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ANALYSIS OF ADVERSE DRUG REACTIONS CAUSED BY ANTIPSYCHOTIC DRUGS IN A MEXICAN HEALTH INSTITUTE

ANÁLISIS DE REACCIONES ADVERSAS A MEDICAMENTOS POR FÁRMACOS ANTIPSICÓTICOS EN UN INSTITUTO DE SALUD MEXICANO

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ABSTRACT

Introduction: Adverse Drug Reactions (ADR) are unwanted clinical or laboratory manifestations that are related to drug use. ADR are common and are associated with significant risk of morbidity, mortality and hospital admissions. Antipsychotics have a reduced therapeutic window, and have been related to the manifestation of a variety of ADR. **Objective:** To evaluate the pattern of ADRs due to antipsychotic drugs detected in patients treated at the Ramón de la Fuente Muñiz National Institute of Psychiatry between December 2021 and May 2022. **Methods:** Observational, descriptive, prospective and cross-sectional study of a series of cases. The seriousness, severity, and quality of the information in the notification of the ADR were defined in accordance with NOM-220-SSA1-2016, Installation and Operation of Pharmacovigilance, while causality was determined using the Naranjo algorithm. **Results:** The incidence of ADRs was 59%, with one or more ADR detected in 52 of the 88 patients who were receiving antipsychotic treatment during the study period. Forty-five percent of the ADR had probable causality and 55% possible; only three ADR were classified as serious as they prolonged the hospital stay and endangered the patient's life. **Conclusions:** The ADR of the gastrointestinal and endocrine systems were the most incidental, with hyperprolactinemia being the most frequent. Olanzapine and clozapine were the medications that caused the most ADR. It is recommended to promote the culture of notification and follow-up of ADR caused by antipsychotic drugs.

Keywords: Adverse drug reactions; Antipsychotic agents; Seriousness; Severity; Causality. (Source: MESH-NLM)

RESUMEN

Introducción: Las reacciones adversas a medicamentos (RAM) son manifestaciones clínicas o de laboratorio no deseadas que se relacionan con el consumo de medicamentos. Las RAM se asocian con un riesgo significativo de morbimortalidad e ingresos hospitalarios. Los antipsicóticos poseen una reducida ventana terapéutica y se han relacionado con la manifestación de una diversidad de RAM. **Objetivo:** Evaluar el patrón de las RAM debido a fármacos antipsicóticos, detectadas en pacientes atendidos en el Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz entre diciembre de 2021 y mayo de 2022. **Métodos:** Estudio observacional, descriptivo, prospectivo y transversal de una serie de casos. La gravedad, la severidad y la calidad de la información de la notificación de las RAM se definieron conforme a la NOM-220-SSA1-2016, instalación y operación de la farmacovigilancia, mientras que la causalidad se determinó mediante el algoritmo de Naranjo. **Resultados:** La incidencia de las RAM fue del 59% y se detectó una o más RAM en 52 de los 88 pacientes que estaban en tratamiento antipsicótico durante el periodo de estudio. El 45% de las RAM tuvo una causalidad probable y el 55%, posible; únicamente tres RAM se clasificaron como graves, debido a que prolongaron la estancia hospitalaria y pusieron en peligro la vida del paciente. **Conclusión:** Las RAM de los sistemas gastrointestinal y endocrino fueron las más incidentes, y la hiperprolactinemia fue la más frecuente. La olanzapina y clozapina fueron los medicamentos que más RAM provocaron. Se recomienda fomentar la cultura de notificación y seguimiento de RAM causadas por fármacos antipsicóticos.

Palabras clave: Reacciones adversas a medicamentos; Agentes antipsicóticos; Gravedad; Severidad, causalidad. (Fuente: DeCS- BIREME)

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INTRODUCTION

Medications are directly used to prevent and treat diseases. However, all medications can also cause harmful effects [1]. According to the World Health Organization, an adverse drug reaction (ADR) is "a harmful and unwanted reaction that occurs after the administration of a drug at doses commonly used in humans, to prevent, diagnose or treat a disease, or to modify any biological function"[2]. Although some ADRs are detected during clinical trials; others, in the post-marketing stage [3]. ADRs are a significant cause of morbidity and mortality, responsible for up to 6% of hospital admissions with an associated mortality of 2%, and represent a substantial financial burden for patients and health systems. Additionally, they affect the patient's quality of life, confidence in the healthcare system, and length of hospital stay[4].

