drug (e.g. a prolactin-sparing anti-psychotic (e.g. aripiprazole), or an anti-psychotic with lower dopamine antagonist potency (Table 1) followed by retesting of serum prolactin levels.

However, any discontinuation or substitution of anti-psychotic agents should be done in consultation with the patient's psychiatric physician. If discontinuation is not possible or if the onset of hyperprolactinemia does not coincide with therapy initiation, obtaining a pituitary MRI is recommended (despite prolactin levels) to differentiate between medication-induced hyperprolactinemia and hyperprolactinemia caused by a pituitary or hypothalamic mass (194).

Before initiating treatment with an anti-psychotic medication, it is advised that clinicians inquire about the patient's previous treatment experience, sexual dysfunction, menstrual history (including irregularities and menopausal status), as well as any history of galactorrhea. Additionally, obtaining a baseline prolactin level is recommended before starting treatment (195). This pre-treatment screening for hyperprolactinemia can help determine whether subsequently elevated prolactin levels are due to medication-induced factors (196) and make the diagnosis easier without the need to perform further imaging.

While treatment of hyperprolactinemia in patients receiving anti-psychotics may not always be necessary, in cases where clinical hypogonadism is evident, several options are available (193). The initial step is to discontinue the drug if clinically feasible. If discontinuation is not possible, switching to a similar anti-psychotic that does not cause hyperprolactinemia is suggested. If neither of these options is feasible, cautious administration of a dopamine agonist may be considered in consultation with the patient's physician (194). It is worth noting that these interventions only result in the normalization of prolactin levels in approximately half of the patients receiving anti-psychotics, and careful psychiatric monitoring is required due to the possibility of psychosis exacerbation with dopamine agonists (193).

For patients with long-term hypogonadism demonstrated by hypogonadal symptoms or low bone mass, the use of estrogen or testosterone replacement is recommended. In rare instances where patients receiving anti-psychotics also present with a pituitary tumor, treatment options primarily revolve around tumor-specific interventions, considering especially optic chiasm compression. When a non-functioning tumor is suspected, the above options to eliminate the drug-induced component of hyperprolactinemia should be considered, with supervised short-term cessation of the medication to clarify drug-induced or tumor-derived hyperprolactinemia (193).

In addition to the interventions mentioned earlier, addressing fertility concerns in patients with drug-induced hyperprolactinemia may require further measures. Normalization of prolactin levels through medication adjustment or dopamine agonist therapy can often lead to the restoration of fertility. In situations

where fertility is not spontaneously regained, fertility treatment with gonadotrophins or assisted reproductive procedures may be necessary.

NEUROLEPTIC-LIKE MEDICATIONS

Metoclopramide and domperidone are anti-emetic and gastrointestinal motility agents known also as neuroleptic-like medications which can increase pituitary prolactin secretion and breast milk production by a dopamine antagonistic action (Figure 1).

Metoclopramide is a central and peripheral D2 receptor antagonist (197). Its administration is followed by an acute increase in prolactin levels up to 15-fold above the baseline that persists in chronic administration of the drug (2). Even though the majority of patients treated with metoclopramide develop hyperprolactinemia (Table 1), related symptoms such as amenorrhea, galactorrhea, gynecomastia, and impotence remain unclear (2).

Domperidone is a peripheral D2 antagonist (it does not cross the blood-brain barrier) used for treating intestinal motility disorders, especially for the prevention of gastrointestinal discomfort with dopaminergic treatment in Parkinson's disease (198), as it antagonizes the D2 receptors in the upper gastrointestinal tract. It also reaches the D2 receptors on lactotroph cells inducing hyperprolactinemia, and can be used for stimulating lactation, for example in women with preterm infants, or an adoptive parent (199,200), and even in transgender women who wish to breastfeed (201,202). It can cause a 10-fold elevation in prolactin levels with normalization of prolactin levels after three days (85,86). Neuroleptic-like medications are summarized in Tables 1 and 3.

Table 3. H2 Receptor Antagonists, Opioids, Anti-Hypertensives, PPIs, Estrogens, and Other Drugs *and Their Ability to Cause Hyperprolactinemia.*

Medication class	High >50% of patients	Moderate 25-50% of patients	Low <25% of patients	Case reports
Anti-emetic and gastrointestinal	Domperidone Metoclopramide		Prochlorperazine	Esomeprazole Omeprazole Lansoprazole Cisapride
H2-receptor antagonists			Cimetidine Ranitidine	
Anti-hypertensives		Methyldopa	Verapamil	
Others	Fenfluramine Opioids		Estrogens	Protease inhibitors Cocaine Bucillamine Clonidine Methylphenidate Guanfascine Valproic Acid Penicillamine

ANTI-DEPRESSANTS

Anti-depressants can be classified based on their structure and mechanism of action into tricyclic anti-depressants (TCAs), selective serotonin reuptake

inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase (MAO) inhibitors, atypical anti-depressants, serotonin modulators, selective noradrenaline reuptake inhibitor, and NMDA (N-Methyl-D-Aspartate) receptor antagonists (203). Data on their ability to cause hyperprolactinemia are controversial, as described below. The two main mechanisms, both related to elevated serotoninergic tonus, explain how anti-depressants can induce hyperprolactinemia by indirect modulation of prolactin release by serotonin and serotonin stimulation of GABAergic neurons (50) Adrenergic receptors involvement in their ability to cause hyperprolactinemia remains unclear. (Figure 1).

Data on the incidence of hyperprolactinemia with anti-depressant medications, especially SSRIs, MAO inhibitors, and some TCAs, suggest that they can cause modest and generally asymptomatic hyperprolactinemia (4,193). Their ability to cause hyperprolactinemia is summarized in Table 1.

