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Pharmacotherapeutic follow-up and pharmacovigilance on a colombian neurological and pain health service provider institution

Seguimiento farmacoterapéutico y farmacovigilancia en una institución especializada en patologías neurológicas y dolor colombiana

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ABSTRACT

BACKGROUND: Pharmacotherapy follow-up and pharmacovigilance are part of the activities performed by pharmacist in different contexts, including healthcare settings. The first is patient-oriented and helps in the detection of drug-related negative medication outcomes – NMO (of necessity, effectiveness, or safety) and drug-related problems – DRP (availability, prescription, dispensing, administration, quality, or use), while the second is oriented to medications and their safety, evaluating, among other aspects, Adverse Drug Reactions – ADRs and their causality. **OBJECTIVE:** To identify potential NMOs and DRPs associated with using medications in ambulatory patients through pharmacotherapeutic follow-up and pharmacovigilance activities. **METHODS:** Of the total number of patients for whom the medication was authorized, the minimum statistical sample (CI=95%, α=5%) was calculated for each drug. A literature review was performed to determine the criteria for evaluating necessity, effectiveness, and safety. **RESULTS:** Patients showed good adherence to the drugs being assessed, the lowest found of 72.4% for acetaminophen/hydrocodone. An incidence of DNO of 24.4% was found, the nonquantitative lack of safety DNOs being the most frequent (17.8%); the incidence of DRP was 22.6%, with the inappropriate use of the medication being the most relevant (17.3%). Drug interactions found during the process were addressed with the patient or physician, as necessary. **CONCLUSIONS:** Pharmacotherapy follow-up and pharmacovigilance are important activities, especially in outpatients, since they allow the identification and early intervention of DNO and DRP to avoid the detriment of the patient's health.

Keywords: Pharmacotherapy follow-up; pharmacovigilance; pharmaceutical care; pharmacist intervention; pharmacist.

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RESUMEN

INTRODUCCIÓN: El Seguimiento Farmacoterapéutico – SFT y la Farmacovigilancia – FV hacen parte de las actividades realizadas por los farmacéuticos en diferentes contextos, como lo es el asistencial. El SFT está orientado al paciente y favorece la detección de Resultados Negativos a la Medicación – RNM (de necesidad, efectividad o seguridad) y Problemas Relacionados con el Uso de los Medicamentos – PRUM (disponibilidad, prescripción, dispensación, administración, calidad o uso), mientras que la FV está orientado al medicamento y su seguridad, evaluando, entre algunos aspectos, Reacciones Adversas a los Medicamentos – RAM y su causalidad. **OBJETIVO:** Identificar posibles RNM y PRUM asociados al uso de medicamentos en pacientes ambulatorios, mediante actividades de seguimiento farmacoterapéutico y farmacovigilancia. **MÉTODOS:** Del total de pacientes a los cuales le fue autorizado el medicamento, se calculó la muestra estadística mínima (IC=95%, α=5%) para cada uno de los medicamentos y se realizó revisión de la literatura para determinar los criterios para la evaluación de la necesidad, efectividad y seguridad. **RESULTADOS:** Los pacientes tienen buena adherencia a los medicamentos evaluados, siendo la menor encontrada de 72,4% para acetaminofén/hidrocodona. Se encontró una incidencia de RNM del 24,4%, siendo más frecuentes los RNM de inseguridad no cuantitativa (17,8%), y una incidencia de PRUM de 22,6%, siendo más relevante el de uso inadecuado del medicamento (17,3%). Las interacciones farmacológicas encontradas durante el proceso se intervinieron con el paciente o con el médico según fuera necesario. **CONCLUSIÓN:** El SFT y la FV son actividades con gran relevancia, sobre todo en pacientes ambulatorios, ya que permite la identificación e intervención temprana de RNM y PRUM para evitar detrimento de la salud del paciente.

PALABRAS CLAVE: Seguimiento farmacoterapéutico; farmacovigilancia; atención farmacéutica; intervención farmacéutica; químico farmacéutico.

BACKGROUND

Pharmacotherapy Follow-up (PFU), according to the definition adapted in 2007 by the Third Consensus of Granada, is a professional practice performed by the pharmacist in which the detection of Drug-related Problems (DRP) and the resolution of Negative Medication Outcomes (NMO) are favored, making the pharmacist responsible for the patient's needs and generating a commitment between both parties for the provision of this service in a continuous, systematic and documented manner, in addition to a relationship with other health professionals, seeking to achieve results aimed at improving the quality of life of patients (1,2). This pharmaceutical practice is patient-oriented, and seeks to achieve results aimed at improving the quality of life of patients (1,2).