While some ADRs are unpredictable, many can be prevented with proper foresight and control[5]. Continuous and constant surveillance, through pharmacovigilance programs, has allowed the reporting of suspected ADRs to generate alerts and prevent or avoid greater harm caused by medications [6]. Unfortunately, underreporting and under-notification remain a key challenge, as it has been estimated that less than 5% of all ADRs are reported in routine practice. This limits the ability of systems to provide accurate incidence data[5].

One group of medications that may be associated with a significant incidence of ADRs is antipsychotics [7], due to their pharmacodynamics and direct effect on the delicate balance of neurotransmitters that control behavior and brain function[8]. Psychiatric disorders are chronic in nature and often require prolonged and continuous medication treatments, increasing the likelihood of an ADR occurring during their use. Monitoring and prevention are crucial to improving clinical practice, enhancing medication safety, and supporting public health programs[9]. In Mexico, there is the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (INPRFM), which is a specialized health center of national and international reference that provides care to patients suffering from mental disorders [10]. It is a public sector institute that belongs to the Mexican Ministry of Health and provides outpatient medical consultations and hospitalization services to psychiatric patients over the age of 13[11]; it is one of the most important and representative health centers in the country. Given this, this study aimed to determine the pattern of ADRs due to antipsychotic drugs, detected at the INPRFM during the period from December 2021 to May 2022.

METHODS

2.1. Study Design

This is an observational, descriptive, cross-sectional case series study with prospective collection of ADR notification reports at the INPRFM. The study period was from December 1, 2021, to May 31, 2022.

2.2. Population and Sample

The population consisted of ADR notifications received at the Institutional Pharmacovigilance Center of the INPRFM. The sample consisted of ADR notifications due to antipsychotic drugs. ADRs detected and reported in patients over 18 years of age, of either sex, and who were being treated with antipsychotic drugs were analyzed. The identity of the patients was protected. The sampling of ADRs was done for convenience considering all cases that occurred during the study period.

2.3. Data Evaluation

A description of the manifestation and type of problem caused and classified as ADR was made. The accumulated incidence of ADR occurrence during the study period was calculated using the following equation:

$$\text{Accumulated incidence} = \frac{\#\text{ of ADR patients due to antipsychotics}}{\#\text{ of patients on antipsychotic treatment}} \times 100$$

The severity of ADRs, defined according to NOM-220-SSA1-2016 "installation and operation of pharmacovigilance" [12], was classified as "serious" and "not serious".

The severity of ADRs, defined according to NOM-220-SSA1-2016 "installation and operation of pharmacovigilance" [12], was classified as "serious" and "not serious". According to the same standards, the severity of ADRs was classified as mild, moderate, and severe. On the other hand, the quality of the information from the ADR notification was also evaluated according to the same standards as grade 0 when the notification only includes the identified patient, at least one suspected adverse reaction, the suspected drug, and the notifier's data. Grade 1 when, in addition, it includes the dates of the start of the suspected adverse reaction, as well as the start and end of the treatment: day, month, and year. Grade 2 when it also includes the generic and distinctive name of the medication used, its posology, the route of administration, the reason for its prescription, the consequence of the event, and the data from the medical history. And grade 3 when, in addition, it includes the reappearance of the clinical manifestation consequent to a new administration of the drug in question.

Finally, the causality of ADRs was determined using the Naranjo algorithm and were also classified according to NOM-220-SSA1-2016 [12] as: 1) Certain when the clinical event manifested with a plausible temporal sequence in relation to drug administration, and could not be explained by concurrent disease, nor by other drugs or substances. The response to drug withdrawal (discontinuation) must have been clinically plausible. The event must have been definitive from a pharmacological or phenomenological point of view, using, if necessary, a conclusive re-exposure procedure. 2) Probable when the event manifested with a reasonable temporal sequence in relation to drug administration; it was unlikely to be attributed to concurrent disease, nor to other drugs or substances, and withdrawing the drug, a clinically reasonable response occurred. Information about drug re-exposure was not required.

3) Possible when the event manifested with a reasonable temporal sequence in relation to drug administration, but could also be explained by concurrent disease, or by other drugs or substances. Information regarding drug withdrawal may have been missing or unclear. 4) Improbable when the event manifested with an improbable temporal sequence in relation to drug administration, and could be explained more plausibly by concurrent disease, or by other drugs or substances. 5) Conditional to a clinical event, reported as an adverse reaction, for which it was essential to obtain more data for a proper assessment, or additional data were under examination. And 6) Not assessable to a notification that suggested an adverse reaction but could not be judged, as the information was insufficient or contradictory, and could not be verified or completed in its data.