TCAs

TCAs, such as amitriptyline, desipramine, clomipramine, and amoxapine, can induce sustained mild hyperprolactinemia (2) (Table 1). They manifest their mechanism of action by blocking the reuptake of noradrenaline and serotonin, through increasing serotoninergic tonus, leading to hyperprolactinemia. Amitriptyline's ability to cause hyperprolactinemia seems to be dose-dependent. A dosage of 150-250 mg/day to 5 patients showed no effect on prolactin levels after 3-7 weeks (204), whereas a dosage of 200-300 mg/day caused a 2-fold increment of prolactin levels in two of nine chronic treated patients (88). In 13 patients with depression taking amitriptyline or desipramine, prolactin levels were studied after intravenous injection of tryptophan (serotonin precursor). It was observed that tryptophan-induced prolactin elevation was significantly increased compared with a preceding placebo period (205). A similar tryptophan test was performed with clomipramine 20 mg vs placebo in 6 normal subjects. Levels of prolactin increased after tryptophan infusion in pretreated patients with clomipramine (206),suggesting serotonin involvement in this hyperprolactinemia.

The effect of the traditional TCA imipramine on serum prolactin levels is controversial. A five-week double-blind study on patients with depression taking imipramine did not show any significant change in serum prolactin (207). However, another study in young healthy men showed that imipramine’s effect on prolactin is dose-dependent (usually therapeutic dose is 50-150 mg): oral administration of 100 mg, but not of 40 mg, led to a consistent rise in prolactin levels after 3 hours of administration, but the rise was mild (maximum 25.85 ng/mL (550 mUI/L) (91).

Data regarding nortriptyline's ability to induce sustained hyperprolactinemia are lacking. Anyway, over a 4-6 week treatment of 8 patients with nortriptyline up to 150 mg/daily, no difference was found between placebo and the medication group. In only one patient was observed a transitional 2-fold elevation in the first 2 weeks (88).

Amoxapine, which is an anti-depressant with neuroleptic properties as well, is found to increase prolactin levels in 10 patients approximately 3.5-fold compared to baseline and more than desipramine in 12 patients, where almost no difference with baseline was observed (89). The proposed mechanism of hyperprolactinemia involves the blockade of the D2 receptor in tuberoinfundibular neurons or the anterior pituitary gland (2).

SSRIs

SSRIs enhance serotonin activity via inhibition of neuronal serotonin reuptake. This could be the most prominent mechanism leading to a prolactin elevation. A review of 13 case reports showed prolactin levels between 28 and 60 ng/mL (595 and 1276 mUI/L) (52).

In a French study, 27 of 159 cases (17%) had SSRI-induced hyperprolactinemia with sertraline being the most prominent, followed by fluoxetine, paroxetine and fluvoxamine. Only citalopram was found not to increase prolactin levels significantly (208). However, in another study fluoxetine, paroxetine, and fluvoxamine were found again to elevate prolactin levels, but they also found citalopram to induce hyperprolactinemia. In this study duloxetine, milnacipran, and sertraline (which was the most prominent in the previous study) were not associated with an increased risk of hyperprolactinemia (93). Fluoxetine-induced hyperprolactinemia was found in patients with major depression (4.5% of men and 22.2% of women) following 12 weeks of fluoxetine treatment (209).Differences in the ability to cause hyperprolactinemia can be attributed to the variations in the affinity of the SSRIs for dopamine, histamine, and GABA receptors.

The Nurses' Health Study and its follow-up study assessed anti-depressant use and circulating prolactin levels in 610 women (including 267 anti-depressant users) with two measurements of prolactin an average of 11 years apart (210). In this study, mean prolactin levels were similar among SSRI users (13.2 µg/L, (280 mUI/L), 95% CI 12.2-14.4), users of other classes of anti-depressants (12.7 µg/L (270 mUI/L), 95% CI 11.0-14.6), and non-users (13.1µg/L, (278 mUI/L), 95% CI 12.8-13.4) (210). However, the duration and dosage of anti-depressant use at the time of prolactin sampling had not been assessed, as the participants had only responded as current anti-depressant users/non-users on a questionnaire.

MAO Inhibitors

Monoamine oxidase is an enzyme responsible for breaking down neurotransmitters such as serotonin, noradrenaline, and dopamine in the brain. Inhibition of this enzyme is expected to increase the levels of all those neurotransmitters. Even though increased dopamine is suspected to be related to lower prolactin levels, probably the serotonin increment prevails and that is why this class of medications is related to hyperprolactinemia; or dopamine and serotonin increment neutralize each other and no difference in prolactin levels is seen.

MAO inhibitors with serotoninergic activity (pargyline and cordyline) can cause modest and generally asymptomatic hyperprolactinemia (2,61). Phenelzine was observed to persistently increase prolactin levels in 4 of11 patients, which returned to normal during a placebo week and rose again in all 4 patients after treatment restart (88).

Atypical Anti-Depressants

Mirtazapine's mechanism of action is different from other anti-depressants, as it does not inhibit the reuptake of serotonin or noradrenaline, but it increase the release of serotonin and noradrenaline (211). In any case, prolactin levels did not show any difference in 8 healthy male subjects pre- and post-mirtazapine 15 mg oral administration (212).

Serotonin Modulators

Trazodone acts through dual inhibition of serotonin reuptake and serotonin type 2 receptors, coupled with antagonism of histamine and α-1-adrenergic receptors (213). In 12 patients with depression, 150 mg of trazodone for 3 weeks caused significantly higher prolactin levels after 12 hours, 1 week, and 2 weeks of treatment compared to baseline. Higher levels were after the first week 15,3+/-8,5 ng/mL (325 +/- 180 mUI/L) compared to baseline 9,1 +/- 5,6 ng/mL (194+/-119 mUI/L) (99).

