Anais da Faculdade de Medicina de Olinda
Annals of Olinda Medical School

afmo.emnuvens.com.br ISSN: 2674-8487 Original Article

Frequency of symptoms in patients with suspected hyperprolactinemia admitted to a private psychiatric clinic in Recife

Frequência dos sintomas em pacientes com suspeita de hiperprolactinemia internados em uma clínica psiquiátrica particular em Recife

Emilly Kelly Paiva Damasceno[1] Gabriel José Paiva Aldeman[1]
Andréia Veras Gonçalves[1]

[1] Faculdade de Medicina de Olinda. Olinda, Pernambuco, Brazil.

Abstract

Objective: To investigate the symptoms of patients with suspected hyperprolactinemia admitted to a private psychiatric clinic in Recife. Methods: This cross-sectional and descriptive study used non-probabilistic sampling and collected data from January to March 2023 using an in-person questionnaire. Participants undergoing clinical rehabilitation for antipsychotic therapy were assessed for the presence of hyperprolactinemia. We consulted medical records to collect data on the medications in use. Data was collected using Excel 2010 and SPSS version 22.0. **Results**: A total of 51 hospitalized patients aged between 16 and 87 years (SD ± 18.3) were included. Approximately 25% of the participants reported symptomatology commonly associated with hyperprolactinemia, including gynecomastia (53.8%), impaired libido (38.5%), and galactorrhea (7.7%). The medications biperiden hydrochloride and quetiapine hemifumarate were the most prevalent among patients who had complaints of gynecomastia. In contrast, quetiapine hemifumarate, zolpidem hemitartrate, and alprazolam were most frequently used by those reporting impaired libido. **Conclusions:** This study verified the prevalence of symptoms associated with hyperprolactinemia in patients using antipsychotics admitted to a psychiatric clinic.

Keywords: Antipsychotropic drugs; Hyperprolactinemia; Macroprolactinemia; Psychiatric patients.

How to cite: Damasceno **EKP**, Aldeman **GJP**, Gonçalves **AV**. Frequency of symptoms in patients with suspected hyperprolactinemia admitted to a private psychiatric clinic in Recife. An Fac Med Olinda 2024; 1(11):62 doi: https://doi.org/10.56102/afmo.2024.305

Corresponding author:
Emilly Kelly Paiva Damasceno.
E-mail: e-millykelly@hotmail.com

Funding: Programa de Desenvolvimento Institucional de Iniciação Científica (PRODIIC), Faculdade de Medicina de Olinda.
Ethics approval: CAAE No. 62091722.8.0000.8033
Received: 06/20/2023
Approved: 04/03/2024

Resumo

Objetivo: Investigar os sintomas de pacientes com suspeita de hiperprolactinemia internados em uma clínica psiquiátrica privada em Recife. **Métodos**: Trata-se de um estudo transversal e descritivo, com amostragem do tipo não probabilístico, realizado por meio de um questionário aplicado presencialmente em contato com os pacientes no período de janeiro a março de 2023, visando delinear o panorama da presença de hiperprolactinemia em pacientes que fazem uso de terapia antipsicótica no período de reabilitação clínica. Além disso, foram selecionados os prontuários de cada paciente para a coleta das medicações que estavam em uso. Foram utilizados os programas Excel 2010 e SPSS versão 22.0 para construção do questionário e tabulação dos dados coletados respectivamente. **Resultados**: Foram avaliados 51 pacientes internados durante o período de avaliação, com idades que variavam de 16 a 87 anos (DP ± 18,3). Em relação à sintomatologia comumente encontrada em pacientes com hiperprolactinemia, observaram-se queixas em 25,4% da população alvo, que relataram ginecomastia (53,8%), seguido de comprometimento da libido (38,5%) e galactorreia (7,7%). Dentre as medicações, o cloridrato de biperideno e hemifumarato de quetiapina foram as mais prevalentes entre os pacientes que apresentavam queixas de ginecomastia, enquanto o hemifumarato de quetiapina, hemitartarato de zolpidem e alprazolam foram as mais encontradas em uso pelo grupo que apresentou comprometimento da libido. **Conclusões**: Este estudo verificou a prevalência dos sintomas associados à hiperprolactinemia em pacientes que fazem uso de antipsicóticos internados em uma clínica psiquiátrica.