2.4. Statistical Analysis

The results were organized and analyzed in a database generated in Microsoft Office Excel®. The statistical analysis of ADRs consisted of applying descriptive statistics using measures of central tendency and dispersion.

2.5. Ethical Statements

It was not necessary to obtain informed consent from patients, as only ADR notification reports were evaluated. The data were worked with total confidentiality and for exclusive use in this research.

RESULTS

A total of 74 ADRs were detected during the study period, presented in 52 patients out of a total of 88 who were being treated with antipsychotics. The accumulated incidence of ADRs in the analyzed population during the study period was 59%. The average number of ADRs per patient was 1.42 (range 1-5). The detected ADRs were mostly in women (54%) and in the adult population between 30 and 59 years old. Also, most of the ADRs were detected in patients diagnosed with schizophrenia (65%). Table 1 shows these results. The 74 ADRs were caused by 24 different types: Olanzapine, risperidone, clozapine, aripiprazole, haloperidol, quetiapine, and paliperidone were the drugs that caused the detected ADRs (Table 2).

Table 1. Description of patients who presented ADRs (Adverse Drug Reactions).

Variable	Patients with at least 1 ADR (n = 52)
Number of ADRs per patient	
1	36 (69%)
2	12 (23%)
3	3 (6%)
4	0 (0%)
5	1 (2%)
Gender, n (%)	
Male	24 (46%)
Female	28 (54%)
Age group (years), n (%)	
Young (18-29)	16 (31%)
Adults (30-59)	28 (54%)
Elderly (>60)	8 (15%)
Diagnosis, n (%)	
Schizophrenia	34 (65%)
Psychosis	9 (17%)
Bipolar disorder	7 (14%)
Obsessive-compulsive disorder	2 (4%)

Table 2. Number of cases and type of ADRs caused by antipsychotic medications.

Variable		Olanzapine	Risperidone	Clozapine	Aripiprazole	Haloperidol	Quetiapine	Paliperidone	Total
1	Hyperprolactinemia	5	9	4	1	4	1	1	25
2	Drowsiness	4	1	-	-	1	2	1	9
3	Sialorrhea	-	-	4	-	-	-	1	5
4	Weight gain	5	-	-	-	-	-	-	5
5	Alteration in the menstrual cycle	-	1	2	-	-	-	-	3
6	Parkinsonism	-	2	-	1	-	-	-	3
7	Insomnia	-	-	-	1	1	-	-	2
8	Dizziness	-	-	1	1	-	-	-	2
9	Akathisia	-	-	-	1	1	-	-	2
10	Sedation	1	-	-	1	-	-	-	2
11	Oculogyric crisis	-	-	-	2	-	-	-	2
12	Muscle stiffness	-	-	-	-	-	-	2	2

13	Palpitations	-	-	-	-	1	-	-	1
14	Hypotension	1	-	-	-	-	-	-	1
15	Bradycardia	1	-	-	-	-	-	-	1
16	Dysphagia	1	-	-	-	-	-	-	1
17	Headache	-	-	-	-	-	1	-	1
18	Stress	-	-	-	-	-	1	-	1
19	Mastalgia	-	1	-	-	-	-	-	1
20	Mastitis	-	1	-	-	-	-	-	1
21	Galactorrhea	-	1	-	-	-	-	-	1
22	Amenorrhea	-	1	-	-	-	-	-	1
23	Extrapyramidal symptoms	1	-	-	-	-	-	-	1
24	Hypoprolactinemia	-	-	-	1	-	-	-	1
Total		19	17	11	9	8	5	5	74

Figure 1-A shows the percentage distribution of antipsychotic-associated ADRs detected. It can be seen that the most frequent were hyperprolactinemia (34%), somnolence (12%), weight gain (7%), and sialorrhea (7%). On the other hand, olanzapine (25%), risperidone (23%), and clozapine (15%) were the drugs that caused the most ADRs (Figure 1-B). Table 3 shows that of the 74 ADRs found, none were severe in intensity and the majority were mild in severity (55%). Only 3 ADRs: hypotension, bradycardia, and sedation were classified as serious, which occurred in the same patient, and olanzapine was the suspected drug. In all cases, the quality of the information was at least grade 2. When analyzing the causality of ADRs using the Naranjo algorithm, 55% were of possible causality and 45% of probable causality.