Selective Noradrenaline Reuptake Inhibitor

Reboxetine is a selective noradrenaline reuptake inhibitor that was shown to increase prolactin in healthy men after acute administration, but this effect can be reversed if reboxetine is simultaneously

administered with α2-blocker mirtazapine, suggesting a role of α2-receptors in the enhancement of prolactin release after reboxetine (214). In any case, conflicting data are present even with this drug, with one other study showing no difference between pre-treatment and after-treatment prolactin levels in patients taking up to 8 mg reboxetine for 4 weeks in 17 patients (215). This discrepancy can be due to the limited number of patients or other neuroendocrine mechanisms still less explored.

SNRI medications are described to cause only mild and rare elevations on prolactin levels, whereas (94), esketamine (NMDA receptor antagonist)is not described to cause hyperprolactinemia.

Summary

In summary, controversial data are available on anti-depressant-induced hyperprolactinemia. Routine monitoring of prolactin levels in patients taking anti-depressants is not recommended unless symptoms related to prolactin increase (in premenopausal women: menstrual cycle dysfunction leading to amenorrhea, oligomenorrhoea, anovulatory cycles, low libido, and energy; in men: erectile dysfunction, decreased energy and libido, decreased muscle mass, decreased body hair; and for both of them osteopenia, galactorrhea and infertility) occur (50,193). If the prolactin serum level is elevated (> 25 µg/L (531 mUI/L), in these patients a differential diagnosis is needed. The proposed approach is to withdraw the anti-depressant drug slowly over 2 weeks and replace it with another anti-depressant less likely to cause hyperprolactinemia, then reassess symptoms and prolactin levels after 2-4 weeks (193). If the serum prolactin remains elevated, other causes of hyperprolactinemia should be addressed by an endocrinologist. Another approach is to perform a pituitary MRI if the replacement of the anti-depressant is difficult to manage.

GASTRIC ACID REDUCERS

Histamine-Receptor Inhibitors

Histamine, a CNS neurotransmitter, binds to both H1 and H2 receptors. It can stimulate prolactin secretion via H1 receptors by inhibiting the dopaminergic system. On the contrary, histamine can also inhibit prolactin secretion via H2 receptors using a non-dopaminergic mechanism involving β-endorphin, vasoactive intestinal peptide, vasopressin, or TRH (216), all of which act as prolactin-releasing factors (49) (Figure 1).

In the French Pharmacovigilance Study, H2 receptor antagonists were found to contribute to 5% of drug-induced hyperprolactinemia, primarily with ranitidine (odds ratio = 4.43; 95% CI: 1.82–10.8) (11). Other studies have shown that H2-receptor antagonists such as cimetidine and ranitidine can elevate prolactin levels (217,218). Specifically, cimetidine caused a three-fold increase in prolactin levels after a 400 mg IV infusion, although this effect was not observed with oral administration of 800 mg cimetidine in healthy individuals (102) (Table 1,3).

Interestingly, it has been observed that systemic administration of the H2 agonist impromidine does not prevent cimetidine-induced hyperprolactinemia. In contrast, pre-administration of benzodiazepines or GABA lowered the prolactin response. This suggests that cimetidine-induced hyperprolactinemia may be mediated through neurotransmitters in the GABA-ergic system (219).

Proton-Pump Inhibitors

Proton-pump inhibitors (PPIs) have been recently reviewed regarding the risk of hyperprolactinemia and related sexual disorders observed with long-term use (220). The exact mechanism by which PPIs increase prolactin levels is not fully understood; possible explanations include inhibition of dopamine receptors, interference with other dopamine receptors,

involvement of the serotoninergic pathway, modulation of the opioid pathway, and a potential role in decreasing prolactin clearance (220) (Figure 2). In addition, PPIs can increase gastrin levels in chronic use especially in females using high doses (221). As gastrin can act as prolactin-inhibitory factor (108), this antagonistic effect may explain the relatively mild hyperprolactinemia occurring with this class of drugs. Esomeprazole has a mild inhibitory effect on CYP3A4, which leads to decreased metabolism of estrogen, thereby increasing serum estrogen levels which can stimulate the production of prolactin (222). Gynecomastia, impotence, irregular menses, and galactorrhea have been described with PPI use. Hyperprolactinemia occurred less often than sexual disorders, and most cases of hyperprolactinemia were reported with omeprazole, esomeprazole, and lansoprazole use (e.g. 4-fold increment with lansoprazole) (104) (Table 1,3). Pantoprazole and rabeprazole were only sporadically associated with hyperprolactinemia. The authors assert that the occurrence of sexual dysfunction in individuals using PPIs, despite having normal prolactin levels, may be attributed to the development of low vitamin B12 levels, hypomagnesaemia and iron deficiency resulting from PPI usage. These nutritional deficiencies have been implicated in the manifestation of sexual disorders in other studies (220,223,224).

OPIOIDS

Endogenous opioids, morphine, and related drugs, activate ε-, μ-, κ- and δ- opioid receptors in the hypothalamus, modulating pituitary hormone secretion. They do not possess direct effects on pituitary cells (225,226). They inhibit the gonadal axis via ε receptors (GnRH suppression) and stimulate prolactin production by reducing the activity of tuberoinfundibular dopaminergic neurons via μ, κ and δ opioid receptors – mostly μ receptors as the μ receptor opioid antagonist naloxone prior to morphine and methadone use prevents opioid-induced hyperprolactinemia (227). Indirect stimulation of prolactin release can be mediated by stimulating prolactin-releasing factors production (the serotoninergic pathways discussed above) (228) (Figure 2). Hyperprolactinemia can then lead to additional gonadal axis suppression. In addition, opioids can modulate the corticotroph axis via κ and δ opioid receptors and the somatotroph axis via μ, κ and δ opioid receptors (226). Additionally, opioids manifest negative effects on bone health through direct inhibition of osteoblasts by opioids, gonadal axis suppression, altered mental status, and other comorbidities (chronic conditions, smoking, alcohol use) (229).

