The Impact of Typical and Atypical Antipsychotics on Prolactin Levels in Adults: A Narrative Review

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ABSTRACT

Background and aim:

Drug-induced hyperprolactinaemia is one of the most common adverse effects of antipsychotic treatment and results primarily from dopamine D_2 receptor blockade within the tuberoinfundibular pathway. This condition may lead to clinically significant consequences, including sexual dysfunction, menstrual disturbances, infertility, and long-term loss of bone

mineral density. The aim of this review is to summarise current evidence on the effects of typical and atypical antipsychotics on prolactin levels in adults.

Current state of knowledge:
First-generation antipsychotics typically cause marked and sustained prolactin elevation. Among second-generation antipsychotics, considerable heterogeneity is observed: risperidone, paliperidone, and amisulpride are associated with substantial prolactin increases, whereas quetiapine and clozapine exert minimal effects. Partial dopamine D_2 agonists, such as aripiprazole, may normalise prolactin levels and represent an effective therapeutic strategy in antipsychotic-induced hyperprolactinaemia. Available evidence also indicates that the prevalence and severity of this adverse effect depend on drug-specific pharmacodynamics, dosage, treatment duration, and individual susceptibility.

Conclusions:
Selection and modification of antipsychotic therapy should account for the risk of hyperprolactinaemia and its potential long-term consequences. Dose reduction, switching to prolactin-sparing agents, or adjunctive treatment with aripiprazole constitute the main management strategies. Routine prolactin monitoring and consideration of endocrine and reproductive factors are essential elements of personalised psychiatric care.

Keywords: Antipsychotic Agents; Hyperprolactinemia; Prolactin; Dopamine Antagonists; Aripiprazole.

1. Introduction

Antipsychotic-induced hyperprolactinaemia is a frequent clinical phenomenon with both short- and long-term implications [1–4,6]. Its consequences include reproductive, sexual, and metabolic disturbances, as well as reduced bone mineral density and increased fracture risk [4,11,16,24,27]. Hyperprolactinaemia is commonly defined as fasting serum prolactin concentrations exceeding 25 ng/mL in women and 20 ng/mL in men [14]. Drug-induced elevations usually remain below 100 ng/mL, whereas levels above 250 ng/mL raise suspicion of prolactinoma [14]. The reported prevalence of hyperprolactinaemia among patients treated

with antipsychotics ranges from 18–72% in men and 42–93% in women, depending on the specific agent used [18].

In recent years, increasing attention has been directed toward the endocrine and metabolic adverse effects of psychotropic medications, reflecting a broader shift toward personalized and long-term psychiatric care. Hyperprolactinaemia represents a paradigmatic example of an adverse effect that bridges psychiatry and endocrinology, highlighting the need for interdisciplinary collaboration. Understanding drug-specific prolactin profiles is therefore essential for optimizing treatment selection and minimizing preventable long-term complications.

2. Materials and Methods

This study is a narrative review and does not involve human or animal participants.
A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar. Publications from the past 15–20 years were considered, including systematic reviews, meta-analyses, and clinical studies addressing the effects of antipsychotics on prolactin secretion [1,2,4,6,7]. Included articles focused on biological mechanisms of hyperprolactinaemia, differential effects of typical and atypical antipsychotics, clinical consequences of elevated prolactin, and management strategies. Non-indexed publications and studies lacking primary data were excluded. No quantitative synthesis was performed. The review is descriptive in nature.

3. Results of the Review

3.1. Prolactin physiology and mechanisms of hyperprolactinaemia

Prolactin is a peptide hormone synthesised primarily by lactotroph cells of the anterior pituitary, although extra-pituitary production has been demonstrated in peripheral tissues such as adipose tissue and the mammary gland [3,9,14]. Under physiological conditions, prolactin secretion is tonically inhibited by dopamine released from hypothalamic neurons acting via D_2 receptors [7,14].
Prolactin release is pulsatile and follows a circadian rhythm, with peak levels occurring during the night and nadir values observed in the afternoon [9,23]. Transient increases may occur in response to stress, physical activity, food intake, and nipple stimulation [15,23].

These physiological fluctuations necessitate standardised conditions for prolactin measurement in clinical practice.