Palavras-chave: Fármacos antipsicotrópicos; Hiperprolactinemia; Macroprolactinemia; Pacientes psiquiátricos.

INTRODUCTION

High serum prolactin (PRL) concentrations may be found in patients with or without symptoms of hyperprolactinemia (HPRL). However, the prevalence rates and degrees of severity of HPRL may differ based on the affinity of antipsychotic drugs for type 2 dopaminergic receptors, different penetration across the blood-brain barrier, and modulation of monoamines other than dopamine.[1]

Although numerous types of drugs can cause hormonal imbalance, the use of drugs that interfere with the neuroendocrine mechanisms is the most commonly associated with the hyperprolactinemic state. More specifically, antipsychotics are commonly associated with HPRL and can interfere with the functioning of the reproductive, endocrine, and metabolic systems.[2]

Most of these drugs are used by specialists in the neuropsychiatric field, including antidepressants, H2 antagonists, opioids, estrogens, and antipsychotics, used for treating schizophrenia and bipolar disorder.[3,4] Furthermore, dopamine is the main inhibitory factor related to the PRL release and acts on binding D2 and D4 receptors in pituitary lactotrophs, which leads to a negative regulation of the PRL gene expression.[5] Because the drugs inhibit dopamine, the PRL release is intensified. Therefore, each drug has a specific mechanism to inhibit dopamine. For ex-

ample, heroin and morphine inhibit the central production of dopamine. In contrast, reserpine and methyldopa cause central depletion of its stocks, and monoamine oxidase inhibitors, cocaine, and amphetamine can inhibit dopamine reuptake.[6,7]

Among patients with psychiatric disorders, the hypersecretion of PRL may be related to two aspects. First, to the antagonist effect to dopamine receptors caused by the conventional antipsychotics (chlorpromazine, butaperazine, thiethylperazine, promethazine, haloperidol, risperidone, pimozide, molindone); and second, to the inhibition of dopamine reuptake caused by antidepressants (buspirone, fluoxetine, paroxetine, tricyclic antidepressants, sulpiride).[8] Therefore, elevated prolactin concentrations are usually found in patients with psychiatric diagnoses because these medications are often part of the treatment for psychiatric conditions.[3,9,10]

PRL is a heterogeneous hormone that can be found in circulation in different ways according to its molecular weight. The main circulating form is the monomeric type with 23kDa molecular weight (mPRL). When found in serum, larger isoforms, such as the covalently linked dimer, are around 45 to 60 kDa ("big PRL"). Lastly, the larger polymeric form is 150-170 kDa ("big-big" PRL), also known as macroprolactin (MPRL). These components can be dosed by the simple and rapid method of precipitation of polyethylene glycol, and an abnormal detection suggests greater attention to the management of antipsychotic-induced HPRL. In turn, MRPL screening is recommended in asymptomatic patients or with unknown etiology.[1,5]

Short-term clinical manifestations of HPRL include sexual dysfunction, infertility, amenorrhea, gynecomastia, and/or galactorrhea. The long-term ones encompass increased risk of osteoporosis, cardiovascular diseases, increased weight gain, and leptin insensitivity. The symptoms of HPRL may impair the physical health of patients undergoing psychotropic therapy, especially when they are not mentioned in consultations and doctors may underestimate their prevalence. Focusing only on short-term effects induced by HPRL, such as amenorrhea or sexual impairment, can contribute to neglecting the long-term effects.[2] Thus, this study aimed to investigate the symptoms of patients with suspected HPRL admitted to a private psychiatric clinic in Recife.

METHODS

This cross-sectional and descriptive study analyzed epidemiological data derived from a psychiatric clinic located in Recife, Pernambuco. We employed a non-probabilistic cluster sampling method.