Acute intravenous or intra-ventricular administration of endogenous opioids leads to a rapid plasma prolactin increase in a dose-dependent manner (44,225). Chronic use of opioids effects on prolactin can vary: oral opioids for chronic pain increase prolactin, but morphine administered intrathecally for chronic non-cancer pain had no effect on prolactin (226). Hyperprolactinemia induced by opioids can be symptomatic: painful gynecomastia, galactorrhea, and hypogonadism have been reported in chronic opioid users. These can be alleviated with discontinuation or reduction of opioid dose, and sometimes dopamine agonists such as bromocriptine (226). Methadone induces a transient increase in prolactin levels, whereas chronic methadone users have normal basal prolactin levels (110), (Table 1, 3).

On the contrary, in a study involving six patients with hyperprolactinemia and amenorrhea, the use of naltrexone, an opioid antagonist, was investigated to determine if blocking endogenous opioids could improve the sexual axis. On the first day of naltrexone administration, significant increases were observed in the mean concentration of luteinizing hormone (LH), LH pulse amplitude, and estradiol levels compared to the control day. This indicated a prompt partial reactivation of the hypothalamic-pituitary-gonadal axis as a result of naltrexone, leading to heightened gonadotrophin levels and subsequent release of estradiol. However, it was found that the effect of

opioid antagonism did not result in a sustained increase in estradiol secretion with chronic treatment. Additionally, prolactin levels continued to increase over time (mean prolactin level 255 ± 121 microgram/L), despite the initial improvement in the gonadal axis. This study demonstrated that although prolactin-induced suppression of the gonadal axis can be reversed to some extent by acute opioid antagonism, it is not an effective treatment for revitalizing the gonadal axis in the long term. Possible explanations for this lack of sustained effect include desensitization of the hypothalamic-pituitary unit for the effects of opioid receptor blockade and other disruptors of the axis, which may counteract the positive effects of opioid antagonism (230,231).

For endocrinopathies caused by opioids, including hyperprolactinemia, potential management choices include reducing or discontinuing opioid usage whenever feasible and exploring alternative pain relief therapies for chronic pain situations. Hormonal replacement therapy can be considered for hypogonadism and hypoadrenalism (226).

ANTIHYPERTENSIVES

Some antihypertensive medications including α-methyldopa, verapamil, labetalol, and reserpine, have been associated with hyperprolactinemia. This phenomenon is attributed mainly to the potential inhibition of dopaminergic pathways, highlighting the complex interplay between anti-hypertensive therapy and endocrine function. Other mechanisms are drug-specific and will be explained below.

α -methyldopa is an α-adrenergic inhibitor that leads to the suppression of monoamine synthesis, including noradrenaline, dopamine, and serotonin, which likely contributes to its anti-hypertensive effect. It causes hyperprolactinemia through the inhibition of dopamine synthesis by competitive inhibition of DOPA decarboxylase which transforms L-dopa into dopamine (61) (Figure 2). Long-term treatment resulted in elevated basal prolactin levels (3-4-fold), while a single dose of 750-1000mg reaches a peak of high prolactin level after 4-6 hours of administration (232). Gynecomastia is the most common endocrine side effect.

Calcium channel blockers are other drugs studied for their potential to cause hyperprolactinemia. The dihydropyridine class was found to have no effects on prolactin levels. Whereas, from the non-dihydropyridine class, which mainly blocks L-type of calcium channel receptors in the heart, only verapamil was found to cause 2-fold persistent hyperprolactinemia (and galactorrhea),while drug discontinuation reversed hyperprolactinemia in all patients (113). A clinical trial suggested that verapamil acts by reducing dopamine release in the tuberoinfundibular pathway through calcium influx inhibition (Figure 2), possibly by N-calcium channels which are known to be involved in the regulation of dopamine release and other neurotransmitters (233).

Labetalol is an α- and β-adrenoceptor blocker anti-hypertensive that has been reported to increase prolactin levels when administered intravenously, but not when administered orally (100 or 200 mg) as labetalol cross the blood-brain-barrier only in negligible amounts. The increase in prolactin release caused by intravenous labetalol is not readily explained by its interference with adrenergic receptors. The exact mechanism underlying this effect of the drug is currently unclear, but it is possible that labetalol's ability to block dopamine activity (anti-dopaminergic activity) might be involved in this response (234) (Figure 2). Pre-treatment with levodopa and carbidopa can prevent prolactin response after labetalol (235), suggesting dopamine pathway involvement suppression inside the blood-brain-barrier.

Reserpine is a rauwolfia alkaloid previously used for the treatment of hypertension as well as psychosis, schizophrenia, and tardive dyskinesia; it reduces dopamine by inhibiting their hypothalamic storage in

secretory granules (236), and by blockade of vesicular monoamine transporter type 2 in monoamine neurons (237), leading to hyperprolactinemia. Prolactin levels are higher during treatment with reserpine than 6 weeks after discontinuation of the drug. Increased incidence of gynecomastia and breast cancer has also been reported among patients on anti-hypertensive therapy with reserpine (236). The ability of anti-hypertensives to cause hyperprolactinemia is summarized in Tables 1 and 3.