Antipsychotic-induced hyperprolactinaemia results primarily from blockade of D_2 receptors in the tuberoinfundibular pathway, which removes dopaminergic inhibition of prolactin secretion [1,6]. The magnitude of prolactin elevation depends on several pharmacological factors, including D_2 receptor affinity, dissociation kinetics, pituitary drug exposure, and serotonergic modulation [6,7,18,23].

Notably, the pituitary gland lies outside the blood–brain barrier, which may result in disproportionately high exposure to certain antipsychotics. Amisulpride, risperidone, and paliperidone demonstrate particularly strong pituitary D_2 occupancy, contributing to their pronounced prolactin-elevating effects [6,23].

Partial D_2 agonists, such as aripiprazole, exhibit a stabilising effect on dopaminergic signalling. In the presence of D_2 antagonists, aripiprazole may restore inhibitory control over prolactin release, leading to normalisation of hormone levels [19,21]. Meta-analyses confirm substantial inter-drug differences in prolactin-related effects across the antipsychotic class [1,2].

3.2. Typical antipsychotics

First-generation antipsychotics are characterised by high D_2 receptor affinity and prolonged receptor occupancy, resulting in rapid and sustained prolactin elevation [1,3,23]. This effect is often dose-dependent and limits their use in patients at risk of endocrine complications, particularly women of reproductive age and individuals with pre-existing bone disease [1,4,16,24,27].

3.3. Atypical antipsychotics

Second-generation antipsychotics display heterogeneous effects on prolactin secretion. Risperidone, paliperidone, and amisulpride are associated with high prolactin-raising potential, often comparable to that of typical antipsychotics [6]. Olanzapine and ziprasidone

generally cause mild or transient prolactin increases [1,2]. In contrast, clozapine and quetiapine are considered prolactin-sparing agents due to rapid D_2 dissociation and serotonergic counterbalance [6].

The prolactin response to second-generation antipsychotics is influenced not only by receptor binding profiles but also by pharmacokinetic properties, including blood–brain barrier penetration and pituitary exposure. Differences in D_2 receptor dissociation rates and serotonergic modulation contribute to inter-drug variability.

These pharmacological nuances explain why agents within the same class may differ substantially in endocrine adverse effects, underscoring the importance of drug-specific rather than class-based clinical decision-making.

3.4. Partial dopamine agonists

Aripiprazole and other partial D_2 agonists effectively reduce prolactin levels and may be used as adjunctive therapy in patients experiencing antipsychotic-induced hyperprolactinaemia [19,21,22,30]. Low doses are often sufficient to achieve hormonal normalisation without compromising antipsychotic efficacy.

Table 1. Effects of antipsychotics on prolactin levels and clinical implications

Antipsychotic agent / class	Effect on prolactin levels	Mechanism	Clinical implications
Typical antipsychotics	Marked and sustained increase	Strong D_2 receptor blockade	High risk of sexual dysfunction, menstrual disturbances, bone loss
Risperidone / Paliperidone	Significant increase	High pituitary D_2 occupancy	Frequent hyperprolactinaemia; requires monitoring
Amisulpride	Significant increase	Preferential tuberoinfundibular D_2	High endocrine risk despite atypical profile

Antipsychotic agent / class	Effect on prolactin levels	Mechanism	Clinical implications
		blockade	
Olanzapine / Ziprasidone	Mild to moderate increase	Mixed dopaminergic–serotonergic effects	Usually transient or dose-dependent
Quetiapine	Minimal effect	Rapid D_2 dissociation	Prolactin-sparing option
Clozapine	Minimal effect	Low D_2 affinity	Suitable for patients with endocrine vulnerability
Aripiprazole	Decrease / normalization	Partial D_2 agonism	Effective adjunctive treatment for hyperprolactinaemia

3.5. Clinical consequences of hyperprolactinaemia

Elevated prolactin levels may lead to menstrual irregularities, sexual dysfunction, infertility, galactorrhoea, and gynaecomastia. Chronic hyperprolactinaemia contributes to hypogonadism and progressive loss of bone mineral density, increasing the risk of osteopenia, osteoporosis, and fractures [11,16]. Population-based studies suggest a higher fracture incidence among patients receiving long-term prolactin-raising antipsychotics [11,27].