The factors associated with ADRs were unknown in 91% of cases; only in seven cases was it possible to know this information, six being of etiology due to dose increase and one due to a change in the route of administration.

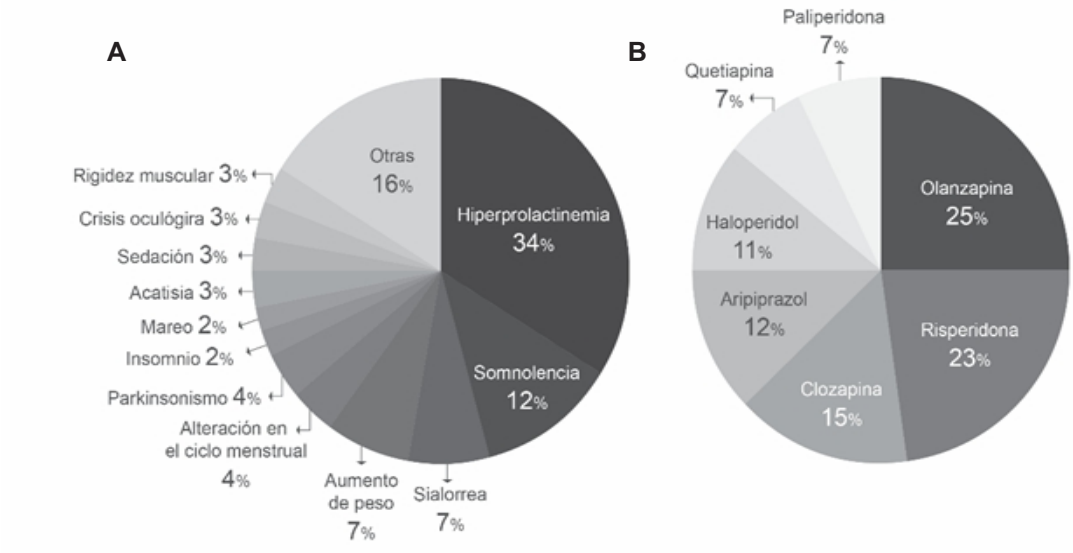

Figure 1. A: Percentage distribution by type of ADR detected in the study period. B: Percentage distribution of ADRs detected by suspected antipsychotic medication during the study period.

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Table 3. Description of identified ADRs.

Variable	ADR(n=74)
Severity, n (%)	
Mild	55 (74%)
Moderate	19 (26%)
Severe	0 (0%)
Seriousness, n (%)	
Serious	3 (4%)
Not serious	71 (96%)
Quality of information, n (%)	
Grade 1	0 (0%)
Grade 2	41 (55%)
Grade 3	33 (45%)
Causality, n (%)	
Certain	0 (0%)
Probable	33 (45%)
Possible	41 (55%)
Improbable	0 (0%)
Conditional	0 (0%)
Not assessable	0 (0%)
Etiology, n (%)	
Dose increase	6 (8%)
Change in route of administration	1 (1%)
Unknown	67 (91%)

DISCUSSION

This study provides current information on ADRs associated with antipsychotics, a group of drugs related to various adverse reactions, detected in the Mexican population attended at one of Mexico's most important and reference health centers, where people from various parts of the country come. We found that olanzapine was the drug responsible for most of the detected ADRs, and hyperprolactinemia was the most incident. The incidence of ADRs found during the analysis period was 59%, which is higher than what was observed in a study conducted at the CAISAME Long Stay Department, the largest hospital in the western region of Mexico, where 29.2% of the patients presented at least one ADR, 17.8% presented extrapyramidal effects, 15% non-extrapyramidal effects, and 3.57% both types of side effects. Although in said study a larger number of patients were analyzed (n = 140), the analysis period was shorter than the one used in our study [13], which may explain why the accumulated incidence of ADRs was higher in the present work. In the same trend, the incidence of ADRs estimated in our study was also higher than that reported in other parts of the world; Lucca et al. reported, in 2014, an incidence of ~42% (n= 517 patients) over a two-year period[9], while Chawla et al., in 2017, reported an incidence of ~17% (n= 224 patients) over a three-month period [14]. Both studies were

conducted in India, which may explain the difference found, given that it is another geographical context.

