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# Laboratory alterations caused by drugs acting on the nervous system which are part of the List of essential drugs of a northeastern Brazilian municipality

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## Abstract

**Objective**: To conduct a survey on the interference of drugs in laboratory tests that are included in the Anatomical Therapeutic Chemical (ATC) N classification (drugs that act on the nervous system), present in the Municipal List of Essential Drugs (REMUME) of the city of Fortaleza, in the state of Ceará. **Methods:** This is exploratory research. We used as search descriptors the names of the drugs present in the 3rd edition REMUME 2022, the Electronic Bulletin of the National Health Surveillance Agency and UpToDate® databases. Next, the laboratory interferences identified were classified into *in vitro* and *in vivo*. Furthermore, *in vivo* changes were grouped according to the frequency of adverse reactions, based on what is recommended by the Medical Dictionary for Regulatory Activities. Data were compiled and analyzed using Microsoft Office Excel® 2013 software. **Results:** Of the 50 drugs analyzed, it was observed that only 16% showed no interference *in vitro* and/or *in vivo*. The following therapeutic classes exhibited the most *in vitro* laboratory alterations; anticonvulsants (12%, n=6), followed by antidepressants (6%, n=3). With regard to *in vivo* alterations, anticonvulsants also were responsible for most of the changes in laboratory testing (22%, n=11), followed by antidepressants (18%, n=9). Biperidene, clobazam, hydroxyzine, nicotine, pramipexole, pyridostigmine, rivastigmine, and rasagiline did not show alterations *in vitro* or *in vivo*, according to the literature consulted. The main organic alterations that affects laboratory results observed in this study, involved the hematological system, with reactions of unknown frequency. **Conclusion:** We found REMUME drugs from the city of Fortaleza-CE, used in clinical situations involving the central nervous system, can cause laboratory changes. Altered laboratory results caused by the drugs and not by the pathology itself may compromise patient's therapy, generating erroneous medical conducts and consequently iatrogenesis, culminating in long hospital stays and increasing health care costs.

**Keywords:** Drug-Related Side Effects and Adverse Reactions, Clinical Laboratory Tests, Psychotropic Drugs.

# Alterações laboratoriais dos medicamentos atuantes no sistema nervoso de uma Relação Municipal de Medicamentos Essenciais do nordeste brasileiro

## Resumo

**Objetivo:** Realizar um levantamento sobre as interferências nos exames laboratoriais dos medicamentos incluídos na classificação *Anatomical Therapeutic Chemical* (ATC) N (medicamentos que atuam no sistema nervoso), presentes na Relação Municipal de Medicamentos Essenciais (REMUME) do município de Fortaleza, no estado do Ceará. **Métodos:** Trata-se de uma pesquisa exploratória. Utilizou-se como descritores de busca os nomes dos medicamentos presentes na 3º edição REMUME 2022, nas bases de dados Bulário Eletrônico da Agência Nacional de Vigilância Sanitária e *UpToDate®*. Em seguida, classificaram-se as interferências laboratoriais identificadas em *in vitro* e *in vivo*. Além disso, agruparam-se as alterações *in vivo* de acordo com a frequência das reações adversas, baseando-se no preconizado pelo *Medical Dictionary for Regulatory Activities*. Os dados foram compilados e analisados usando o software Microsoft Office Excel® 2013. **Resultados:** Dos 50 medicamentos analisados, observou-se que 16% não apresentaram nenhuma interferência *in vitro* e/ou *in vivo*. As classes terapêuticas que apresentaram mais alterações laboratoriais *in vitro* foram os anticonvulsivantes (12%, n=6), seguido dos antidepressivos, com 6% (n=3). No que tange às alterações *in vivo*, os anticonvulsivantes também foram a classe farmacológica com mais alterações (22%, n=11), seguidos também dos antidepressivos (18%, n=9). Biperideno, clobazam, hidroxizina, nicotina, pramipexol, piridostigmina, rivastigmina e rasagilina não apresentaram nenhuma alteração *in vitro* ou *in vivo*, de acordo com a literatura consultada. As principais alterações orgânicas envolviam sistema hematológico, com destaque para reações que apresentavam frequência desconhecida. **Conclusão:** Constatamos que medicamentos da REMUME do município de Fortaleza-CE, utilizados em situações clínicas que envolvem o sistema nervoso central, podem ocasionar alterações laboratoriais. Resultados laboratoriais alterados provocados pelos medicamentos em uso e não pela doença em si, podem vir a comprometer a terapêutica do paciente, gerando condutas médicas errôneas e consequentemente iatrogenias, culminando em mais tempo de hospitalização e gastos para os serviços de saúde.

