International Journal of Health Science

ISSN 2764-0159 vol. 6, n. 2, 2026

ARTICLE 5

Acceptance date: 26/01/2026

DRUG-INDUCED HYPERPROLACTINEMIA: A NARRATIVE REVIEW

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Abstract: Introduction: Hyperprolactinemia is characterized by persistently elevated serum prolactin levels and is a common condition in clinical practice. Among non-tumor causes, medication use stands out as one of the main etiologies, especially in patients treated with antipsychotics, prokinetics, and other drugs that interfere with dopaminergic neurotransmission. The condition may be asymptomatic or associated with significant reproductive, sexual, and bone repercussions. **Objective:** To describe the pathophysiological mechanisms, the main drugs involved, the clinical manifestations, the diagnostic methods, and the therapeutic strategies related to drug-induced hyperprolactinemia. **Methodology:** This is a narrative review of the literature, based on scientific articles indexed in the PubMed, SciELO, and MEDLINE databases, as well as reference textbooks on endocrinology. Priority was given to publications from the last fifteen years, including clinical studies, systematic reviews, international guidelines, and relevant case reports. **Results:** Antipsychotics, especially risperidone, paliperidone, amisulpride, and haloperidol, are the drugs most frequently associated with hyperprolactinemia due to the blockade of D2 dopaminergic receptors in pituitary lactotrophs. Other classes involved include prokinetics, antidepressants, H2 antagonists, and opioids. Clinical manifestations vary according to the intensity and duration of the hormonal elevation and may include menstrual disorders, infertility, sexual dysfunction, hypogonadism, and reduced bone mineral density. Diagnosis is based on serum prolactin measurement and careful review of pharmacotherapy, while management prioritizes withdrawal or replacement of the causative medication. **Conclusion:** Drug-induced hyperprolactinemia is a common

and potentially reversible condition. Early recognition and appropriate management are essential to prevent endocrine complications and improve patients' quality of life.

Keywords: Drug Use; Hyperprolactinemia; Antipsychotics.

Introduction

Hyperprolactinemia is defined as a persistent elevation of serum prolactin levels above the reference values established for sex and age group, and is generally considered pathological when it exceeds 20 ng/mL in non-pregnant women and 15 ng/mL in men. It is a relatively common condition in clinical practice, observed both in primary care services and in specialized contexts, such as endocrinology, gynecology, and psychiatry. Its etiologies are diverse and include physiological, pathological, and pharmacological causes, the latter being responsible for a significant portion of diagnosed cases.

Among the non-tumor causes of hyperprolactinemia, medication use stands out as one of the most prevalent, especially in patients undergoing prolonged therapy with drugs that interfere with dopaminergic neurotransmission. It is estimated that up to 30–45% of cases of hyperprolactinemia are related to medication use, a percentage that may be even higher in psychiatric populations due to the widespread use of typical and atypical antipsychotics. In this context, the condition is often underdiagnosed, either due to the absence of obvious symptoms or due to the inappropriate attribution of clinical manifestations to other causes.

From a physiological point of view, prolactin secretion by the adenohypophysis has unique characteristics when compared to other pituitary hormones. While most are regulated by positive hypothalamic stimuli, prolactin is under predominantly inhibitory control exerted by dopamine, which acts on D2 receptors located in the pituitary lactotrophs. Thus, any drug capable of directly antagonizing these receptors or reducing the central availability of dopamine can lead to a sustained elevation of serum prolactin levels.

The drugs most frequently implicated include antipsychotics, especially risperidone, paliperidone, and amisulpride, as well as typical agents such as haloperidol and chlorpromazine. Other classes also associated are prokinetics, such as metoclopramide and domperidone, antidepressants, H2 receptor antagonists, opioids, and sex hormones, such as estrogens and progestogens. Clinically, drug-induced hyperprolactinemia can range from asymptomatic to significant manifestations such as galactorrhea, menstrual disorders, infertility, and hypogonadism, with a significant impact on quality of life. In addition, chronic suppression of the hypothalamic-pituitary-gonadal axis can result in reduced bone mineral density and an increased risk of osteoporosis, especially in cases that are not recognized early.

Objective

This article aims to describe in depth the pathophysiological mechanisms involved in drug-induced hyperprolactinemia, addressing the main associated pharmacological groups, the clinical profile of manifestations, recommended diagnostic strategies, and available therapeutic options. The aim is to provide healthcare professionals with a comprehensive overview to assist in the early identification and appropriate management

of this condition, minimizing endocrine, reproductive, and metabolic complications.