Previously, it has been reported that ADRs in psychiatric patients are more frequent in women than in men [15], and the data derived from our study do not differ from this observation. The group of people most affected by ADRs was adults between 30 and 59 years old, with an average age of 38 years; according to other reports, the higher incidence in this age group may be due to the onset of psychiatric disorders such as schizophrenia and psychosis, which were the most prevalent diagnoses in our study; typically occur in early adulthood [9], so it is expected that the prevalence of these disorders is high in adulthood.

Hyperprolactinemia was the most frequently detected ADR in the analyzed patients. In the literature, it has been estimated that it is induced in up to 70% of patients with schizophrenia who consume antipsychotics [16]. In our study, the incidence was 48%. Hyperprolactinemia caused by antipsychotics is due to blocking the dopaminergic D2 receptors, which in turn are responsible for inhibiting the hormone prolactin, which causes hyperprolactinemia [17], which has short- and long-term consequences that can seriously affect the patient's quality of life, commonly causing menstrual disorders, sexual dysfunction, galactorrhea, amenorrhea, among others [18]. In addition, hyperprolactinemia can lead to other pathologies such as osteoporosis [19]. Therefore, pharmacovigilance programs are important within public institutions to propose risk management plans for antipsychotic-induced hyperprolactinemia and its possible clinical implications.

On the other hand, the three drugs most frequently associated with the ADRs detected in the study were olanzapine, risperidone, and clozapine. This could be because olanzapine and risperidone were the most frequently used drugs in the clinical practice of schizophrenia at the INPRFM, a place that treated the most patients and where most ADRs were detected. This finding coincides, both in order and frequency, with the results of the study conducted by Piparva et al. regarding the suspected drugs related to antipsychotic ADRs [20] and with the publication of Prajapati et al. in 2013, who found clozapine and risperidone among the three main drugs that caused the most appearance of ADRs [21]. On the other hand, regarding the characteristics of the ADRs found, all were mild or moderate in intensity, and it was not necessary to withdraw the suspected antipsychotic drug or change the treatment. However, the cases of hypotension, bradycardia, and sedation detected were considered serious, as they prolonged hospital stay and endangered the patient's life.

Continuous monitoring and timely detection of all ADRs are important, as rare or infrequent ADRs can be identified [22], and for those that are already known, the manifestation from patient to patient can be variable [23]. Chawla et al. reported, in 2017, the analysis of ADRs associated with antipsychotic drugs and observed that the causality of all ADRs analyzed using the Naranjo algorithm was classified as possible and probable [14]; we obtained similar results, as all the ADRs detected were classified in the same causality categories and no definite causality was identified. It is important to note that all the cases of ADRs found had an information quality classification above grade 1 and have sufficient information about the patient, the drug, the start date of the suspicion and the treatment used and, for the cases classified with grade 3, data on re-exposure to the suspected drug, complying with international and national recommendations for ADR notifications.

CONCLUSION

This study provides additional information to that currently existing on the incidence and frequencies of ADRs of antipsychotic drugs in Mexico. In general, a high incidence of ADRs was found in patients treated at the INPRFM, over 50%, most of them found in schizophrenic patients. Most were mild in severity. ADRs of the gastrointestinal and endocrine systems were the most incident, due to the use of atypical

antipsychotic drugs. Olanzapine and clozapine were the drugs that caused the most ADRs. The most frequent gastrointestinal system ADRs were sialorrhea and weight gain, while in the endocrine system it was hyperprolactinemia. It is necessary to give importance to the monitoring of hyperprolactinemia, since it was an ADR caused by all the antipsychotics analyzed in this study. A protocol should be implemented that clearly establishes the prolactin concentration, which should begin to be gradually suspended and, in a timely manner, the drug that is causing this ADR or switch to antipsychotics that do not cause an increase in prolactin in the blood: the so-called prolactin-sparing antipsychotics or consider the use of dopamine agonists. It is recommended to promote the culture of ADR reporting at the INPRFM, both expected and unexpected, and to strengthen the follow-up of ADRs caused by antipsychotic drugs.

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Authorship contribution: JMM-N and IA-S participated in the conception and design of the article, in the analysis and interpretation of data, and in the critical revision of the article. ER-V conducted the collection of results and the preliminary analysis and interpretation of the data. JMMN and IH-V were responsible for writing the article. KS-H and JB-M contributed to the data analysis and interpretation, and the critical revision of the article. All authors approved the final version of the article.

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