We employed a non-probabilistic cluster sampling method. The medical records of patients treated from January to March 2023 were initially selected. Before proceeding with data collection, all patients were informed about the project and signed the informed consent form.

Inclusion and exclusion criteria ensured the adequacy of the participants to the scope of the research. We included hospitalized patients with psychiatric diagnoses who were under med-

ical follow-up and antipsychotic therapy. Patients whose clinical information was not available in the medical records were excluded from the study.

Data was collected using a questionnaire developed by the authors, which is yet to be validated. This questionnaire was applied in person and collected demographic information (gender and age of patients), in addition to the type of antipsychotic treatment and the main symptoms associated with hyperprolactinemia (galactorrhea, mild/oligomenorrhea, libido impairment, gynecomastia, and erectile dysfunction).

The questionnaire was carefully designed using the Microsoft® Word for Microsoft 365 MSO program (Version 2211 Build 16.0.15831.20098) 32 bits to address the relevant aspects of the research.

Data was exported to SPSS version 22.0 (IBM SPSS Statistics Inc., Somers, NY, USA) and Microsoft® Excel 2010 for analysis. The software were used to calculate and analyze the variables and extract meaningful insights.

RESULTS

The research analyzed the medical records of 51 hospitalized patients aged 16 to 87 years (SD ± 18.3). Of these, 60.8% were men, and 39.2% were women.

Most participants were over 60 years, representing 29.4% of the total, followed by participants in the 40- to 49-year-old group, representing 21.6% of the total. Therefore, the most prevalent group analyzed by this study included older adults, as shown in Table 1.

Table 1. Characterization of the sample

Age group	Male		Female		Total	
	n	%	n	%	n	%
Under 18	3	**9.7**	0	**0.0**	3	5.9
18 to 29	2	**6.5**	2	**10.0**	4	7.8
30 to 39	9	**29.0**	1	**5.0**	10	19.6
40 to 49	6	**19.4**	5	**25.0**	11	21.6
50 to 59	3	**9.7**	5	**25.0**	8	**15.7**
60 or above	8	**25.8**	7	**35.0**	15	29.4
Total	31	**60.8**	20	**39.2**	51	**100.0**

Regarding the clinical assessment, 13 participants reported symptoms related to hormonal changes. Of these, 7.7% complained of galactorrhea, 0% presented oligomenorrhea or amenorrhea, 38.5% reported impaired libido, 53.8% of patients complained of gynecomastia, and 0% reported complaints of erectile dysfunction, as shown in Table 2.

Table 2. Clinical symptoms reported by participants

Clinical Manifestations	Male		Female		Total	
	n	%	n	%	n	%
Galactorrhoea	1	**10**	0	-	1	**7.7**
Amenorrhea/Oligomenorrhea*	0	**-**	0	-	0	**-**
Impaired libido	2	**20**	3	**100**	5	**38.5**
Gynecomastia	7	**70**	0	-	7	**53.8**
Erectile dysfunction**	0	**-**	0	-	0	**-**
Total	10	**77.00**	3	**23,0**	13	**100**

*only considered the female group in this variable.
**only males are considered in this variable.

Fourteen different types of medications were retrieved from the medical records, as shown in Table 3. Quietapine hemifumarate and biperiden hydrochloride were the most frequently used, being used by 60.0% and 52.7% of participants. In turn, phenobarbital, diazepam, and chlorpromazine appeared to be less used.

Table 3. Medications in use by participants

Medications	Masculino	Feminino	Total	n%
Risperidone	14	5	19	34.5
Olazanpine	9	5	14	25.5
Chlorpromazine	1	-	1	1.8
Venlafaxine	1	3	4	7.3
Phenobarbital	-	1	1	1.8
Flurazepam	18	7	25	45.5
Diazepam	-	1	1	1.8
Biperiden Hydrochloride	23	6	29	52.7
Levomepromazine	11	4	15	27.3
Haloperidol	6	2	8	14.5
Zolpidem Hemitartrate	19	9	28	50.9
Quietapine Hemifumarate	21	12	33	60.0
Alprazolam	8	1	9	16.4
Escitalopram Oxalate	1	1	2	3,6

Biperiden hydrochloride and quetiapine hemifumarate were the most prevalent medications among patients reporting gynecomastia. The group with impaired libido mostly used quetiapine hemifumarate, zolpidem hemitartrate, and alprazolam.

