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Pharmacovigilance of carbamazepine in the treatment of Central Nervous System conditions

Farmacovigilancia de la carbamazepina en el tratamiento de afecciones del Sistema Nervioso Central

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Abstract

Anticonvulsants are crucial for treating neurological diseases, necessitating close pharmacovigilance due to their potential risks. For this reason, a prospective descriptive study was conducted to characterize drug-related adverse reactions associated with the use of carbamazepine in the health area of the "Ramon Lopez Peña" Polyclinic, covering the period from July to December 2022. The sample consisted of 35 patients, characterized based on demographic, clinical, and pharmacotherapeutic variables. The detected drug-related adverse events were classified according to causality, severity, and frequency of occurrence. The results showed that the age group of 40-75 years (45.7%) predominated, along with female gender, mixed ethnicity, pre-university education level, and 54.2% did not have any unhealthy habits. The most common diagnosis was epilepsy (68.4%) and among the associated diseases, hypertension was prevalent. The most consumed medications were captopril, hydrochlorothiazide, paracetamol, and metamizole (dipirona). Drug interactions were detected, and 73 adverse reactions occurred, with the nervous system being the most affected at 56.0%. Possible adverse reactions (42.5%), frequent (49.4%), and mild (58.9%) predominated. This study underscores the importance of continuous and effective monitoring in pharmacovigilance to enhance patient safety under carbamazepine treatment, thereby promoting a more rational use of this medication.

Keywords: carbamazepine, Adverse drug reaction, pharmavigilance.

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Resumen

Los anticonvulsivantes son cruciales para el tratamiento de enfermedades neurológicas y requieren una estrecha farmacovigilancia debido a sus riesgos potenciales. Por este motivo se realizó un estudio descriptivo prospectivo con el objetivo de caracterizar las reacciones adversas medicamentosas asociadas al consumo de la carbamazepina en el área de salud del Policlínico" Ramón López Peña", en el período comprendido de julio a diciembre del 2022. La muestra consistió en 35 pacientes, caracterizados según variables demográficas, clínicas y farmacoterapéuticas. Las reacciones adversas medicamentosas detectadas se clasificaron según causalidad, severidad y frecuencia de aparición. Los resultados mostraron que predominó el grupo de edad de 40-75 años (45,7%), el sexo femenino, los mestizos, el nivel de escolaridad pre-universitario y el 54,2% no presentó ningún hábito no saludable. El diagnóstico predominante fue epilepsia 68,4% y entre las enfermedades asociadas la hipertensión arterial. Los medicamentos más consumidos fueron el captopril, hidroclorotiazida, paracetamol y metamizol (dipirona). Se detectaron interacciones medicamentosas y 73 reacciones adversas siendo el sistema nervioso el más afectado con un 56,0 %. Predominaron las RAM posibles 42,5 %, las frecuentes 49,4 % y las leves 58,9 %. Este estudio destaca la importancia de una vigilancia continua y efectiva en farmacovigilancia para mejorar la seguridad del paciente bajo tratamiento con carbamazepina, promoviendo así un uso más racional de este medicamento.

Palabras Claves: Carbamazepina, Reacción adversa a medicamentos, farmacovigilancia.

Introduction

Pharmacovigilance, a multidisciplinary field inherently linked to epidemiological and pharmacological studies, plays a crucial role in the continuous evaluation of the safety and effectiveness of medicines after their post-marketing approval. This process is essential as it allows for the monitoring of medication safety in real-use scenarios, thereby ensuring that the benefit-risk ratio remains favorable throughout the drug lifecycle. This activity involves rigorous control of biomedical and pharmacological risks, which is vital for public health protection (Bihan et al., 2020; Choudhury et al., 2023).