4. Discussion

The available evidence highlights substantial variability among antipsychotics with respect to prolactin elevation. Typical antipsychotics and selected atypical agents demonstrate the highest prolactin-raising potential, whereas prolactin-sparing drugs and partial D_2 agonists provide clinically meaningful alternatives [5,16,23]. Long-term consequences, particularly regarding bone health and reproductive outcomes, warrant further longitudinal investigation.

The clinical relevance of antipsychotic-induced hyperprolactinaemia is often underestimated in routine psychiatric practice. Symptoms such as sexual dysfunction, menstrual irregularities, and fatigue may remain unreported unless actively assessed, leading to prolonged exposure to

elevated prolactin levels. Routine monitoring of prolactin, particularly in patients treated with high-risk agents, allows for early identification of endocrine disturbances and timely intervention. Incorporating prolactin assessment into standard follow-up protocols may improve treatment adherence, quality of life, and long-term outcomes, especially in vulnerable populations such as women of reproductive age and patients receiving long-term maintenance therapy.

Management of antipsychotic-induced hyperprolactinaemia includes dose reduction, switching to prolactin-sparing agents, or adjunctive pharmacological treatment. Dose reduction may be effective but is often limited by the risk of symptom relapse. Switching to agents such as quetiapine or clozapine may reduce prolactin levels; however, this approach is not always feasible due to differences in efficacy or tolerability. Adjunctive treatment with low-dose aripiprazole has emerged as a particularly effective strategy, supported by multiple randomized trials and meta-analyses demonstrating prolactin normalization without compromising antipsychotic efficacy.

Despite extensive research on short-term prolactin changes, data on long-term outcomes remain limited. The cumulative effects of chronic hyperprolactinaemia on bone health, cardiovascular risk, and reproductive function require further longitudinal investigation. Future studies should also explore individual susceptibility factors, including genetic predisposition and sex-related differences, to support more personalized treatment strategies.

5. Limitations

This narrative review has several limitations that should be acknowledged. First, due to its narrative design, the study does not provide a quantitative synthesis of the available evidence, and the selection of included studies may be subject to publication and selection bias. Although efforts were made to include high-quality systematic reviews, meta-analyses, and clinically relevant studies, the conclusions rely on the interpretation of heterogeneous sources.

Second, the reviewed literature encompasses studies with substantial methodological variability, including differences in study design, patient populations, diagnostic criteria for hyperprolactinaemia, and prolactin measurement protocols. These inconsistencies limit direct

comparability between studies and may contribute to variability in reported prevalence rates and effect sizes.

Third, many studies focus on short- to medium-term prolactin changes, whereas data on long-term endocrine, reproductive, and skeletal outcomes remain limited. Consequently, the long-term clinical significance of chronic antipsychotic-induced hyperprolactinaemia, particularly regarding fracture risk and fertility outcomes, cannot be fully determined based on the currently available evidence.

Finally, individual susceptibility factors, such as sex-related differences, genetic predisposition, and comorbid endocrine conditions, are not consistently addressed in the literature. Future well-designed longitudinal studies are needed to clarify these aspects and to support more personalized management strategies.

6. Conclusions

Antipsychotic-induced hyperprolactinaemia remains a common and clinically relevant adverse effect of pharmacological treatment in adult psychiatric populations. The available evidence demonstrates substantial variability in prolactin responses among both typical and atypical antipsychotics, underscoring the importance of drug-specific rather than class-based clinical decision-making. Agents with high dopamine D_2 receptor affinity and prolonged receptor occupancy are consistently associated with marked prolactin elevation, whereas prolactin-sparing antipsychotics and partial dopamine agonists offer clinically meaningful alternatives.

From a clinical perspective, unrecognised and untreated hyperprolactinaemia may lead to significant reproductive, sexual, and skeletal complications, negatively affecting quality of life and long-term health outcomes. Routine monitoring of prolactin levels, particularly in patients receiving high-risk agents or long-term maintenance therapy, should therefore constitute an integral component of comprehensive psychiatric care. Early identification of endocrine disturbances enables timely therapeutic modifications and may improve treatment adherence and overall patient satisfaction.