**Palavras-chave:** Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos, Testes Laboratoriais Clínicos, Psicotrópicos.

## Introduction

In laboratory practice, it can be seen that the interference of drugs in clinical analysis is very important, since it can alter the patient's clinical and laboratory outcome[1,2]. Medications can alter laboratory tests through *in vivo* and/or *in vitro* mechanisms. When there is a change in some biological parameter through a pharmacological or physiological mechanism caused by a drug, there is *in vivo* interference or an adverse reaction of the organism to the medication. On the other hand, *in vitro* interference by the drug or metabolite can occur during some analytical phase, causing a false analysis result[3].

The use of drugs can generate false positive or false negative results. It is therefore necessary for the professional to be vigilant if the results are outside the normal range. It is important to collect information about all the medications the patient has used in the 10 days prior to the collection of the biological material for the test, as well as the time of use[4]. False-positive results can result in misinterpretations of the patient's clinical condition or lead to therapeutic failure, while false-negative results can lead to a health problem not being treated and can worsen, causing future problems for the patient, physician and laboratory[5].

The medications that are commonly associated with these alterations are anticoagulants, antipsychotics, antidepressants, chemotherapy, antibiotics, anti-inflammatories and analgesics6. Among these, the class of drugs that act on the nervous system, represent a large part of the medications used by the Brazilian population and are associated with various adverse effects in addition to important laboratory changes as described by Cosci and Chouinard (2020), that the safety profile of these substances can result in a variety of harmful events, such as withdrawal symptoms related to benzodiazepines and antipsychotics[7,8].

In addition, alterations observed in laboratory tests can help to identify adverse drug reactions (ADRs), when they are able to detect some undesirable and unintentional variation[10]. For this reason, knowledge of possible changes in laboratory tests and the practice of pharmacovigilance by health professionals, including pharmacists, is of great importance in clinical practice. As part of their clinical practice, pharmacists identify and monitor patients' laboratory alterations and, when necessary, intervene with the team to prevent future complications to the patient's health and ensure safe treatment[6].

However, due to the complexity of the subject, recognizing laboratory interference caused by medications is still a challenge in clinical practice. This becomes even more significant when analyzing medications that act on the central nervous system, since the studies published on this subject deal with other classes of medication[9].

Studying the interference of medications, including those in the ATC N class, in laboratory tests is crucial for safe and effective healthcare. By understanding how these medications affect test results, healthcare professionals can make more accurate interpretations, avoiding misdiagnoses and optimizing therapeutic plans. This not only contributes to decision-making, but also favors pharmacovigilance, the drafting of clinical guidelines and general improvement in the quality of healthcare[9].

With this in mind, the aim of this study was to survey the *in vivo* and *in vitro* interference in laboratory tests of medications included in the Anatomical Therapeutic Chemical (ATC) N classification (medications that act on the nervous system), present in the Municipal List of Essential Medications (REMUME) of the municipality of Fortaleza, in the state of Ceará.