DISCUSSION

Hyperprolactinemia in patients using antipsychotic drugs is a common side effect observed at the expense of traditional treatment options. Health professionals in charge should carefully implement and manage antipsychotics in the clinical practice, prioritizing dose reduction, discontinuation of the therapy, or preferring antipsychotics with lower risks of HPRL.[11] However, drug tapering can be associated with a high risk of relapse in patients being treated for psychiatric illness. Therefore, the combined participation of psychiatrists and endocrinologists is essential to the provision of patient-centered care.[5]

The increase in PRL is related to the body site at which these drugs work, i.e., antagonist to the dopamine receptor, inhibiting dopamine reuptake, or depleting the dopamine and leading to HPRL. Antipsychotics are divided into first-generation (FGAs) and second-generation classes, and their primary indication is for treating psychotic disorders, specifically schizophrenia.[12] Studies[13,14] confirm that untreated schizophrenic patients did not have high PRL, which was present in those under treatment. Therefore, the high PRL levels observed in patients with schizophrenia under treatment with antipsychotics are not related to the disease itself but to the drug side effects.[14]

Montgomery[14] investigated the prevalence of HPRL in patients with schizophrenia and observed its presence in 71% of patients treated with first-generation antipsychotics (> 18.4 ng/ml for men, > 26 ng/ml for women, with a mean PRL level of 42.1 ng/ml). In line with this study, symptoms such as gynecomastia and libido impairment were frequently found in patients using neuroleptics. Those symptoms were found in 92.3% of the patients participating in the research who reported the symptoms. The medications most associated with symptoms were risperidone, which acts as FGAs, as well as quetiapine hemitartrate (a new generation antipsychotic), and zolpidem hemifumarate (a non-benzodiazepine sedative-hypnotic). The symptoms reported by the participants of this study are consistent with previous studies[3,4]. Decreased libido, erectile dysfunction, decreased sperm production, infertility, gynecomastia, and galactorrhea can occur as short-term consequences of HPRL[4,7]. Long-term symptoms can also occur, including the enhanced risk of decreased bone mineral density.[15]

Although HPRL is commonly associated with the use of antipsychotics, the intensity of PRL elevation differs according to the medication class. For example, the use of FGAs are associated to elevations about two to three times the reference values. In turn, second-generation antipsychotics may potentially increase PRL and include amisulpride, risperidone, and paliperidone in

up to 80-90% of women.[16] In this sense, many physicians had to accept HPRL as one of the side effects of traditional antipsychotic therapy. However, this can change with the emergence of the new generation of prolactin-sparing antipsychotics, such as clozapine, olanzapine, ziprasidone, and aripiprazole. Moreover, selective mesolimbic and mesocortical dopamine blockers may also contribute to preventing antipsychotic-induced HPRL.[17]

Physiologically, prolactin acts on the development of the mammary glands in pregnancy and milk production during lactation. However, prolactin hypersecretion by the adenohypophysis can cause neuroendocrine and metabolic disorders. HPRL can lead to ovular dysfunction due to the insufficient release of progesterone from the corpus luteum, which shortens the luteal phase of the ovarian cycle and may cause infertility. Oligomenorrhea or amenorrhea can also be stimulated by the abnormal feedback in the hypothalamic-pituitary-ovarian axis as a response to an increase in prolactin levels up to 50-100 ng/mL.[18,19]

Individuals chronically treated with antipsychotics that are not regularly monitored have a prolonged state of HPRL. Such a state generates a chronic suppression of GnRH, which can lead to hypoestrogenism in women and hypogonadism in men. Consequently, they are at greater risk of developing osteoporosis due to loss of control between bone maintenance and remodeling.[15,20]