Anticonvulsants, such as carbamazepine (CBZ), are essential for treating epilepsy and other neurological disorders. However, the use of these medications is not without risks, as they can cause serious adverse reactions, some potentially fatal, such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (NET). Carbamazepine, initially synthesized with properties similar to tricyclic antidepressants like Imipramine, has proven effective not only in convulsive disorders but also in managing bipolar affective disorder and trigeminal neuralgia, providing relief in conditions of intense facial pain (Montastruc & de Laportaliere, 2024)

Despite its efficacy, numerous adverse reactions associated with its use were reported, such as vertigo, somnolence, ataxia, skin rashes, thrombocytopenia, and leukopenia, raising concerns in various studies conducted in countries like Peru, Italy, and Malaysia (Balbuena Veliz, & Damian Ricaldi, 2018; Hariraj et al., 2023; Guarnieri, et al., 2024). Additional research in Colombia and Cuba has highlighted the prevalence of skin conditions and the importance of understanding adverse effects to optimize the clinical use of CBZ (García Torres, & Aldana Becerra, 2016; Adrián,2022). Specifically, recent studies haveunderscored the lack of effective strategies for patient-reported adverse effect notification, as well as the need to expand the scientific evidence supporting policies for the prevention and management of adverse reactions in the region (Barrero Viera, & Bestard Pavón, 2022; Trabanca Beltrán et al., 2018).

Given the increasing use of carbamazepine in Cuba and the insufficient documentation regarding its most frequent adverse reactions, this study aims to characterize these reactions in the population served at the "Ramón LópezPeña" Polyclinic in Caimanera, Guanánamo Province. This analysis seeks not only to fill a knowledge gap but also to improve risk mitigation strategies and strengthen pharmacovigilance in the context of Cuban community medicine.

Theoretical Framework

Pharmacovigilance: is defined as the science and activities related to the detection, evaluation, understanding, and prevention of adverse effects or any other medication-related problem (MRP) (World Health Organization, 2002). The European Commission (EU) defines it as "the process and science of monitoring the safety of medications and taking actions to reduce risks and enhance the benefits of medications" (Narayanan, et al., 2020).

Medication-Related Problems: are defined as any undesirable event experienced by the patient, which involves or is suspected to involve drug therapy, and that interferes or has the potential to interfere with desired health outcomes (Cipolle et al., 2012; Calvo-Salazar et al., 2018).

Adverse Drug Reaction: is any harmful and unintended response to a medication. (Sychev et al., 2020)

Materials and Methods

A prospective descriptive study was conducted on patients using carbamazepine to detect adverse reactions associated with this medication in the healthcare area of the "Ramón LópezPeña" Polyclinic in Caimanera, Guantánamo Province, from July to December 2022.

Study Population and Sample

The study population consisted of patients consuming carbamazepine from the Main Municipal Pharmacy of Caimanera Municipality and the Community Pharmacy in the locality of "Boquerón" in Guantánamo Province in Cuba. The sample included patients who met the inclusion criteria:

Inclusion Criteria: Patients consuming carbamazepine who gave their consent to participate in the research.

Exclusion Criteria: Patients with any cognitive disorder (dementia, severe mental retardation) that prevents information gathering, and patients who were hospitalized at the time of the study.

Exit Criteria: Patients who voluntarily decide to discontinue their participation in the study, those who die during the research, and those who move out of the health area and municipality.

Ethical Considerations

The research was conducted in accordance with the ethical standards of the Declaration of Helsinki (Williams, 2008) and the regulations stipulated by the Cuban Ministry of Public Health concerning clinical research. This work was approved by the ethics committee of the "Ramón LópezPeña" Polyclinic in Caimanera, Guantánamo Province.

Data Collection

Data collection was conducted through the review of medical certificates of patients consuming carbamazepine who are registered in the National Medication Program (NMP) and dispensed via a control card. Additionally, data obtained through patient interviews and the analysis of medical histories were considered.

Sample Characterization

The sample was characterized considering biosocial, clinical, and pharmacotherapeutic variables:

Biosocial Variables:
Gender: Female and Male
Age: in completed years (≤15, 16-39, 40-75)

Educational level: (Elementary, Secondary, Pre-university, Technical, Higher)
Skin color: Mixed, White, and Black
Unhealthy habits: Coffee, Alcohol, Tobacco, No toxic habits

Clinical Variables:
Reason for prescribing carbamazepine.
Personal pathological history.