In recent years, PFU has been implemented and studied in diverse contexts, demonstrating its applicability and benefits across various patient populations. Examples include improvements in clinical profiles of overweight patients (3), optimization of pharmacotherapy in hospitalized patients receiving anxiolytics and antidepressants (4), implementation of comprehensive follow-up programs for patients with diabetes (5), and identification of potentially inappropriate prescriptions in polymedicated elderly patients (6), among others.

In the 2007 Granada Consensus, NMO were defined as all those results obtained on the patient's health that are neither expected nor appropriate according to the proposed therapeutic objectives, and which are directly related to the use or failure in the use of a drug, which can trigger therapeutic failures or new health problems in the patient, with negative repercussions on their state of health (1,7,8). These can be evaluated and classified as NMO of necessity, presented when the patient has a health problem for which they have not received pharmacological treatment (untreated health problem), or when the patient presents a health problem due to a drug they are using and do not need for any of their diagnoses (unnecessary drug effect); NMO of effectiveness, evidenced when the expected therapeutic results are not achieved due to factors related to the dose the patient is taking (quantitative ineffectiveness) or due to factors unrelated to the dose of medication used (non-quantitative ineffectiveness); and safety NMOs, which occur when the patient has additional health problems due to the use of a drug (Adverse Drug Reactions - ADRs), which can be directly related to the dose used by the patient (quantitative insecurity), or be independent of the used dose of the drug (non-quantitative insecurity) (1,7,9).

Amariles Muñoz defines drug-related Problems (DRP) as *"deviations in the correct way in which a medication should be used therapeutically"* (10). The antecedent for the inclusion of this term was given in the Second Consensus of Granada (11), when processes were identified that were related to the availability of drugs in pharmaceutical services, the technical-scientific and quality characteristics, or to the information and education for the patient, which when having some deficiency finally favored the appearance of a DRP (10,11); subsequently DRPs were classified into errors of availability, prescription, dispensing, administration (by the patient, caregiver or nursing staff), quality and use (10,11).

PFU, included during the pharmaceutical practice in the health care setting, is framed in Pharmaceutical Care (PC), which involves the active and direct participation of the pharmacist in the patient's needs related to their pharmacological treatment, from the moment of dispensing and throughout the time of use of the drug through active follow-up, with the main objective of improving the quality of life of patients (12–14). However, for the pharmacist to contribute to improving patients' quality of life, interdisciplinary collaboration among healthcare professionals involved in the patient's care process is required (15).

Pharmacovigilance, on the other hand, is the professional practice *"related to the detection, evaluation, understanding and prevention of adverse events or any other drug-related problem";* that is, activities oriented to drugs, in which their safety is evaluated by identifying Adverse Drug Reactions (ADRs) and establishing causal relationships between drugs and the identified ADRs, medication errors, lack of efficacy, off-label use, quality issues, among others (16,17).

Pharmacotherapy Follow-up and pharmacovigilance were performed in a group of outpatients of a Colombian Health Care Provider Institution (HCP) for 4 months, each month focusing on a different drug, in order to identify NMO and DRP that could be occurring with the use of these drugs. The medications considered for this follow-up were acetaminophen/ hydrocodone, acetaminophen/ caffeine, entacapone/ levodopa/ carbidopa, and clozapine.

METHODS

Pharmacotherapy Follow-up and pharmacovigilance activities were carried out in an HCP specialized in neurological pathologies and pain, in charge of dispensing drugs to outpatients of a Colombian insurance company (known as Entidades Administradoras de Planes de Beneficios de Salud - EAPB), for four months (June 2022 to September 2022). For each of the months, a specific drug was defined according to prioritization criteria defined by the insurance company. To determine the study population, the authorizations generated by the EAPB in the months before the study for each of the drugs were taken, the patients for whom during these three months the EAPB generated an order for the drug of interest were filtered out, and duplicates were eliminated so that each patient was registered only once; the minimum statistical sample was determined with a confidence level of 95% and a margin of error of 5%. Subsequently, a review of the literature on the study drug was conducted to define the criteria for evaluating the need, effectiveness, and safety of the drug. Additionally, adherence, concomitant medications, and the presence of DRP (administration, inappropriate use by the patient, quality of the medication, availability, dispensing, prescription, authorization processes) were evaluated during the pharmacological interview, which included the Morisky-Green test questions and others agreed upon by the medical and pharmaceutical staff.