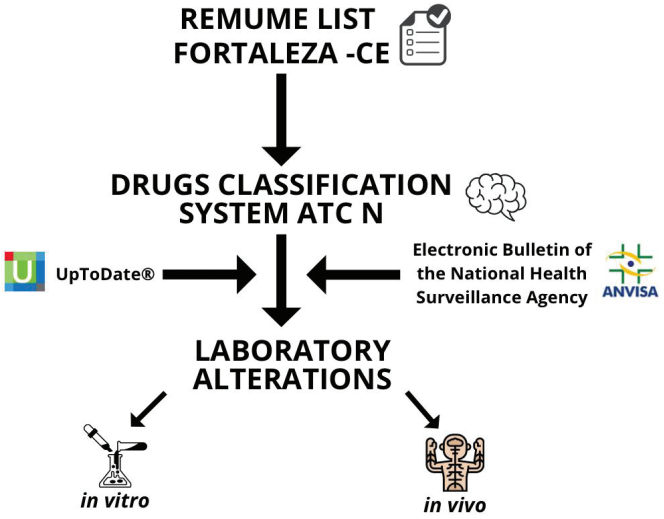
## Methods

The study is exploratory in nature, aiming to initially characterize the problem, providing more familiarity with the issue. The research design used the list of ATC N medications (acting on the Central Nervous System) from the 3rd edition of REMUME 2022 (130 medications belonging to different classes) from the municipality of Fortaleza, in the state of Ceará (2,703,391 inhabitants), made freely available by the Municipal Health Department. After obtaining the names of the medications of interest, investigations were carried out into the laboratory alterations of each medication in the class.

To investigate laboratory alterations, the Electronic Bulletin Board of the National Health Surveillance Agency (ANVISA) and the *UpToDate*®[11,12] website were used as databases. The search keywords used were the names of the medications, according to the Brazilian Common Denomination, in Portuguese for the ANVISA Electronic Bulletin and the International Common Denomination for UpToDate® (Figure 1).

Then, based on the results obtained in the searches, a table was constructed to be used as a quick reference tool by health professionals, patients and/or caregivers. *In vivo* alterations were classified according to the frequency of adverse reactions, based on the recommendations of the Medical Dictionary for Regulatory Activities (MedDRA)13. Thus, the adverse reactions analyzed were classified as: very common (≥ 10%), common or frequent (≥ 1% and < 10%), uncommon or infrequent (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%) or unknown (cannot be estimated). The data was compiled and analyzed using Microsoft Office Excel® 2013 software.

**Figure 1.** Graphic diagram of the study design.




Source: Prepared by the authors, 2023.

## Results

The medications classified as ATC N (acting on the nervous system) in the REMUME of the municipality of Fortaleza and their respective *in vitro* and *in vivo* laboratory alterations are shown in full in Table 1. Of the 50 medications (100%) analyzed, 16% (n=8) do not show any *in vitro* or *in vivo* alterations described in the literature. 24% (n=12) of the medications analyzed can cause laboratory alterations *in vitro* and *in vivo*. 60% (n=30) can only cause laboratory alterations *in vivo*. Of all the medications analyzed, no medications were found to cause only *in vitro* alterations.

The therapeutic classes that showed the most laboratory alterations *in vitro* were anticonvulsants (12%, n=6), followed by antidepressants, with 6% (n=3). In relation to in *vivo* changes, anticonvulsants were also the pharmacological class with the most changes (22%, n=11), followed by antidepressants (18%, n=9). Biperidene, clobazam, hydroxyzine, nicotine, pramipexole, pyridostigmine, rivastigmine and rasagiline showed no changes *in vitro* or *in vivo*, according to the literature consulted.

The main analytical interferences documented and described in Table 1 are related to false positives or false negatives, especially in urinalysis tests. Among the systems that can have their organic functions altered by the use of medications and verified by laboratory tests, we can highlight the hematological, gastrointestinal, metabolic/endocrine and electrolyte balance. In relation to the frequency of adverse reactions (*in vivo* alterations) analyzed for each medication, those with an unknown frequency predominated, i.e. reactions that cannot be estimated in detail from the available data.

## Discussion

The identification of laboratory alterations that can be caused by medications that act on the nervous system at REMUNE in the municipality of Fortaleza-CE, highlights the need for knowledge on the subject. Recognition by health professionals and patients of the organic variations that can occur during the use of these medications can facilitate the identification and management of adverse reactions, improving patient adherence to treatment.