Methodology

A narrative review of the literature was conducted, based on a search of scientific articles published in the PubMed, SciELO, and MEDLINE databases, as well as chapters from classic and updated textbooks in the field of endocrinology. The search prioritized publications from the last fifteen years, without excluding older studies considered fundamental references on the subject. The descriptors used included "drug-induced hyperprolactinemia," "antipsychotics and prolactin," "dopamine antagonists," and "prolactin physiology." Observational clinical studies, systematic reviews, meta-analyses, and international guidelines were selected, with emphasis on recommendations from the Endocrine Society. Relevant case reports were also included when they contributed to the understanding of atypical clinical presentations or outcomes associated with prolonged use of hyperprolactinemic drugs.

Discussion

Understanding drug-induced hyperprolactinemia requires a detailed understanding of the neuroendocrine regulation of prolactin. Dopamine, synthesized in the tuberoinfundibular neurons of the hypothalamus, is released into the pituitary portal circulation and exerts a continuous inhibitory effect on lactotrophs. Pharmacological blockade of D2 receptors removes this physiologic control , leading to increased prolactin gene transcription, lactotroph proliferation, and increased hormone release into the systemic circulation.

Typical antipsychotics, such as haloperidol and chlorpromazine, have a high affinity for D2 receptors and are classically associated with significant and persistent elevations in prolactin. Among atypical antipsychotics, there is significant heterogeneity in terms of hyperprolactinemic potential. Risperidone and paliperidone stand out for their potent dopaminergic antagonist action, while drugs such as quetiapine, clozapine, and, above all, aripiprazole—the latter with partial agonist action—have less impact or even a reducing effect on prolactin levels.

In addition to psychotropic drugs, prokinetics such as metoclopramide and domperidone are classic causes of drug-induced hyperprolactinemia, often associated with galactorrhea, even after short periods of use. Antidepressants, particularly selective serotonin reuptake inhibitors, can elevate prolactin through indirect mechanisms involving serotonergic modulation of hypothalamic dopaminergic neurons. Other classes, such as H2 antagonists and opioids, although less frequently implicated, should also be considered in etiological investigation.

The clinical presentation of drug-induced hyperprolactinemia depends on the magnitude and duration of the hormonal elevation, as well as individual susceptibility. Many patients remain asymptomatic, especially in the presence of macroprolactinemia, a molecular form with greater weight and lower biological activity. In symptomatic cases, women often experience menstrual changes, anovulation, and infertility, while men may report erectile dysfunction, decreased libido, gynecomastia, and loss of

muscle mass. Chronic sex steroid deficiency can significantly compromise bone health, warranting densitometric evaluation in prolonged or symptomatic cases.

The diagnosis is based on a detailed medical history, with emphasis on a complete review of current and recent pharmacotherapy, associated with serum prolactin dosage under standardized conditions, preferably on an empty stomach and in a low-stress environment. Physiological causes, such as pregnancy and lactation, as well as other associated clinical conditions, should be excluded. When feasible, temporary suspension of the suspected medication for at least 72 hours is recommended, followed by a new hormone dosage. In situations where discontinuation is not possible, especially in psychiatric patients, replacement with drugs with lower hyperprolactinemic potential should be considered. Magnetic resonance imaging of the sella turcica is indicated in cases of very high prolactin levels or when diagnostic doubts persist.

The treatment of drug-induced hyperprolactinemia is primarily based on withdrawal or replacement of the causative agent. In persistent symptomatic cases, dopamine agonists such as cabergoline or bromocriptine may be used with caution in patients with psychiatric disorders due to the risk of exacerbation of psychotic symptoms. Hormone replacement may be considered in situations of persistent hypogonadism when it is not possible to modify the basic therapy. Regular clinical and laboratory follow-up is essential to monitor therapeutic response and prevent long-term complications.

Conclusion

Drug-induced hyperprolactinemia is a frequent, often underdiagnosed, and potentially reversible cause of endocrine and reproductive dysfunction. Its recognition requires a high degree of clinical suspicion and careful investigation, with special attention to the patient's medication history. Understanding the pharmacological mechanisms involved allows for the adoption of individualized and safe therapeutic strategies, reducing symptoms and preventing long-term complications. In a scenario of increasing use of psychotropic drugs and other drugs that impact prolactin, multidisciplinary follow-up, combined with continuing medical education, is essential to minimize the adverse effects of this condition on patients' health and quality of life.

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