Pharmacotherapeutic Variables:
Other consumed medications: generic name and pharmacological group (according to the ATC classification, from the Anatomical Therapeutic Chemical classification system), dosage, frequency of administration, and drug interactions.

Classification of Adverse Drug Reactions by Causality, Severity, and Frequency

Adverse drug reactions were classified according to different criteria:

Causality: categorized as definite or certain, probable, possible, conditional, improbable, or unclassifiable according to the Karch and Lasagna Algorithm.

Severity: classified as mild, moderate, or severe as established by the Cuban Pharmacovigilance System (CPS).

Frequency of occurrence: classified as frequent, occasional, rare, and not described as per the CPS.

Data Processing

The data obtained were analyzed using descriptive statistics. As summary measures, percentage calculations and comparisons of absolute and relative frequencies were used.

Results

The sample consisted of 35 patients undergoing treatment with carbamazepine, dispensed at the Main Municipal Pharmacy of Caimanera and the Community Pharmacy located in the locality of Boquerón in the same municipality, Guantánamo Province. Table I presents the distribution of patients according to biosocial variables, where female patients predominated in the age range of 40-75 years, of mixed race, with a pre-university level of education, and without unhealthy habits.

Table I.
Distribution of patients according to biosocial variables

Biosocial Variables		**N**	**%**
Gender	Female	18	51.3
	Male	17	48.7
Age (years)	≤15 years	8	22.8
	16-39 years	11	31.5
	40-75 years	16	45.7
Educational level	Elementary	2	5.7
	Secondary	9	25.7
	Pre-University	13	20
	Technical	7	37.1
	Higher education	4	11.5
Skin color	Mixed	19	54.3
	White	9	25.7
	Black	7	20
Unhealthy habits	Coffee	13	37.1

	Alcohol	1	2.9
	Tobacco	2	5.7
	No toxic habits	19	54.3

N: Number of patients
Source: Registered medical certificates of carbamazepine consumers enrolled in the NMP and interviews conducted.

Figure 1 shows the main diagnoses that motivate the use of carbamazepine. The most prevalent pathology was epilepsy with 24 patients (68.4%), which were classified into: generalized epilepsy 15 patients, tonic-clonic epilepsy 5 patients, and finally focal epilepsy with 4 patients. Another predominant diagnosis was trigeminal neuralgia with 5 patients.

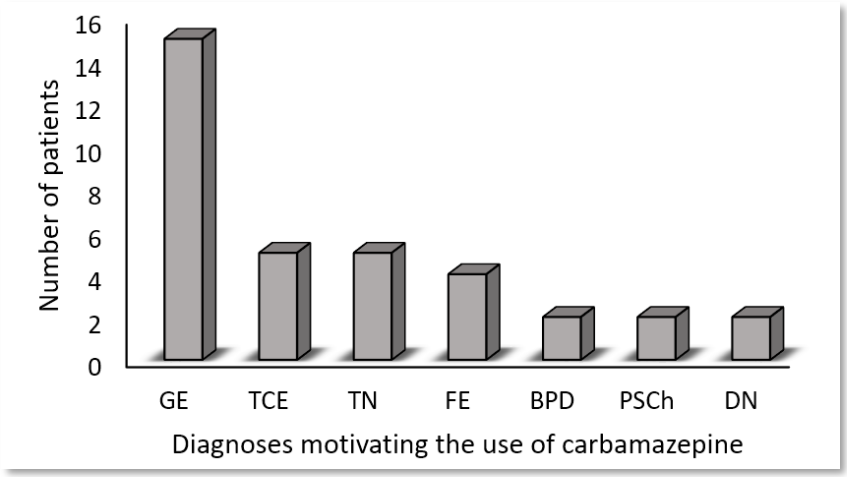

Figure 1. Diagnoses motivating the use of carbamazepine.
Source: Medical certificates
Legend: GE: Generalized Epilepsy, TCE: Tonic-Clonic Epilepsy, TN: Trigeminal Neuralgia, FE: Focal Epilepsy, BPD: Bipolar Affective Disorder, PSCh: Paranoid Schizophrenia, DN: Diabetic Neuropathy