Current management strategies include dose reduction, switching to prolactin-sparing antipsychotics, and adjunctive treatment with partial dopamine agonists, most notably aripiprazole. Among these options, adjunctive aripiprazole has accumulated the strongest

evidence base and represents an effective and well-tolerated approach in many clinical settings. Nevertheless, treatment decisions should be individualised and balanced against psychiatric stability, tolerability, and patient-specific risk factors.

In conclusion, addressing antipsychotic-induced hyperprolactinaemia requires an integrated, patient-centred approach that bridges psychiatry and endocrinology. Further longitudinal and mechanistic research is needed to clarify long-term outcomes and to support the development of personalised treatment algorithms.

7. Disclosure

Conflict of Interest Statement: The authors declare no conflict of interest related to the publication of this article.

8 Author Contributions

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9. References:

1. Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy*. 2009;29(1):64–73. doi:10.1592/phco.29.1.64
2. Gupta S, Lakshmanan DAM, Khastgir U, Nair R. Management of antipsychotic-induced hyperprolactinaemia. *BJPsych Adv*. 2017;23(4):278–286. doi:10.1192/apt.bp.115.014928
3. Peveler RC, Branford D, Citrome L. Antipsychotics and prolactin: clinical recommendations. *J Psychopharmacol*. 2008;22(2 Suppl):98–103. doi:10.1177/0269881107088436
4. Wieck A, Haddad PM. Antipsychotic-induced hyperprolactinaemia in women. *Br J Psychiatry*. 2003;182:199–204. doi:10.1192/bjp.182.3.199
5. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs. 2004;64(20):2291-314. doi: 10.2165/00003495-200464200-00003. PMID: 15456328.
6. Lin X, Siafis S, Tian J, Wu H, Qin M, Correll CU, et al. Antipsychotic-related prolactin changes: systematic review and dose–response meta-analysis. *CNS Drugs*. 2025. doi:10.1007/s40263-024-01093-3
7. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of antipsychotics: systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939–951.
8. Grigg J, Worsley R, Thew C, Gurvich C, Thomas N, Kulkarni J. Antipsychotic-induced hyperprolactinaemia: synthesis of guideline recommendations. *Ther Adv Psychopharmacol*. 2017;7(2):53–66. doi:10.1177/2045125316675578
9. Montejo AL, Arango C, Bernardo M, Carrasco JL, Crespo-Facorro B, Cruz JJ, et al. Multidisciplinary consensus on therapeutic strategies for antipsychotic-induced hyperprolactinaemia. *Rev Psiquiatr Salud Ment*. 2017;10(2):70–86. doi:10.1016/j.rpsm.2016.06.002
10. Inder WJ, Castle D, Corker J, Gleeson J, Worsley R, Singh B. Hyperprolactinemia in antipsychotic-treated patients: guidelines for assessment and management. *Aust N Z J Psychiatry*. 2011;45(10):830–837. doi:10.3109/00048674.2011.595686
11. Solmi M, Murru A, Pacchiarotti I, Undurraga J, Veronese N, Fornaro M, et al. Antipsychotic use and fracture risk: a population-based study. *Schizophr Bull*. 2023;49(1):121–130. doi:10.1093/schbul/sbac125
12. Jiang Q, Li T, Zhao L, Sun Y, Mao Z, Xing Y, et al. Treatment of antipsychotic-induced hyperprolactinemia: umbrella review. *Front Psychiatry*. 2024;15:1338912. doi:10.3389/fpsyt.2024.1338912
13. Roke Y, van Harten PN, Boot AM, Buitelaar JK. Antipsychotic-induced hyperprolactinaemia in mentally ill patients. *Eur Child Adolesc Psychiatry*. 2012;21:223–231. doi:10.1007/s00787-012-0264-z

14. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *Endocr Rev*. 2013;34(1):1–34. doi:10.1210/er.2012-1043

15. Kar N, Nair S. Prolactin monitoring and risk factors in patients receiving antipsychotics. *Arch Biol Psychiatry*. 2025;3:11–18. doi:10.25259/ABP_17_2025

16. Meaney AM, Smith S, Howes OD, O'Brien M, Murray RM, O'Keane V. Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. Br J Psychiatry. 2004 Jun;184:503-8. doi: 10.1192/bjp.184.6.503. PMID: 15172944.