RESULTS

Table 1, Part A, shows the drug defined for each month, the months from which the authorization information for each drug was extracted, the total authorizations generated for the drug after eliminating duplicate patients, and the statistical sample for evaluation. Additionally, parts B and C show the results obtained from the NMO and DRP for each drug.

Table 1, part A. Drugs defined for evaluation each month, population and sample.

Drug (month)	Authorizations previous months	Population	Sample min. (IC=95%, α =5%)
Acetaminophen/ hydrocodone (June) [a]	March, April, May	12411	373
Acetaminophen/caffeine (July) [b]	May*	16668	376
Entacapone/levodopa/carbidopa (August) [c]	May, June, July	703	249
Clozapine (September) [d]	June, July, August	11	11

Concentrations available in the institution: [a] 325/5 mg; 325/7.5 mg; 325/10 mg. [b] 325/65 mg; 500/50 mg; 500/65 mg. [c] 200/50/12.5 mg; 200/100/25 mg; 200/150/37.5 mg; 200/200/50 mg. [d] 25 mg; 100 mg. *Data from the previous month were taken for acetaminophen/caffeine only due to the number of patients with authorizations for this drug; although the minimum sample calculated was 376 patients, only 371 could be contacted, so the results are based on the number of patients contacted.

Table 1, part B. Consolidated NMOs found for drugs.

Drug (month)	NMO				
	Quantitative ineffectiveness	Non-quantitative ineffectiveness	Quantitative insecurity	Non-quantitative insecurity	Total NMO
Acetaminophen/ hydrocodone (June)	1 (0.3%)	37 (9.9%)	-	45 (12.1%)	83 (22.3%)
Acetaminophen/caffeine (July)	6 (1.6%)	3 (0.8%)	-	40 (10.6%)	49 (13.0%)
Entacapone/levodopa/ carbidopa (August)	7 (2.8%)	7 (2.8%)	10 (4.0%)	99 (39.6%)	123 (49.2%)
Clozapine (September)	-	-	-	5 (45.4%)	5 (45.4%)

Table 1, part C. Consolidated DRPs found for drugs.

Drug (month)	DRP				
	Availability	Dispensing	Prescription	Use	Total DRP
Acetaminophen/ hydrocodone (June)	15 (4.0%)	4 (1.1%)	8 (2.1%)	77 (20.6%)	104 (27.8%)
Acetaminophen/caffeine (July)	8 (2.1%)	-	9 (2.4%)	73 (19.4%)	90 (23.9%)
Entacapone/levodopa/ carbidopa (August)	4 (1.6%)	-	8 (3.2%)	34 (13.6%)	46 (18.4%)
Clozapine (September)	-	-	-	-	-

Acetaminophen/hydrocodone:

Acetaminophen/hydrocodone is a drug indicated for the treatment of moderate to moderately severe pain (18), which presents analgesic relief after 30 minutes to 1 hour of its intake (19). Since it is an opioid, it is recommended that the therapeutic objectives be defined jointly between the doctor and the patient, mainly aimed at reducing pain and improving functionality (20); the Visual Analog Scale (VAS) being a good tool to evaluate changes in pain intensity (21). According to the literature, frequently reported ADRs are nausea, vomiting, dizziness and sedation; while severe ADRs (frequency not defined) are acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, thrombocytopenia, hepatotoxicity, hepatic failure and respiratory depression (19). The maximum daily dose of acetaminophen is 4 g/day, and that of hydrocodone is 60 mg/day (19).

Pharmacotherapy follow-up and Pharmacovigilance activities were performed in 373 patients, of whom 29.2% were men and 70.8% were women; half were between 50 and 69 years of age (50.5%). According to the criteria for evaluating need, effectiveness, and safety, 38 patients were found to have treatment ineffectiveness (1 quantitative, 37 non-quantitative), and 45 patients had insecurity, all of them non-quantitative. Of the patients presenting insecurity due to ADRs, those described by them were: dizziness (24%), dry mouth/throat (16%), drowsiness (16%), headache (10%), nausea/vomiting (10%), gastritis (7%), constipation (5%), difficulty urinating (2%), bitter taste (2%), rash (2%), swelling (2%), tachycardia (2%) and dental involvement (2%). A total of 104 DRPs were found: 15 for availability, 4 for dispensing, 8 for prescription, and 77 for inappropriate use by the patient.