Laboratory alterations caused by medications are relatively common situations in clinical practice. Various medications interfere with organic systems, culminating in adverse reactions that are detected in laboratory tests. This becomes a relevant problem due to the fact that various clinical diagnoses permeate laboratory findings[14,15,16]. Therefore, altered laboratory results caused by the medications in use and not by the disorder itself, can compromise the patient's therapy, generating erroneous medical conduct and consequently iatrogenies, culminating in longer hospital stays and costs for health services[17].

In view of this, from the results obtained, it can be seen that the vast majority of the *in vivo* laboratory alterations presented in this study are classified as unknown, i.e. they could not be quantified to determine their frequency of appearance[18]. Despite the lack of robustness of these data, it is important to bring them up for discussion when making clinical decisions, because despite the low probability of their appearance, their potential to cause harm to the patient should not be overlooked.

Another important issue is the fact that the class of medications analyzed (which act on the nervous system) are mainly used for diseases that are stigmatized (schizophrenia, depression, mood disorders, substance use disorders) by society[19]. This may explain the scarcity of reactions identified, as these diseases are not the target of major studies and investments by the pharmaceutical industry, unlike other diseases such as cancer[20]. Among the classes of medications that cause hematological alterations (anticonvulsants, anxiolytics, and antidepressants) are phenytoin, chlorpromazine and clomipramine[14,15,16]. The secondary pancytopenia caused by these drugs is related to the hematopoietic stem cells, which, when damaged, cause a reduction in the number of neutrophils, platelets and erythrocytes[14].

The mechanism related to the condition may be linked to toxicity in the hematopoietic cells in the bone marrow, which are directly damaged by the drug, by the generation of metabolites or by immune-mediated mechanisms. Symptoms depend on the severity with which each cell line is suppressed, and include fatigue, weakness, signs of infection, petechiae and bleeding[14].

The medications clozapine, valproic acid, alprazolam, carbamazepine, clomipramine, chlorpromazine, phenytoin, and haloperidol can interfere with leukocyte levels, i.e. they can cause leukocyte alterations, especially leukopenia, neutropenia, and agranulocytosis, so their use should be monitored regularly[22,23].

Granulocytes or polymorphonuclear leukocytes are a group of blood cells that include basophils, eosinophils, and neutrophils, responsible for defending the body against microorganisms[24,25,21]. Medication-induced neutropenia (or agranulocytosis) is related to immune-mediated mechanisms in which drugs act as haptens that induce the formation of antibodies against neutrophils. Others can accelerate neutrophil apoptosis or cause direct effects on myeloid precursors[24,21].

Phenytoin and carbamazepine, for example, are associated with eosinophilia. Anticonvulsants are more related to Drug Reaction Syndrome with Eosinophilia and Systemic Symptoms or DRESS, which is characterized as a systemic reaction in which the patient presents with eosinophilia, skin rashes, fever and liver, kidney, and heart damage[21].

Other medications interfere with hemostasis, such as valproic acid, carbamazepine, clomipramine, chlorpromazine and phenytoin[26]. Some of these can cause the appearance of Immune Thrombocytopenic Purpura (ITP), which is characterized by the destruction of platelets by antibodies that bind to glycoproteins on the platelet membrane, leading to clearance by the reticuloendothelial system. It is important to note that thrombocytopenia can be severe and accompanied by bleeding[21].

In relation to the classes associated with gastrointestinal alterations, the drugs amitriptyline, fluoxetine, paroxetine, sertraline, and venlafaxine are strongly associated with hepatotoxic side effects. All these drugs show idiosyncratic, unpredictable, and reversible liver damage. The damage can begin a few days or up to six months after taking the medication and is usually reversed after withdrawal[27]. Commonly prescribed first-generation antipsychotics such as chlorpromazine and haloperidol are linked to high serum levels of liver enzymes, as well as severe liver damage. The hepatotoxicity induced by chlorpromazine is caused by its bioactivation in hepatocytes, which can occur in two ways: Via catalysis by Cytochrome p450, which produces the highly reactive quinone imine metabolite, or by oxidation catalyzed by peroxidase, which generates toxic radicals[28].