17. Byerly MJ, Marcus RN, Tran QV, Eudicone JM, Baker RA, Acharya N. Effects of aripiprazole during cross-titration with risperidone or olanzapine. *Schizophr Res*. 2009;107(2–3):218–226. doi:10.1016/j.schres.2008.10.004

18. Bushe C, Shaw M. Hyperprolactinaemia in antipsychotic-treated patients: prevalence and clinical relevance. *J Psychopharmacol*. 2007;21(4 Suppl):38–42. doi:10.1177/0269881107077715

19. Chen CK, Huang YS, Ree SC, Hsiao CC. Differential effects of aripiprazole add-on therapy on prolactin levels. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6):1046–1049. doi:10.1016/j.pnpbp.2010.05.018

20. Zheng W, Cai DB, Yang XH, Ungvari GS, Ng CH, Shi ZM, Hu ML, Ning YP, Xiang YT. Adjunctive aripiprazole for antipsychotic-related hyperprolactinaemia in patients with first-episode schizophrenia: a meta-analysis. Gen Psychiatr. 2019 Oct 17;32(5):e100091. doi: 10.1136/gpsych-2019-100091. PMID: 31673677; PMCID: PMC6802974.

21. Qiao Y, Yang F, Li C, Guo Q, Wen H, Zhu S, Ouyang Q, Shen W, Sheng J. Add-on effects of a low-dose aripiprazole in resolving hyperprolactinemia induced by risperidone or paliperidone. Psychiatry Res. 2016 Mar 30;237:83-9. doi: 10.1016/j.psychres.2015.12.033. Epub 2015 Dec 28. PMID: 26921057.

22. Krøigaard SM, Rask CU, Plessen KJ, Thomsen PH. Antipsychotic-induced hyperprolactinemia in children and adolescents: meta-analysis. *J Clin Psychopharmacol*. 2022;42(3):247–257. doi:10.1097/JCP.0000000000001540

23. Peuskens J, Pani L, Detraux J, De Hert M. Effects of novel antipsychotics on serum prolactin levels. *CNS Drugs*. 2014;28:421–440. doi:10.1007/s40263-014-0159-1

24. Riecher-Rössler A, Rybakowski JK, Pflueger MO, et al. Impact of prolactin-raising antipsychotics on reproductive health. *Acta Psychiatr Scand*. 2013;127(5):341–351. doi:10.1111/acps.12061

25. Holt RI, Peveler RC. Antipsychotics and hyperprolactinaemia: mechanisms, consequences and management. Clinical Endocrinology. 2011 Feb;74(2):141-147. DOI: 10.1111/j.1365-2265.2010.03814.x. PMID: 20455888.

26. Mittal S, Lee S, Fung C. Antipsychotic drug-induced hyperprolactinaemia: case review. *Prim Care Companion CNS Disord*. 2018;20(2):17nr02212. doi:10.4088/PCC.17nr02212

27. Howard L, Kirkwood G, Leese M. Risk of hip fracture in patients with a history of schizophrenia. Br J Psychiatry. 2007 Feb;190:129-34. doi: 10.1192/bjp.bp.106.023671. PMID: 17267929.

28. Besnard I, Auclair V, Callery G, Gabriel-Bordenave C, Roberge C. Hyperprolactinémies induites par les antipsychotiques : physiopathologie, clinique et surveillance [Antipsychotic-drug-induced hyperprolactinemia: physiopathology, clinical features and guidance]. Encephale. 2014 Feb;40(1):86-94. French. doi: 10.1016/j.encep.2012.03.002. Epub 2013 Aug 5. PMID: 23928066.

29. Montejo ÁL, De la Gándara J, et al. Prolactin-related adverse effects of antipsychotics: clinical guide. *Rev Psiquiatr Salud Ment*. 2011;4(4):193–204. doi:10.1016/j.rpsm.2011.06.002

30. Jiang Q, Zhao L, Sun Y, Mao Z, Xing Y. Adjunctive aripiprazole, metformin and PGD: network meta-analysis. *Front Psychiatry*. 2021;12:650674. doi:10.3389/fpsyt.2021.650674