In Figure 2, the concomitant diseases of the studied population group are shown. These include Hypertension (HT) present in 20% of the patients, followed by Diabetes Mellitus (11.4%) and Bronchial Asthma (8.5%). It is noteworthy that 60.1% of the patients did not present with any other associated diseases.

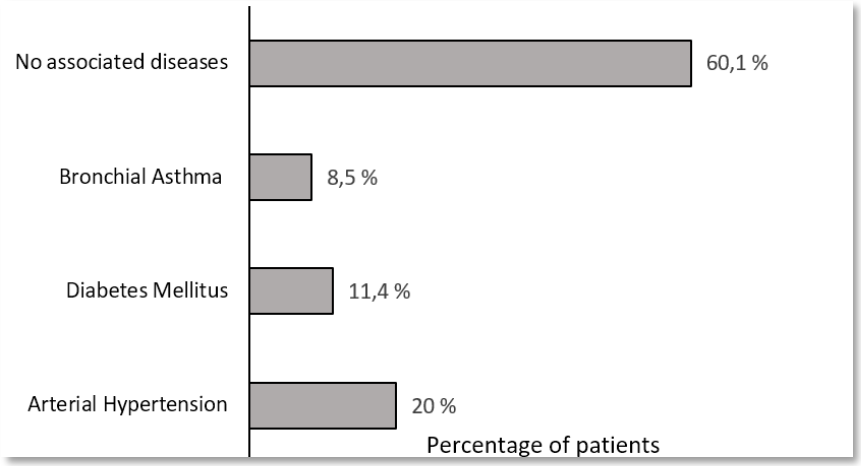

Figure 2 Patients according to concomitant diseases
Source: Medical Certificates

When analyzing the distribution of the sample according to the pharmacotherapeutic variables studied, it was observed that antihypertensive medications were the most used, such as hydrochlorothiazide (20%), and captopril (20%), followed by insulin and salbutamol aerosol. Metamizole (dipyrone) and acetaminophen appear in 100% of the patients, as they self-medicate with these medications for pain or use them as antipyretics, the latter more frequently in the children participating in the study.

Table II shows the relationship between the dose used and the diagnosis for which the medication under study is prescribed. Where the majority of patients present a correct dose at 91.6%, according to the National Formulary of Medications of Cuba (NFM). Only 8.4% of patients (3) had an inadequate dose.

Table II.
Dose used according to diagnosis and age group

Diagnosis	Age group(years)	Established dose by the NFM	Patients with the right dose		Patients with the wrong dose	
			No	%	No	%
Generalized Epilepsy	0-15	100-200mg/day for3 months up to1year	5	14.4	1	2.8
	16-39	100-200mg/day for3 months up to1year	7	20.2	-	-
	40-75	800-1200mg/day maintenance dose	2	5.7	-	-
Tonic-Clonic Epilepsy	0-15	100-200mg/1-2 times/day/ for3 months up to1 yearaño	1	2.8	1	2.8
	16-39	100-200mg/day for3 months up to1year	3	8.6		
Focal Epilepsy	16-39	100-200mg/1-2 times/day/ for3 months up to1 year	1	2.8		
	40-75	800-1200mg/day maintenance dose	3	8.6		
Bipolar Affective Disorder	40-75	400mg/day divided into several doses	2	5.7		
Trigeminal Neuralgia		100mgfor 3 month	4	11.5	1	2.8
Paranoid Schizophrenia		200-400mgfor 3 month	2	5.7		
Diabetic Neuropathy		200mg/day for 3 month	2	5.7		
Total	-	-	32	91.6	3	8.4

Source: Medical certificates.