The drugs that patients were found to be taking concomitantly with acetaminophen/ hydrocodone were NSAIDs (naproxen, ibuprofen, etoricoxib, ergotamine/caffeine, dipyrone, diclofenac, acetaminophen), low-potency opioid analgesics (tramadol, acetaminophen/tramadol, acetaminophen/codeine), high-potency opioid analgesics (tapentadol, oxycodone, hydromorphone, buprenorphine), and pain management adjuvants (trazodone, pregabalin, methocarbamol, lidocaine, imipramine, gabapentin, carbamazepine, amitriptyline). On the other hand, according to the information provided by the patients, it was determined that 24.9% were not adherent to the pharmacological treatment. Table 2 shows the results obtained.

Table 2. Results obtained for acetaminophen/hydrocodone.

Characterization of the population		Concomitant drugs			
Gender		**AINES**		**High-potency**	
Masculine	109 (29.2%)	Acetaminophen	45 (12.1%)	**opioids**	
Feminine	264 (70.8%)	Acetaminophen/		Buprenorphine	5 (1.3%)
		caffeine	44 (11.8%)	Hydromorphone	1 (0.3%)
Age		Diclofenac	13 (3.5%)	Methadone	2 (0.5%)
< 50 years	48 (12.9%)	Dipyrone	2 (0.5%)	Oxycodone	1 (0.3%)
50 – 59 years	75 (20.1%)	Ergotamine/caffeine	6 (1.6%)	Tapentadol	2 (0.5%)
60 – 69 years	113 (30.3%)	Etoricoxib	6 (1.6%)		
70 – 79 years	86 (23.0%)	Ibuprofen	4 (1.1%)	**Adjuvants**	
> 80 years	51 (13.7%)	Naproxen	26 (1.6%)	Amitriptyline	2 (0.5%)
				Carbamazepine	3 (0.8%)
Adherence		**Low-potency**		Gabapentin	3 (0.8%)
Adherent	270 (72.4%)	**opioids**		Imipramine	2 (0.5%)
Non-adherent	93 (24.9%)	Acetaminophen/		Lidocaine	2 (0.5%)
Not evaluated	10 (2.7%)	codeine	19 (5.1%)	Methocarbamol	2 (0.5%)
		Acetaminophen/		Pregabalin	22 (5.9%)
		tramadol	13 (3.5%)	Trazodone	2 (0.5%)
		Tramadol	36 (9.7%)		

Acetaminophen/caffeine:

Acetaminophen/caffeine is an analgesic and antipyretic (18), which relieves symptoms 30 minutes to 1 hour after administration, and has a duration of effect between 4 and 6 hours (22). Since it is also a drug for pain treatment, its effectiveness can be evaluated based on the Visual Analog Scale (VAS). According to the literature, frequently reported ADRs are pruritus, laryngeal edema, angioedema, thrombocytopenia, leukopenia, agranulocytosis (typical of acetaminophen); and insomnia, nervousness, irritability, nausea, vomiting and tachycardia (typical of caffeine) (22). The maximum daily dose of acetaminophen is 4 g/day (22).

Pharmacotherapy follow-up and Pharmacovigilance activities were performed in 371 patients, of whom 22.1% were men and 77.9% were women; more than half were between 50 and 69 years of age (53.4%). According to the related ICD-10 code, 67.1% were prescribed this drug for a disease of the musculoskeletal system and connective tissue.

According to the criteria for evaluating the need, effectiveness, and safety, it was found that 64 patients presented ineffectiveness to the treatment (61 quantitative, 3 non-quantitative), and 40 patients presented insecurity, all of them non-quantitative. Of the patients presenting insecurity due to ADRs, those described by them were: gastritis (35%), insomnia (30%), dizziness (30%), nausea (20%), headache (15%), tachycardia (12.5%), somnolence (7.5%), blood pressure changes (7.5%), visual disturbances (5%), tremor (5%), cough (2.5%), bitter taste (2.5%), nervousness (2.5%), bradypnea (2.5%) and dry mouth (2.5%). A total of 90 DRPs were found: 8 due to availability, 9 due to prescription, and 73 due to inappropriate use by the patient.