Hypogonadotropic hypogonadism in men due to HPRL can manifest as reduced libido, erectile dysfunction, gynecomastia, impaired spermatogenesis, and galactorrhea and has been discussed in the literature. These individuals may also present secondary changes, including anemia, decreased energy, and loss of muscle mass.[1]

In the presence of HPRL symptoms, discontinuing the antipsychotic is a possibility. However, relapse and worsening of psychosis may occur. Therefore, the severity of HPRL symptoms should always be evaluated before medication discontinuation to ensure effective decision-making with less stress for the individual.[21,22]

CONCLUSION

The presence of symptomatic hormonal changes associated with HPRL is common among patients under treatment with first and second-generation antipsychotics, specifically risperidone, quetiapine hemifumarate, zolpidem hemitartrate, and biperiden hydrochloride. Although some studies point to the presence of endocrine and sexual symptoms associated with HPRL, further studies are needed to clarify the long-term consequences of continued pharmacological therapy. Careful investigations are necessary to early detect the hyperprolactinemic state and appropriately manage their care, leading to a better quality of life. Therefore, the relationship between the hyperprolactinemic state and the psyche must be monitored by medical professionals.

CONFLICT OF INTEREST

Nothing to declare.

CONTRIBUIÇÕES DOS AUTORES:

EKPD: Conceptualization, data analysis, manuscript preparation, writing, discussion of results, project administration, resources, validation, writing of the original draft, review, and editing; **GJPA:** Conceptualization, data collection, data analysis, methodology, manuscript preparation, writing, resources, review and editing; **GVA:** Conceptualization, manuscript preparation, data analysis, discussion of results, project administration, review and editing.

REFERENCES

1. Samperi I, Lithgow K, Karavitaki N. Hyperprolactinaemia. J Clin Med. 2019; 13;8(12):2203. doi: https://doi.org/10.3390/jcm8122203.
2. Lu Z, Sun Y, Zhang Y, Chen Y, Guo L, Liao Y, Kang Z, et al. Pharmacological treatment strategies for antipsychotic-induced hyperprolactinemia: a systematic review and network meta-analysis. Transl Psychiatry. 2022 Jul 5; 12(1):267. doi: https://doi.org/10.1038/s41398-022-02027-4.
3. Brand BA, Haveman YRA, de Beer F, de Boer JN, Dazzan P, Sommer IEC. Antipsychotic medication for women with schizophrenia spectrum disorders. Psychol Med. 2022 Mar; 52(4):649-663. doi: https://doi.org/10.1017/S0033291721004591.
4. Ruljancic N, Bakliza A, Vuk Pisk S, Geres N, Matic K, Ivezic E, et al. Antipsychotics-induced hyperprolactinemia and screening for macroprolactin. Biochem Med (Zagreb). 2020; 31(1): 1-8. doi: https://doi.org/10.11613/BM.2021.010707.
5. Rizzo LFL, Mana DL, Serra HA, Danilowicz K. Hyperprolactinemia associated with psychiatric disorders. Medicina (B Aires). 2020; 80(6):670-680. PMID: 33254112.
6. Nahas EAP, Nahás-Neto J, Pontes A, Dias R, Fernandes CE. Estados hiperprolactinêmicos: inter-relações com o psiquismo. Arch Clin Psychiatry (São Paulo). 2006; 33(2). doi: https://doi.org/10.1590/S0101-60832006000200006.
7. Serri O, Chik CL, Ur E, Ezzat S. Diagnosis and management of hyperprolactinemia. CMAJ. 2003; 16;169(6): 575-81. PMID: 12975226; PMCID: PMC191295.
8. Vilar L, Vilar CF, Lyra R, Freitas MDC. Pitfalls in the Diagnostic Evaluation of Hyperprolactinemia. Neuroendocrinology. 2019; 109(1): 7-19. doi: https://doi.org/10.1159/000499694.
9. Llácer JMB, Hortelano AM, Albelda BR. Hyperprolactinemia in psychotic patients treated in monotherapy with long-acting injectable antipsychotics. Int J Psychiatry Clin Pract. 2019 Sep; 23(3):189-193. doi: https://doi.org/10.1080/13651501.2019.1576905.
10. Barata PC, Santos MJ, Melo JC, Maia T. Olanzapine-Induced Hyperprolactinemia: Two Case Reports. Front Pharmacol. 2019 Jul 29; 10:846. doi: https://doi.org/10.3389/fphar.2019.00846.