Classification of Adverse Drug Reactions by Causality, Severity, and Frequency

Table III reflects the ADRs detected in the patients studied during the intervention. Within the central nervous system disorders, somnolence (21.9%), vertigo (19.1%), blurred vision (13.7%), and loss of balance (1.3%) were represented; in terms of dermatological reactions, skin rashes were reported at (6.8%); gastrointestinal system disorders: nausea (10.6%), as well as abdominal pain with the same percentage, and dry mouth was present in (11%).

Table III.
Adverse reactions detected in patients consuming carbamazepine.

Affected systems	RAMs	No. notifications	%
Central nervous system	Somnolence/sleep disorders	16	21.9
	Dizziness	14	19.1
	Blurred vision	10	13.7
	Overbalance	1	1.3
	Total	**41**	**56.0**
Gastrointestinal system	Dry mouth	11	15.2
	Nauseas	8	11
	Abdominal pain	8	11
	Total	**27**	**37.2**
Skin conditions	Skin rash	5	6.8
	Total	**5**	**6.8**
Grand total		**73**	**100**

Source: Clinical histories and patient interviews.

In line with Table IV, we can observe the classification of ADRs according to causality by applying the Karch-Lasagna algorithm, which has been in use since 1981. These are categorized as possible, definite, and probable. The results show a considerable number of ADRs classified as probable (34.2%), which indicates a high correlation that the adverse reaction is related to the medication.

Table IV.
Classification of ADRs by causality, frequency of occurrence, and severity

Classification of ADRs		N	%
Causality assessment	Possible	31	42.5
	Probable /likely	25	34.2
	Definite/ certain	17	23.3
Frequency of appearance	Frequent	36	49.4
	Occasional	27	36.9
	Rare	10	13.7
Severity	Mild	43	58.9
	Moderate	25	34.3
	Severe	5	6.8

Discussion

Carbamazepine has proven effective in treating seizures and mood disorders. However, its use is associated with a variety of adverse effects, some of which can be serious and potentially life-threatening. Therefore, monitoring the safety of this drug is essential to ensure its proper use and minimize risks to patients.

In this study, female patients predominated in the age range of 40 to 75 years, a finding consistent with other authors who have reported an increase in the consumption of carbamazepine among elderly patients in recent years (Mula, 2009). Similarly, other authors have noted the occurrence of epileptic phenomena early in life, where carbamazepine, along with valproic acid and lamotrigine, were the most indicated anticonvulsant drugs (Anderson et al., 2015). This pattern was similarly observed in our research, with a noteworthy number of patients ≤ 15 years old.

The educational level of the interviewees was predominantly pre-university, aligning with Cuban educational policy and facilitating comprehension during interviews. Similarly, the prevalence of mixed-race skin color corresponds with data published by the National Office of Statistics and Information, which

indicates that regions with the highest levels of mixed ethnicity are Guantánamo, Santiago de Cuba, and Granma, in that order, with over 54% of their population (Zabala Arguelles, 2021).

Coffee consumption prevailed among the older adults, who claim to drink a cup, preferably in the mornings. Caffeine is a nervous system stimulant, acting by blocking adenosine A1 and A2a receptors. This blockade increases excitement, which makes us more "active" when we drink coffee. Epileptic patients are more susceptible to this neuronal hyperexcitability and, therefore, to experiencing a crisis after consuming stimulant substances, not only directly but also indirectly if they affect sleep, preventing proper rest. However, the relationship between caffeine and epileptic seizures is not entirely clear, as large-scale studies proving this have yet to be conducted. Researchers estimate that high coffee consumption in epileptic patients is associated with up to twice the risk of suffering focal to bilateral tonic-clonic seizures compared to moderate coffee consumption in this patient population (Bourgeois-Vionnet et al., 2022).