ESTROGENS

Estrogens stimulate prolactin secretion by several mechanisms: They bind to specific intracellular lactotroph cells receptors, though enhancing prolactin gene transcription and synthesis (238). They also inhibit tuberoinfundibular dopamine synthesis, stimulate lactotroph cell hyperplasia, downregulate dopamine receptor expression, and modify lactotroph responsiveness to other regulators (23,239) (Figure 2). Estrogen-induced hyperprolactinemia is dependent on the degree of estrogenization. Higher levels of estrogens in pregnancy and during ovulation increase prolactin levels with the last, contributing to a higher normal range of prolactin in pre-menopausal women.

Studies documenting the incidence of hyperprolactinemia showed that women on oral contraceptives were reported to have higher prolactin levels by 12% to 30% (240,241). Some, but not all, studies suggest that there is a dose-dependent effect (4). No increase in basal prolactin levels is reported during therapy with modern contraceptives with lower amounts of estrogen (242)or estrogen plus cyproterone acetate alone (243).

In transgender patients, estradiol or ethinyl estradiol treatment, the prolactin level rise was dependent on the dose of estrogen, duration of exposure, and alteration of SHBG levels. Estradiol infusion at levels above 10,000 pg/mL for as short as 6-7 hours significantly elevated prolactin levels by 3- to 4-fold, whereas ethinyl estradiol 2 mg/day for 1 month did not consistently elevate prolactin in all patients, which can be due to its ability to increase SHBG binding and maintaining free portion in the normal range (114) (Table 1, 3).

For women on post-menopausal hormone replacement therapies over 2.5 years, serum prolactin measured were within the normal range (244). In another study on 75 women, who were randomly assigned to three groups: control (receiving placebo), transdermal hormonal replacement (biphasic 17β-estradiol and progesterone, natural hormones), and oral ethinyl-estradiol and desogestrel, prolactin levels significantly increased in the oral group, but not in the transdermal group. There was a significant difference in hormone levels: in the oral group, estradiol levels increased five times and estrone levels eleven times. In the transdermal group, estrone and estradiol levels were increased three times (245).

GONADOTROPHINS AND GNRH AGONISTS

In addition to the known prolactin function in lactation, several studies have suggested other benefits of prolactin in oocyte development, formation of corpus luteum and its survival, steroidogenesis and implantation (246). In natural cycles there is a transient increase in late follicular phase of prolactin, but this increment is higher in stimulated cycles (246). In a cohort study were included 79 patients; 60 individuals underwent in vitro fertilization, 14 received clomiphene citrate treatment, and five patients with premature ovarian failure were administered estradiol. During the course of human menopausal gonadotrophin (hMG) treatment, a notable increase in both serum estradiol and prolactin concentrations were observed from early to late follicular days ($P < 0.01$). Specifically, prolactin levels increased from an initial mean value of 367±38 mIU/L (17.25±1.8 ng/mL) to 991±84 mIU/L (46.6±4 ng/mL) (Table 1). Bromocriptine effectively mitigated the increase in

prolactin levels but was associated with a significant elevation in estradiol levels ($P < 0.05$) because prolactin itself works as a controller of estradiol increment. Clomiphene treatment led to a significant increase in serum estradiol levels ($P < 0.01$) but a significant decrease in serum prolactin concentrations during the late follicular phase ($P < 0.01$), indicating disruption of the estradiol-prolactin feedback mechanism. Among patients with premature ovarian insufficiency, serum prolactin concentrations increased concomitantly with rising serum of estradiol concentrations (after estradiol administration). Additionally, it was observed that the presence of prolactin significantly reduced estradiol production by granulosa cells ($P < 0.05$) (116).

An increment of prolactin levels is found even after hCG administration with a maximum prolactin level of 93.2 ng/mL; 1983 mIU/L (115).Notably, knowing that prolactin is a stress hormone, during assisted procedures it is increased, but this is a transitory increment without consequences in fertility outcome (247).

Not only gonadotrophins but also GnRH agonists are widely used during invitro fertilization to maintain a controlled and synchronized ovarian stimulation. Use of leuprolide acetate (GnRH agonist) concomitantly with hMG, resulted in higher prolactin and estradiol levels in comparison with patients receiving only hMG (prolactin 24.2 vs 16.8 ng/mL; 515 vs 358 mIU/L) (117). In another randomized study, along protocol with 0.1 mg subcutaneous triptorelin starting from day 10 of the preceding stimulation cycle and short protocol, where 0.1 mg subcutaneous triptorelin is given in the stimulating cycle, were compared. Prolactin levels were measured at 9 am in the first day of hCG administration. The long protocol correlated with higher prolactin levels (31.3 ± 16.9 vs 23.7 ± 11 ng/mL; 666 ± 359 vs 504 ± 234 mIU/L) (248).

In children, GnRH agonists are used in precocious puberty (CPP)as well as growth hormone deficiency (GHD)who do not properly respond to exogenous growth hormone treatment. In a study involving 119 children with CPP and 93 with GHD, treated with triptorelin or leuprolide, prolactin levels were measured before and every six months for 6 years for CPP group and for 2 years for GHD group. Moreover, prolactin levels were checked after 6 and 12 months of treatment withdrawal. In this study was concluded that even though prolactin levels were higher in triptorelin treated patients (only 3.8% developed hyperprolactinemia in triptorelin group which was solved after withdrawal – baseline 12.5 ± 3.7 ng/mL (266 ± 79 mIU/L) to max 45.6 ± 4.5 ng/mL; 970 ± 96 mIL/L), no significant difference was found in prolactin in basal condition and during GNRH agonist treatment in CPP and GHD (190) (Table 2).

OTHER DRUGS

A lot of other drugs have been reported to cause mild (less than 2-fold increment) increases in prolactin levels. A synthesized visualization of these mechanisms is shown in Figure 2.