The medications patients were found to be taking concomitantly with acetaminophen/caffeine were NSAIDs (celecoxib, diclofenac, etoricoxib, lysine clonixinate/cyclobenzaprine, acetaminophen/tizanidine), low-potency opioid analgesics (acetaminophen/codeine, acetaminophen/hydrocodone, tramadol), high-potency opioid analgesics (tapentadol), and pain management adjuvants (pregabalin, duloxetine, cyclobenzaprine, gabapentin, tizanidine, imipramine, lidocaine, methocarbamol, topiramate, amitriptyline, desvenlafaxine, sertraline, venlafaxine). On the other hand, according to the information provided by the patients, it was determined that 19.7% were not adherent to pharmacological treatment. Table 3 shows the results obtained.

Table 3. Results obtained for acetaminophen/caffeine.

Characterization of the population		**Concomitant drugs**			
Gender		**NSAIDs**		**Adjuvants**	
Masculine	82 (22.1%)	Acetaminophen/		Amitriptyline	2 (0.5%)
Feminine	289 (77.9%)	tizanidine	2 (0.5%)	Cyclobenzaprine	22 (5.9%)
		Celecoxib	8 (2.1%)	Desvenlafaxine	2 (0.5%)
Age		Diclofenac	15 (4.0%)	Duloxetine	30 (8.1%)
< 50 years	99 (26.7%)	Etoricoxib	13 (3.5%)	Gabapentin	17 (4.6%)
50 – 59 years	109 (29.4%)	Lysine clonixinate /cyclobenzaprine	3 (0.8%)	Imipramine	7 (1.9%)
60 – 69 years	89 (24.0%)			Lidocaine	5 (1.3%)
70 – 79 years	45 (12.1%)	**Low-potency**		Methocarbamol	5 (1.3%)
> 80 years	29 (7.8%)	**opioids**		Pregabalin	96 (25.9%)
		Acetaminophen/		Sertraline	2 (0.5%)
Adherence		codeine	3 (0.8%)	Tizanidine	9 (2.4%)
Adherent	286 (77.1%)	Acetaminophen/		Topiramate	3 (0.8%)
Non-adherent	73 (19.7%)	hydrocodone	7 (1.9%)	Venlafaxine	2 (0.5%)
Not evaluated	12 (3.2%)	Tramadol	23 (6.2%)		
		High-potency			
		opioids			
		Tapentadol	5 (1.3%)		

Entacapone/levodopa/carbidopa:

Entacapone/levodopa/carbidopa is a drug indicated for the treatment of patients with Parkinson's disease and fluctuations of motor response at the end of a dose, who have not been stabilized with a therapy based on levodopa and a dopa-decarboxylase inhibitor (carbidopa or benserazide) (12). The therapeutic response stabilizes after 2 to 4 weeks of continuous intake, following the treatment (17):

a) Restore brain dopaminergic activity levels to attenuate motor symptoms (gait disturbances, tremors, etc.) and non-motor symptoms (cognitive impairment, de pressive episodes, etc.).

b) To delay the evolution of cognitive deterioration.

c) To preserve the autonomy and promote the socio-psychological well-being of the affected person.

According to the literature, the ADRs frequently reported are involuntary movements, nausea, diarrhea, decreased body movements, dizziness, fatigue, hallucinations, anxiety, somnolence, abdominal pain, constipation, dry mouth (23). The recommended dose of levodopa is 300 - 400 mg/day, and the recommended dose of carbidopa is between 70 - 100 mg/day, and a maximum of 200 mg/day (23). Additionally, for safety assessment it is necessary to consider that among the serious interactions reported is the concomitant use of entacapone/levodopa/carbidopa with amisulpride, aripiprazole, clozapine, desvenlafaxine, haloperidol, olanzapine, paliperidone, quetiapine and risperidone (23).