In Cuba, several studies agree that carbamazepine is the most used antiepileptic drug in monotherapy or bitherapy and is very effective in treating trigeminal neuralgia, findings that coincide with other studies reported in the literature which demonstrated a pattern similar to that obtained in this investigation (Adrián, 2022; Ruíz López, 2023; Hernández et al., 2020).

It is important to note the predominance of arterial hypertension as an associated pathology in the studied patients, a chronic disease with a high incidence in the Guantánamo province of 198.8 per 1000 inhabitants according to the Cuban Health Statistical Yearbook 2020 (MINSAP, 2020). This results in antihypertensives like captopril and diuretics such as hydrochlorothiazide being frequently associated with the therapeutic regimen, as well as NSAIDs like dipyrone and acetaminophen, which are often self-medicated by the studied patients, leading to various drug interactions.

Considering that carbamazepine is a drug with complex pharmacokinetics that induces CYP3A4 (a family of cytochrome 450 enzymes playing a key role in the hepatic metabolism of many drugs), glucuronidation, and epoxide hydroxylation, it consequently favors the metabolism of other drugs and vice versa. One such drug is acetaminophen; in this regard, carbamazepine accelerates the biotransformation of acetaminophen into its excretable inactive metabolites, causing a precipitous drop in the latter's plasma levels and the early disappearance of its analgesic and antipyretic effect, presenting a drug interaction (Hata et al., 2008).

Moreover, the pharmacodynamic drug interaction phase of hydrochlorothiazide and carbamazepine is pharmacologically based on the anticonvulsant's ability to erratically increase or decrease potassium currents entering and leaving cells. This effect, combined with the potassium depletion caused by the diuretic effect of hydrochlorothiazide, synergistically leads to potassium excretion, potentially causing hyponatremia, especially at high doses of carbamazepine (Flórez et al., 2014).

We highlight that most of the patients studied were administered the correct dosage; only 8.4% of the patients had an inadequate dose. The majority of these patients who received an inadequate dose were in pediatric ages (5.6%) under the diagnosis of generalized and tonic-clonic epilepsy, where the prescription made by the physician for the initiation of treatment was higher than recommended in these cases. This incorrect prescription poses a severe danger, especially in pediatric ages, where there are significant differences in drug bioavailability, sensitivity of different target organs, or specific receptors to medications. Thus, very different treatment guidelines are needed compared to those prescribed for adults. Children, for ethical reasons, participate very limitedly in clinical studies that test the pharmacokinetics, safety, and efficacy of a drug, which requires using medications according to very conservative criteria in this population. Therefore, special attention is needed regarding prescription criteria in this age group. It is also noteworthy that all patients in the study had monotherapy, and the scientific literature recognizes that polytherapy with this group of drugs for the treatment of epilepsy is more likely to be associated with medication toxicity. (Ministerio de Salud Pública, 2014)

The ADRs detected during the intervention were reported in the model 33-36-1 Notification of Suspected Adverse Drug Reaction by the Cuban Ministry of Public Health. Possible, frequent, and mild adverse reactions predominated, mostly linked to the CNS. These results coincide with the study of the most

frequent adverse reactions in different populations (Anderson et al., 2015). Additionally, adverse effects associated with the consumption of carbamazepine reported in the literature include nystagmus, ataxia, diplopia, blurred vision, lens opacity, gastrointestinal disorders, serious skin reactions, liver damage, altered cardiovascular function, and worsening of seizures at high concentrations. Cognitive dysfunction is much less common than with other anticonvulsants but can occur even within the therapeutic range, especially if used in polytherapy.

However, it is worth highlighting the detection of five severe adverse reactions, 6.8% of the total, corresponding to serious mucocutaneous reactions. It is recognized that Stevens-Johnson syndrome and toxic epidermal necrolysis are associated with the administration of carbamazepine, which eventually led the FDA to add a warning to this medication in 2007. These reactions are considered immune disorders induced by carbamazepine. While the exact mechanism is still unknown, it is believed that Stevens-Johnson syndrome and toxic epidermal necrolysis result from cumulative risks related to the drug's structure and the patient's genetic predisposition (drug metabolism, immunogenic clonotypes, and T cells) (Noguchi et al., 2020).