The acute administration of buspirone, an anxiolytic medication, was investigated in a study involving 8 healthy volunteers. The findings revealed an increase in plasma prolactin levels across all participants compared to the baseline levels observed in 8 control subjects. During the study, blood samples were collected at 30-minute intervals over a duration of 2 hours. The zenith of prolactin levels was observed between minutes 90 and 120 for all individuals, with the maximum elevation reaching 37 ng/mL (787 mIU/L) (249). It is noteworthy that the augmentation of prolactin is believed to exhibit a dose-dependent relationship. Furthermore, it was observed that chronic usage of buspirone did not lead to significant alterations in prolactin levels, indicating a potential adaptation to the acute changes induced by the medication. The underlying mechanism responsible for this phenomenon is posited to involve both serotoninergic and dopaminergic implications (119).

Carbamazepine, a widely used anticonvulsant, was examined in a cohort comprising 4 patients with complex partial seizures undergoing chronic carbamazepine treatment (200 mg administered three times daily). Blood samples were collected at intervals of 2 hours. Additionally, a group of 5 patients with untreated epileptic seizures participated, wherein a thyrotrophin-releasing hormone (TRH) stimulation test was performed both prior to and 35-50 days post the administration of 200 mg carbamazepine three times daily. Blood samples were obtained 10, 30, and 60 minutes following intravenous injection of 200µg TRH. Furthermore, 4 normal volunteer subjects were included in the study. On the first day, a placebo was administered, followed by the administration of 400 mg carbamazepine at 8 AM on the second day. Blood samples were collected at baseline on both days and subsequently at hourly intervals until 4 PM. After a span of two weeks, a nocturnal study was conducted, spanning from 6 PM to 6 AM. The investigation revealed that there were no discernible alterations in spontaneous prolactin release or TRH-stimulated prolactin levels. However, a slight increase in sleep-entrained prolactin values was observed, while retaining the secretory circadian rhythm. Given that the release of prolactin during sleep is largely attributed to serotoninergic activity, it is plausible that the modest increment (less than 2-fold) may implicate serotoninergic modulation (working as a serotonin-releasing factor and reuptake inhibitor) facilitated by carbamazepine (120,121).

Sympathomimetic amines fenfluramine and sibutramine, formerly used for appetite suppression due to their stimulatory effect on the synaptic concentration of serotonin, have been shown to induce hyperprolactinemia as a result of increased serotoninergic activity and postsynaptic stimulation of 5HT2Areceptors. In a case report, after starting sibutramine, a 38-year-old female patient developed hyperprolactinemia (prolactin levels 46 and 89.6 ng/mL (978 and 1906 mUI/L) with amenorrhea and galactorrhea. Discontinuation of sibutramine, confirmed by a sella MRI, led to rapid normalization of prolactin levels within 15 days, and symptoms resolved during a 90-day follow-up (2,127).

Cholinomimetic drugs have been reported controversially in the literature regarding their ability to cause hyperprolactinemia. However, in collaborative studies from the National Institute of Mental Health and the University of California, San Diego, three separate experiments were conducted involving volunteers of different genders and ages. In the first experiment, nine volunteers received physostigmine salicylate at 33 µg/kg, while in the second experiment, eleven male volunteers were given 22 µg/kg of physostigmine salicylate. The third experiment involved six volunteers receiving 3 mg of arecoline hydrobromide. Placebo saline was administered in all experiments as well. It was shown that intravenous injection of physostigmine or arecoline can elevate prolactin correlating with raised β-endorphin levels in the blood. Prolactin elevation was less than 100 ng/mL (2127 mUI/L). Cholinergic activation in the hypothalamus, particularly focusing on β-endorphin, might help in explaining how peptides modify primary neurochemical effects on hormone regulation in the hypothalamus and pituitary (44).

Bucillamine, an analogue of D-penicillamine used as an antirheumatic drug in Japan, has been reported to induce hyperprolactinemia (109 ng/mL (2319 mUI/L)) after 30 months of treatment start, associated with gynecomastia and galactorrhea in one case report. The mechanism remains unclear (133).

‘Ecstasy’ (MDMA) was shown to increase prolactin secretion in rhesus monkeys by stimulating serotonin release and by direct-acting as a 5HT2A agonist (250); In nine studies, five of them observed an increase in prolactin levels due to the intervention. However, in the remaining studies, there was no significant change in prolactin levels, and these unresponsive results tended to occur when a lower dose of the intervention

was used on average. This suggests a potential relationship between the dosage of the intervention and its effect on prolactin levels (135).

Smoking, particularly the consumption of high-nicotine cigarettes, has been associated with a significant acute elevation in prolactin levels, ranging from 50% to 78% above the baseline, within 6 minutes after smoking. These elevated levels persist for approximately 42 minutes and return to baseline within 120 minutes of initiating smoking (136). The underlying mechanism probably involves the stimulation of rapid prolactin release through the augmentation of endogenous opioids, which subsequently inhibits dopamine release (251). However, prolonged nicotine exposure leads to desensitization of dopamine receptors, and lowers dopamine turnover (48) probably contributing to hyperprolactinemia. It has been hypothesized that the increased incidence of osteopenia and osteoporosis could be at least partly related to this effect (252).