11. Rusgis MM, Alabbasi AY, Nelson LA. Guidance on the treatment of antipsychotic-induced hyperprolactinemia when switching the antipsychotic is not an option. Am J Health Syst Pharm. 2021 May 6; 78(10):862-871. doi: https://doi.org/10.1093/ajhp/zxab065.

12. Aringhieri S, Carli M, Kolachalam S, Verdesca V, Cini E, Rossi M, McCormick PJ, et al. Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. Pharmacol Ther. 2018 Dec; 192:20-41. doi: https://doi.org/10.1016/j.pharmthera.2018.06.012.

13. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs. 2014; 28(5): 421-53. doi: https://doi.org/10.1007/s40263-014-0157-3.

14. Montgomery J, Winterbottom E, Jessani M, Kohegyi E, Fulmer J, Seamonds B, et al. Prevalência de hiperprolactinemia na esquizofrenia: associação com tratamento antipsicótico típico e atípico. J Clin Psychiatry. 2004; 65(11): 1491-8. doi: https://doi.org/10.4088/jcp.v65n1108.

15. di Filippo L, Doga M, Resmini E, Giustina A. Hyperprolactinemia and bone. Pituitary. 2020 Jun; 23(3):314-321. doi: https://doi.org/10.1007/s11102-020-01041-3.

16. Bushe C, Shaw M, Peveler RC. Uma revisão da associação entre o uso de antipsicóticos e hiperprolactinemia. J Psychopharmacol. 2008; 22 (2 suplementos) : 46-55. doi: https://doi.org/10.1177/0269881107088435

17. Haddad PM, Wieck A. Hiperprolactinemia induzida por antipsicóticos: mecanismos, características clínicas e manejo. Drogas. 2004; 64(20):2291-314. doi: https://doi.org/10.2165/00003495-200464200-00003.

18. Edinoff AN, Silverblatt NS, Vervaeke HE, Horton CC, Girma E, Kaye AD, Kaye A, et al. Hyperprolactinemia, clinical considerations, and infertility in women on antipsychotic medications. Psychopharmacol Bull. 2021 Mar; 16;51(2):131-148. PMID: 34092827. PMCID: PMC8146565.

19. Yoshida K, Takeuchi H. Dose-dependent effects of antipsychotics on efficacy and adverse effects in schizophrenia. Behav Brain Res. 2021 Mar 26; 402:113098. https://doi.org/10.1016/j.bbr.2020.113098.

20. González-Rodríguez A, Labad J, Seeman MV. Antipsychotic-induced Hyperprolactinemia in aging populations: prevalence, implications, prevention and management. Prog Neuropsychopharmacol Biol Psychiatry. 2020 Jul 13; 101:109941. doi: https://doi.org/10.1016/j.pnpbp.2020.109941.

21. Rusgis MM, Alabbasi AY, Nelson LA. Guidance on the treatment of antipsychotic-induced hyperprolactinemia when switching the antipsychotic is not an option. Am J Health Syst Pharm. 2021 May 6; 78(10):862-871. doi: https://doi.org/10.1093/ajhp/zxab065.

22. Pisk SV, Matić K, Gereš N, Ivezić E, Ruljančić N, Filipčić I. Hyperprolactinemia - side effect or part of the illness. Psychiatr Danub. 2019 Jun; 31(Suppl 2):148-152. PMID: 31158115.