Pharmacotherapy follow-up and Pharmacovigilance activities were performed in 309 patients, 55.3% of whom were men and 44.7% women, mainly over 65 years of age (75.7%). According to the criteria for evaluating need, effectiveness and safety, 14 patients were found to have treatment ineffectiveness (7 quantitative, 7 non-quantitative), and 109 patients had insecurity (10 quantitative, 99 non-quantitative). Of the patients presenting insecurity due to ADRs, those described by them were: Constipation (19.2%), dry mouth (16.2%), dizziness (15.2%), involuntary movements (13.1%), drowsiness (11.1%), nausea (11.1%), hallucinations (6.1%), color changes in urine (6.1%), fatigue (6.1%), gastritis (5.1%), tremor (4.0%), vomiting (4.0%), lethargy (3.0%), abdominal pain (3.0%), decreased body movements (3, 0%), anxiety (2.0%), chills (2.0%), speech inconsistencies (2.0%), stiffness (2.0%),

cardiac arrhythmia (1.0%), warmth (1.0%), diarrhea (1.0%), difficulty sleeping (1.0%), difficulty urinating (1.0%), hypersalivation (1.0%), poor appetite (1.0%), insomnia (1.0%), fetid urine (1.0%), nightmares (1.0%). A total of 46 DRPs were found: 4 due to availability, 8 due to prescription, and 34 due to inappropriate use by the patient.

The medications that patients were found to be taking concomitantly with entacapone/levodopa/carbidopa were, for the treatment of motor symptoms rotigotine, pramipexole, safinamide, amantadine, rasagiline, apomorphine, and levodopa/carbidopa, and for the treatment of non-motor symptoms quetiapine, pregabalin, sertraline, escitalopram, rivastigmine, memantine, trazodone, melatonin, venlafaxine, desvenlafaxine, clonazepam, mirtazapine, duloxetine, fluoxetine, levomepromazine, clozapine, imipramine and olanzapine. On the other hand, according to the information provided by the patients, it was determined that 12.0% were not adherent to the pharmacological treatment. Table 4 shows the results obtained.

Table 4. Results obtained for entacapone/levodopa/carbidopa.

Characterization of the population		**Concomitant drugs**			
Gender		***Treatment motor symptoms***		Rivastigmine	9 (2.9%)
Masculine	171 (55.3%)	Rotigotine	76 (24.6%)	Memantine	7 (2.3%)
Feminine	138 (44.7%)	Pramipexol	66 (21.4%)	Trazodone	7 (2.3%)
		Safinamide	56 (18.1%)	Melatonin	5 (1.6%)
Age		Amantadine	52 (16.8%)	Venlafaxine	5 (1.6%)
< 50 years	6 (1.9%)	Rasagiline	35 (11.3%)	Desvenlafaxine	4 (1.3%)
50 – 64 years	69 (22.3%)	Apomorphine	3 (1.0%)	Clonazepam	3 (1.0%)
> 65 years	234 (75.7%)	Levodopa/ carbidopa	2 (0.6%)	Mirtazapine	3 (1.0%)
				Duloxetine	2 (0.6%)
Adherence		**Treatment non-motor symptoms**		Fluoxetine	2 (0.6%)
Adherent	268 (86.7%)	Quetiapine	22 (7.1%)	Levomepromazine	2 (0.6%)
Non-adherent	37 (12.0%)	Pregabalin	13 (4.2%)	Clozapine	1 (0.3%)
Not evaluated	4 (1.3%)	Sertraline	12 (3.9%)	Imipramine	1 (0.3%)
		Escitalopram	10 (3.2%)	Olanzapine	1 (0.3%)

Clozapine:

Clozapine is a neuroleptic medication with antipsychotic action (18); it is indicated for (24):

a) Treatment of resistant schizophrenia, in treatment-resistant schizophrenic patients and in schizophrenic patients presenting severe neurological adverse reactions not treatable with other antipsychotic drugs, including an atypical antipsychotic. Treatment resistance is defined as the absence of satisfactory clinical improvement despite the use of at least two different antipsychotic treatments, including an atypical antipsychotic, at the appropriate doses and for the appropriate length of time.

b) Treatment in the course of Parkinson's disease, in patients with psychotic disorders appearing during Parkinson's disease, in cases where standard treatment has failed.

Therapeutic improvement begins to occur after consistent intake of the drug for 2 to 4 weeks (25). The therapeutic objectives sought with the use of clozapine are mainly to eliminate or reduce symptoms, prevent relapses, achieve and maintain remission, avoid or reduce hospitalizations, and initiate or resume normal daily activities, such as working, studying, living independently or maintaining social relationships (26–28).