It is noteworthy that the largest percentage of patients in this study was found in the 40-75 years age group. This group is more vulnerable to ADRs due to physiological changes and diseases that modify pharmacokinetics and pharmacodynamics, altering drug response, high comorbidity with long-term treatments, polypharmacy and drug interactions, non-compliance with treatment, self-medication, and decreased compensatory capacity to pharmacological actions.

Conclusions

In the study, patients between 40-75 years of age (45.7%), female, mixed race, with pre-university educational level predominated, and 54.2% presented no unhealthy habits. Epilepsy (68.4%) was highlighted as the main reason for prescribing carbamazepine, and it was estimated that the indications and therapeutic guidelines for treatment with carbamazepine were appropriate, considering the clinical individualities of the patients. There were 73 adverse reactions detected, with the nervous system being the most affected at 56.0%, with possible ADRs being the most common at 42.5%, frequent at 49.4%, and mild at 58.9%.

Bibliographic References

Adrián, R. L. (2022, May). Fármaco vigilancia de la Carbamazepina, Policlínico Marta Abreu, Santa Clara 2022. In *jorcienciapdcl 2022*.

Anderson, M., Egunsola, O., Cherrill, J., Millward, C., Fakis, A., & Choonara, I. (2015). A prospective study of adverse drug reactions to antiepileptic drugs in children. *BMJ open*, *5*(6), e008298.

Balbuena Veliz, F. M., & Damian Ricaldi, M. E. (2018). *Incidencia de las Reacciones Adversas Detectadas en Gestantes que fueron Atendidas en el Hospital Regional Docente Materno Infantil "El Carmen"* (Tesis de grado), Universidad Privada de Huancayo Franklin Roosevelt.

Barrero Viera, L., & Bestard Pavón, L. A. (2022). La notificación espontánea de las reacciones adversas a medicamentos. *Revista cubana de medicina militar*, *51*(1).

Bihan, K., Lebrun-Vignes, B., Funck-Brentano, C., & Salem, J. E. (2020). Uses of pharmacovigilance databases: an overview. *Therapies*, *75*(6), 591-598.

Bourgeois-Vionnet, J., Ryvlin, P., Elsensohn, M. H., Michel, V., Valton, L., Derambure, P., ... & SAVE study Group. (2022). Coffee consumption and seizure frequency in patients with drug-resistant focal epilepsy. *Epilepsy & Behavior*, *126*, 108486.

Calvo-Salazar, R. A., David, M., Zapata-Mesa, M. I., Rodríguez-Naranjo, C. M., & Valencia-Acosta, N. Y. (2018). Problemas relacionados con medicamentos que causan ingresos por urgencias en un hospital de alta complejidad. *Farmacia Hospitalaria*, *42*(6), 228-233. https://dx.doi.org/10.7399/fh.10996

Choudhury, A., Singh, P. A., Bajwa, N., Dash, S., & Bisht, P. (2023). Pharmacovigilance of herbal medicines: Concerns and future prospects. *Journal of Ethnopharmacology*, *309*, 116383.

Cipolle, R. J., Strand, L.M., & Morley, P.C. (2012). *The Patient Centered Approach to Medication Management. En: Pharmaceutical Care Practice.* Cipolle RJ, Strand LM, Morley PC. 3rd Edition. New York: McGraw Hill.

Flórez, J., Armijo, J. A., & Mediavilla, Á. (2014). *Farmacología humana*. Barcelona [etc.]: Elsevier Masson.

García Torres, A. M., & Aldana Becerra, O. E. (2016). *Caracterización de eventos adversos y problemas relacionados con Carbamazepina reportados al programa distrital de Farmacovigilancia Bogotá DC 2008-2015*. Universidad de Ciencias Aplicadas y Ambientales U.D.C.A. Disponible en: https://repository.udca.edu.co/handle/11158/616

Guarnieri, N. M., Pompilio, A., Marini, C., Ortenzi, G. B., Andresciani, E., Garzone, A. M. F., ... & Polidori, C. (2024). A pharmacovigilance study on antiepileptic medications in a paediatric hospital in Italy. *European Journal of Hospital Pharmacy*, *31*(1), 46-49.