Recently, an association has been reported between HIV-1 protease inhibitors and the adverse effect of galactorrhea and hyperprolactinemia in four HIV-1 infected women treated with indinavir, nelfinavir, ritonavir, or saquinavir. The cause of this unexpected toxicity could be attributed to several possible mechanisms: 1) Protease inhibitors may enhance the stimulatory effects of prolactin due to their inhibition of the cytochrome P450 system, leading to longer half-life of prolactin; 2) opportunistic infections in AIDS patients may induce cytokine-driven prolactin production by pituitary or immune cells; 3) protease inhibitors might exert direct endocrine effects on the pituitary or hypothalamus (253,254). To explore mechanisms of hyperprolactinemia induced by protease inhibitors, experiments were conducted using rat pituitary cells and hypothalamic neuronal endings. The results showed that both ritonavir and saquinavir could directly stimulate prolactin secretion, while not affecting dopamine release. This suggests that these protease inhibitors might interact with specific mammalian proteins in the anterior pituitary involved in prolactin secretion, leading to the observed galactorrhea and hyperprolactinemic effect (137).

Regarding chemotherapy and immunosuppression, there are some controversial data on the effect of chemotherapy and immunosuppression on prolactin levels, as significant prolactin increases are not frequent and usually mild (2). Prolactin and growth hormone have been involved as part of a cytokine system in the recovery of the immune response after chemotherapy and bone marrow transplantation (255). In a study of 20 breast cancer patients undergoing high-dose chemotherapy and autologous stem-cell transplantation, plasma prolactin levels increased within and 30 days after transplant, yet still remaining within the normal range. The use of antiemetic drugs further raised prolactin levels. Patients in continuous complete remission after transplantation exhibited higher prolactin levels, while elevated prolactin did not impact disease-free survival, suggesting potential for further research into post-transplant immune response (256).

Radiotherapy for intracranial germ cell tumors was shown to induce hyperprolactinemia with a prevalence of 35.3% (138).
Other drug inducing hyperprolactinemia are described in Table 1.

DRUGS REPORTED TO DECREASE PROLACTIN LEVELS OR HAVE AN EQUIVOCAL EFFECT

Several medications, beyond the established treatments like cabergoline, bromocriptine, carbidopa and levodopa, have reported effects on reducing prolactin levels. For instance, pseudoephedrine, an α-adrenergic stimulant primarily affecting α1 receptors, shares structural similarities with amphetamine and moderately stimulating dopamine release in the brain by acting on D2 receptors in the pituitary, consequently lowering prolactin levels. Studies have indicated pseudoephedrine's potential to decrease

milk production, at least partly attributed to its effect on prolactin levels through dopaminergic actions in the pituitary (132). Moreover, indirect evidence suggests that α-1 receptors stimulation leads to decreased prolactin levels (41).

Amphetamine was seen to produce a poor prolactin suppressant effect in either normal- or hyperprolactinemic subjects. The proposed mechanism of prolactin lowering potential is due to their ability to stimulate the release of dopamine (257). However, during the withdrawal period of cocaine use, hyperprolactinemia has been observed, probably due to a decrease in dopamine levels, leading to dysregulation in the dopamine system and increased prolactin. Moreover, during withdrawal, prolactin can be secreted as a stress hormone (129).

Guanafascine, an α2 adrenergic agonist, used to treat ADHD, has been shown to decrease prolactin levels. In a longitudinal study spanning three years involving 15 patients diagnosed with hyperprolactinemia, the noteworthy suppressive impact of guanfacine on prolactin levels suggests potential involvement of hypothalamic or extrahypothalamic adrenergic pathways in the intricate regulation of prolactin secretion (131). Even though α2 stimulation has been shown to increase prolactin levels in rats, this is not fully understood in humans making the explanation in this case confusing (42).

The impact of benzodiazepines (BDZ) on prolactin secretion is a subject of debate. Research findings have yielded conflicting results. Some studies conducted on both non-epileptic patients and healthy volunteers have not detected significant modifications in prolactin levels following BDZ treatment (258). A study on 30 adolescent patients with schizophrenia with gradually increasing doses of diazepam to a maximum of 100-400 mg/day, with 4 weeks of treatment, showed that only doses higher than 250 mg/day give a significant but mild increase in prolactin levels. Proposed mechanisms are inhibition of TIDA neurons by activation of the GABA system, or activation of the endorphin-ergic system leading to hyperprolactinemia (118). On the contrary, diazepam was found to suppress the secretion of prolactin in vitro through one of two mechanisms: it either strengthens the direct inhibitory action of GABA on prolactin release, or it hinders a benzodiazepine-sensitive Ca2+-calmodulin dependent protein kinase at micromolar concentrations leading to a reduction of prolactin secretion (259).

Moreover, phenytoin, an anticonvulsant impeding sodium channels in nerve cells, have generated conflicting data regarding their impact on prolactin levels. In animal studies, phenytoin showcased a rapid decline in both prolactin release and mRNA concentrations, functioning as a partial T3 agonist by binding to T3 nuclear receptors (260). However, clinical observations revealed elevated resting levels of prolactin in phenytoin-treated patients compared to untreated counterparts. Remarkably, responses to metoclopramide and bromocriptine remained unaltered, indicating a limited effect of phenytoin on the D2 receptors present on lactotrophs (261). Even the conclusions drawn from these findings remain contentious. Evidence suggests that phenytoin treatment may enhance the growth hormone response to levodopa, implying a phenytoin-induced dopaminergic activity at the hypothalamic-pituitary level (122). More specifically, it is postulated that phenytoin might enhance dopamine receptor sensitivity by inhibiting the Ca2+ calmodulin complex. This effect could contribute to reduced prolactin secretion (122). On the contrary, other studies have not demonstrated any notable alterations in prolactin levels due to phenytoin administration (262). The discordant outcomes surrounding phenytoin's impact on prolactin levels underscore the complexity of its effects and necessitate further investigation for conclusive insights into its mechanisms of action.