According to the literature, frequently reported ADRs are hypersalivation, sedation/somnolence, weight gain, dizziness/vertigo, tachycardia, constipation, insomnia, nausea, vomiting, dyspepsia, hypotension, fever, headache, tremor, syncope, sweating, dry mouth, visual disturbances, nightmares, restlessness, hypokinesia/akinesia, agitation, hypertension, convulsions, rigidity, akathisia, confusion, leukopenia/neutropenia, fatigue, diarrhea, urine abnormalities, and rash (25). Taking into account the alterations in blood cells that clozapine presents as ADR, one parameter used to evaluate safety is the performance of periodic hemograms, depending on the time of use of the drug: weekly during the first three months of treatment with clozapine, then monthly hemogram until completing the first year of treatment, and continuing with the biannual evaluation throughout the time the patient has been on treatment (29).

The maximum daily dose of clozapine is 900 mg (25). In addition, for the safety assessment it is necessary to take into account that among the contraindications is the joint use of clozapine with amisulpride, cabergoline, dopamine, dronedarone, eliglustat, flibanserin, fluconazole, irinotecan, lisuride, lomitapide, lonafarnib, methyldopa, nirmatrelvir, pimozide, posaconazole, primipexole, quinidine, ropinirole, saquinavir and thioridazine; and serious interactions reported for concomitant use of clozapine occur with abametapir, amiodarone, apomorphine, aripiprazole, avapritinib, azithromycin, buprenorphine, bupropion, carbamazepine, chlorpromazine, ciprofloxacin, citalopram, clarithromycin, erythromycin, fentanyl, fluvoxamine, hydrocodone, hydroxyzine, ketoconazole, itraconazole, ivadabrine, levodopa, lithium, loperamide, lopinavir, methadone, metoclopramide, midazolam, moxifloxacin, olanzapine, ondansetron, paliperidone, quetiapine, safinamide, sevoflurane, and trazodone (25).

Of the 11 patients in whom Pharmacotherapy Follow-up and Pharmacovigilance activities were performed, 81.8% were men and 18.2% were women, with a wide age distribution (18.2% under 30 years, 18.2% between 30 and 39 years, 18.2% between 40 and 49 years, and 45.4% over 50 years). According to the criteria for evaluation of need, effectiveness and safety, it was found that no patient presented ineffectiveness to the treatment, while 5 patients presented insecurity, all of them non-quantitative. Of the patients who presented insecurity due to ADRs, those described by them were: insomnia (20%), weight gain (40%) and drowsiness (60%). DRPs were not found in patients on clozapine treatment.

It was found that the medications that patients took concomitantly with clozapine were paliperidone, sodium divalproate, fluoxetine, amisulpride, aripiprazole and sertraline. On the other hand, according to the information provided by the patients, it was determined that 100% were adherent to the pharmacological treatment. Table 5 shows the results obtained.

Table 5. Results obtained for clozapine.

Characterization of the population		**Concomitant drugs**		**Maintenance dose**	
Gender		Paliperidone	3 (27.3%)	100 mg/day	1 (9.1%)
Masculine	9 (81.8%)	Sodium divalproate	2 (18.2%)	150 mg/day	1 (9.1%)
Feminine	2 (18.2%)	Fluoxetine	2 (18.2%)	200 mg/day	3 (27.3%)
		Amisulpride	1 (9.1%)	300 mg/day	1 (9.1%)
Age		Aripiprazole	1 (9.1%)	400 mg/day	2 (18.2%)
< 30 years	2 (18.2%)	Sertraline	1 (9.1%)	500 mg/day	1 (9.1%)
30–39 years	2 (18.2%)			700 mg/day	2 (18.2%)
40–49 years	2 (18.2%)				
> 50 years	5 (45.4%)	**Last hemogram**			
		< 6 months	3 (27.3%)		
		6 – 12 months	4 (36.3%)		
		1 – 2 months	3 (27.3%)		
		> 2 months	1 (9.1 %)		

DISCUSSION

In general, most patients showed good adherence to treatment for the four drugs, with the highest adherence found for clozapine (100%), an antipsychotic agent, compared to the lowest adherence found for acetaminophen/hydrocodone (72.4%), an analgesic for moderate to moderately severe pain.