Hariraj, V., Wo, W. K., Lee, S. C., & Ramli, A. (2023). Carbamazepine Induced Severe Cutaneous Adverse Drug Reactions: A 21 Year Comparison Between Children and Adults in Malaysia. *The Journal of Clinical Pharmacology*, *63*(10), 1126-1132.

Hata, M., Tanaka, Y., Kyoda, N., Osakabe, T., Yuki, H., Ishii, I., ... & Hoshino, T. (2008). An epoxidation mechanism of carbamazepine by CYP3A4. *Bioorganic & medicinal chemistry*, *16*(9), 5134-5148

Hernández, Y. S., Avila, D. P., & Vázquez, Y. E. G. (2020). Usos terapéuticos de la carbamazepina en gestantes del Policlínico Alex Urquiola, Holguín, marzo a abril del 2019. *Revista Estudiantil HolCien*, *1*(1).

Ministerio de Salud Pública. (2014). *Formulario nacional de medicamentos*. 4aEd. Cuba: ENCIMED.

MINSAP. (2020). Anuario Estadístico de Cuba. Estados y datos. Oficina Nacional. Available in: https://instituciones.sld.cu/ucmvc/files/2023/10/Anuario-Estad%C3%ADstico-de-Salud-2022-Ed-2023.pdf

Montastruc, F., & de Laportaliere, T. T. (2024). Drug-induced psychiatric disorders: A pharmacovigilance update. *Therapies*, *79*(2), 173-179.

Mula, M. (2009). New antiepileptic drugs: molecular targets. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents)*, *9*(2), 79-86.

Narayanan, A. S., Lakshmi, K. S., & Kamaraj, R. (2020). An Overview on Good Pharmacovigilance Practices and New Operational Plan Milestones of Eudravigilance in European Union. *Research Journal of Pharmacy and Technology*, *13*(4), 1795-1800

Noguchi, Y., Takaoka, M., Hayashi, T., Tachi, T., &Teramachi, H. (2020). Antiepileptic combination therapy with Stevens-Johnson syndrome and toxic epidermal necrolysis: Analysis of a Japanese pharmacovigilance database. *Epilepsia*, *61*(9), 1979-1989.

Ruíz López, A. (2023). Fármacovigilancia de la carbamazepina en el Policlínico Marta Abreu. Santa Clara, 2022. *MediSur*, *21*(1), 83-89.

Sychev, D. A., Ostroumova, O. D., Pereverzev, A. P., Kochetkov, A. I., Ostroumova, T. M., Klepikova, M. V., ... & Goloborodova, I. V. (2020). Drug-induced diseases: approaches to diagnosis, correction and prevention. Pharmacovigilance. *Pharmateca*, *27*(6), 113-126. https://doi.org/10.18565/pharmateca.2020.6.113-126

Trabanca Beltrán, Y. A., Jiménez López, G., Alfonso Orta, I., Pavón Guibert, K., & Albear Caró, F. (2018). Implementación del Programa de Notificación de efectos adversos por pacientes en Guantánamo. *Revista Información Científica*, *97*(2), 281-297.

Williams, J. R. (2008). The Declaration of Helsinki and public health. *Bulletin of the World Health Organization*, *86*, 650-652. https://www.scielosp.org/article/bwho/2008.v86n8/650-652

World Health Organization. (2002). *The importance of pharmacovigilance*. https://www.who.int/publications/i/item/10665-42493

Zabala Arguelles, M. del C. (2021). Los estudios de las desigualdades por color de la piel en Cuba: 2008-2018. *Revista Estudios del Desarrollo Social: Cuba y América Latina*, *9*(1). https://acortar.link/Pdxkhd