In another comprehensive study involving 126 subjects, both males and females, with generalized or

partial epilepsy receiving phenobarbital as monotherapy or in combination with phenytoin or benzodiazepines, a distinct pattern emerged. Specifically, the administration of phenobarbital, either alone or in combination, resulted in elevated prolactin levels, but this elevation was found to be statistically significant only in the male participants. Notably, knowing that an epileptic attack itself can cause hyperprolactinemia, those data remain confusing. The proposed mechanism in this study is phenobarbital interaction with GABA receptors, leading to increased prolactin levels (263). However other studies do not show any change in prolactin levels (123).

Valproic acid, an anticonvulsant working as a central stimulant of GABAergic neurons, has demonstrated the ability to reduce prolactin basal levels as well as TRH-stimulated prolactin levels. This is indirect proof of the synergically acting of GABA neurons with dopaminergic tracts (124). However, in another study, no effect of valproic acid on prolactin levels was noticed during the night (264).

Lithium carbonate, a pharmaceutical agent employed as a mood stabilizer, has undergone investigation in different studies, as it decreases dopamine release and glutamate, and increases inhibitory GABA (265). One of them encompassed a longitudinal examination involving 9 patients diagnosed with bipolar disorder. The focus of this study was the assessment of plasma prolactin levels before and 12 hours after the evening administration of lithium. Evaluations were conducted on days 1, 6, 8, 13, 30, 60, and 90. Notably, this investigation yielded no discernible correlation between lithium concentration and prolactin levels, and no statistically significant alterations in prolactin levels were observed. The second part of this study adopted a cross-sectional design, involving 26 patients with an established history of long-term lithium treatment spanning durations of 3 months to 20 years. A comparative analysis revealed that prolactin levels, measured at 9 AM following a one-hour period of rest, did not demonstrate elevation in comparison to 16 controls. It is noteworthy that in both studies, lithium concentrations ranged from 0.4 to 1.4 mmol/L (normal range 0.5-1.2 mmol/L) (266). Additionally, the administration of lithium did not exert an impact on the plasma prolactin response to thyrotrophin-releasing hormone (TRH) stimulation compared to pre-treatment levels (267). The combined findings from these investigations provide compelling evidence that lithium does not contribute to hyperprolactinemia, thereby distinguishing it from medications with such an effect.

Cocaine has been shown to decrease prolactin levels beginning at 30-min following cocaine administration reaching statistical significance at the 90- and 120-minute time points (134).

Those medications are mentioned in Table 1. Their mechanism of altering prolactin levels is summarized in Figure 2.

HERBAL MEDICINES AFFECTING PROLACTIN LEVELS

In Table 4 is list of herbal medicines has been used traditionally to stimulate lactation (268). However, firm scientific evidence that they actually induce hyperprolactinemia is scarce.

Table 4. Lactogenic Herbs (268)		
Family name	Species name	Common name
Amaryllidaceae	Allium sativum	Garlic
Annonaceae	Xylopia aethiopica	African Pepper or Ethiopian Pepper
Asclepiadaceae	Secamoneafzelii	-
Costaceae	Costusafer	African Ginger
Euphorbiaceae	Euphorbia hirta	Asthma Plant or Tawa-Tawa
	Euphorbia thymifolia	Petty Spurge
	Hymenocardiaacida	African Almond or Honeytree
	Plagiostylesafricana	-
	Ricinus communis	Castor Bean Plant
Leguminosae	Tamarindus indica	Tamarind
	Acacia nicolita	-
	Desmodiumadscendens	-
Malvaceae	Hibiscus sabdariffa	Roselle or Red Sorrel
	Gossypium herbaceum	Cotton Plant
Moraceae	Milicia excelsa	African Teak or Iroko
	Ficus species	Ficus or Fig trees
Musaceae	Musa paradisiaca	Plantain
Ranunculaceae	Nigella sativa	Black Cumin or Black Seed
	Actaea (Cimiciguga)	Black Cohosh
Solanaceae	Solanum torvum	Turkey Berry or Devil's Fig
Verbanaceae	Lippia multiflora	Bush Tea or False Green Tea
Zingiberaceae	Aframomummelegueta	Grains of Paradise or Alligator Pepper
Fabaceae	Trifolium pratense	Red Clover
	Trigonella foenum-graecum	Fenugreek
Apiaceae	Foeniculum vulgare	Fennel

Some herbs are known to decrease prolactin levels. For example, chaste tree (Vitex agnus-castus) decrease prolactin levels by activating to D2-receptors and suppressing prolactin release, as shown in in vitro experiments on lactotroph cell cultures and in in vivo animal experiments (269). Another herb, Mucuna pruriens, which is a natural source of l-dihydroxyphenylalanine (a dopamine precursor) is found to decrease prolactin levels in humans (270). Vitamin B6 (pyridoxine), by acting as a coenzyme in dopamine synthesis and aspartame, a sweetener metabolized in phenylalanine (dopamine precursor), have been shown to interfere with milk production by reducing prolactin levels (271). Ashgawanda (Withania somnifera) is found to decrease prolactin levels up to 12% (272). Moreover, oral zinc is found to decrease prolactin levels below the normal range in all 17 subjects with normal prolactin levels, in scenario of increased zinc levels in the blood (273).

While none of the mentioned herbs are currently established within clinical guidelines for specifically lactogenic or prolactin-reducing purposes, ongoing research and anecdotal evidence suggest potential roles for these botanicals as adjunctive therapies.

CONCLUSION

In summary, this review underscores the significant role of drug-induced hyperprolactinemia in causing higher prolactin levels and provides detailed insights into how pharmaceutical agents contribute to this effect. However, understanding the complex mechanisms behind drug-induced hyperprolactinemia is still a work in progress. More research is needed to delve deeper into these mechanisms and gain better insights. These efforts will contribute to refining treatment strategies and improving patient care.

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