The total NMOs found during the four-month evaluation period were 260 in 1064 patients (24.4%), with the presence of non-quantitative insecurity being more frequent (189 patients, 17.8%) compared to the other identified NMOs. These insecurities, derived from the presence of ADRs in patients, are consistent with those described in the literature and the incidence percentages in the patients evaluated are consistent with the frequency of occurrence reported in the literature for each drug (19,22,23,25).

On the other hand, the total DRPs found were 240 (22.6%), the most relevant in all cases being the inappropriate use of the drug by the patient/caregiver (184 patients, 17.3%). Table 1 shows the comparison of the results of population characterization, NMO and DRP of the four drugs evaluated.

Regarding the concomitant pharmacological therapies that patients mentioned having in place with the drug evaluated, for acetaminophen/hydrocodone there were 68 duplications (18.2% of the sample) for low-potency opioids, including acetaminophen/codeine, acetaminophen/tramadol and tramadol (19).

For acetaminophen/caffeine, although it was evident that some patients had another prescription for a drug containing acetaminophen, the total daily dose of acetaminophen did not exceed for any of the patients the maximum daily dose (4 g/day); however, during the pharmacological interview these patients were reminded of the importance of following the doctor's instructions regarding the dosage of the drug to avoid overdosing.

For entacapone/levodopa/carbidopa, the concomitant use of four drugs was identified as having serious interactions in the literature: quetiapine, clozapine and olanzapine due to pharmacodynamic antagonism with entacapone/levodopa/carbidopa, decreasing its effect (23), and desvenlafaxine for both increasing serotonin levels and generating the risk of serotonin syndrome (23). These criteria were evaluated in the patients and it was determined that those who had concomitant use with quetiapine, clozapine and olanzapine presented a good response to treatment with entacapone/levodopa/carbidopa due to the improvement presented in their motor symptoms. For the patients in concomitant treatment with desvenlafaxine, the alarm symptoms for serotonin syndrome were ruled out. They were reminded of the importance of going to a health service in case they presented them.

Finally, in the case of patients with clozapine, concomitant use with amisulpride was found in one patient, an event reported in the literature as a contraindicated interaction because both increase the toxicity of the other (25), so an escalation was made to the treating doctor to validate the relevance of this pharmacological therapy and evaluate its risk/benefit. Concomitant use of clozapine with paliperidone and aripiprazole was also found, reported as a serious interaction due to increased QT interval (25), so these patients were escalated to the treating doctor recommending an electrocardiogram to verify that the concomitant use was not altering the QT interval of the patients.

In patients with clozapine, the follow-up of blood cell counts during the use of the drug was also verified by means of a complete blood count. It was found that 8 of the 11 patients had more than 6 months since the last blood test, so they were escalated to the treating doctor recommending to request a complete blood count to rule out blood cell alteration due to clozapine use (29). Additionally, it is important to include clozapine in active pharmacovigilance programs to prevent this type of hematological ADR, and to ensure that complete blood counts are performed periodically.

CONCLUSIONS

This study identified a 24.4% incidence of Negative Medication Outcomes (NMOs), with non-quantitative safety-related NMOs—mainly adverse drug reactions—being the most frequent. Additionally, 22.6% of patients experienced at least one Drug-Related Problem (DRP), particularly inappropriate medication use (17.3%). These findings highlight the relevance of Pharmacotherapy Follow-up (PFU) and Pharmacovigilance (PV) in detecting and addressing medication-related risks, reinforcing their role in improving patient safety and health outcomes in outpatient settings.

Despite good adherence rates, inappropriate use remains the most common DRP, underscoring the

need to strengthen patient education during medical prescription and pharmaceutical dispensing. The frequency of NMOs among older adults also points to the importance of individualized monitoring due to age-related pharmacotherapy complexity.

PFU and PV facilitate early identification and intervention of risks, and promote interprofessional collaboration in patient-centered care. Future studies should integrate active PV and PFU programs to prevent avoidable ADRs and strengthen health systems.

CONFLICT OF INTEREST

The manuscript's authors declare that no conflicts of interest are associated with this work.

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AUTHORS' CONTRIBUTION

The authors confirm their contribution to the paper as follows: study conception and design: MOR and LCA, acquisition of data and information: MOR and LCA, analysis and interpretation of data: MOR and LCA, planning of the article: MOR and LCA, revision of the intellectual content: MOR and LCA, final approval of the version to be published: MOR and LCA.

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