As for second-generation antipsychotics, clozapine is mainly associated with hepatotoxicity[29]. According to Chou and colleagues (2014), an asymptomatic increase in serum transaminase levels is observed in up to 60% of patients treated with clozapine, with 15 to 30% showing a double or triple increase. The increase in serum levels of liver enzymes is, in most cases, transient and asymptomatic. Even so, there are many reports of clozapine-induced liver damage accompanying moderate doses, but in most cases, patients recover from clozapine-induced liver damage after stopping treatment[30].

In relation to the use of quetiapine, it has been observed that abnormalities in liver tests can occur in up to 30% of patients on long-term therapy, however the elevations are rarely more than three times the upper limit of normal. Alterations in aminotransferases are usually mild, asymptomatic, and transient, and are reversed even when the medication is discontinued[31,32]. Rare cases of clinically apparent acute liver injury have been reported due to quetiapine. Jaundice begins within one to four weeks of starting the drug, and the pattern of elevated serum enzymes is typically hepatocellular. Most cases are mild to moderate in severity and have a self-limiting course. Instances of acute liver failure have been reported, but not bile duct disappearance syndrome or chronic liver damage[33, 34].

In relation to anticonvulsants, valproic acid is mostly metabolized by the liver, which can lead to an increase in serum levels, especially ALT and AST and, in some cases, liver failure. Depending on the degree, this adverse effect may or may not be reversible[35,36]. Carbamazepime, on the other hand, is associated with stimulating cell apoptosis, as well as increasing serum ALT, AST, and PAL levels. The pathophysiology of the hepatotoxicity of this drug is linked to chronic intrahepatic cholestasis caused by impairment of the ducts and inflammatory infiltrate, since this drug is also metabolized to a large extent by the liver[37].

Prolonged therapy with paracetamol at doses above four grams a day generates transient elevations in serum aminotransferase levels in a proportion of individuals, most often from three to seven days, and with peak values above three times elevated in 39% of patients. These elevations are generally asymptomatic and disappear rapidly with the cessation of therapy or reduction in dosage and, in some cases, disappear even with the continuation of the total dose[38].

It should be noted that one of the main limitations of this study lies in the sample analyzed (REMUME of Fortaleza), which may not be representative of the diversity of drugs available and consequently compromises the generalizability of the results to other populations and clinical scenarios. The lack of longitudinal data is another significant limitation, which makes it more difficult to understand the temporal evolution of laboratory interference over the course of treatment. The exclusive reliance on the databases used (the ANVISA Electronic Bulletin and UpToDate®) may prevent other sources from including pertinent information.

Several lines of research can be explored to advance our understanding of the subject. Firstly, to provide a more comprehensive view, it is important to expand the database used to include more recent medications and a variety of clinical conditions. In addition, long-term studies should be considered in order to understand how laboratory alterations change over time and their consequences. Further investigation into the molecular mechanisms that cause laboratory interferences, in conjunction with genomic data, could help in the development of prevention and management techniques, as well as improving the understanding of individual responses to medications.

## Conclusion

The medications in the REMUME of the municipality of Fortaleza-CE, used in clinical situations involving the central nervous system, can cause laboratory alterations. It is therefore necessary for health professionals to be aware of and able to recognize the adverse reactions that can be identified from these laboratory alterations, thus avoiding drug-related problems. In addition, it is necessary to carry out pharmacovigilance reports on adverse reactions to this class of medications, in order to contribute to the clinical management of other patients.

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**Collaborators**

**Falta texto**

**Conflict of interest declaration**

The authors declare no conflicts of interest in relation to this article.

## References

1. Ferraro S, Braga F, Panteghini M. Laboratory medicine in the new healthcare environment. Clin Chem Lab Med. 2016;54(4):523-33. DOI: 10.1515/cclm-2015-0803.
2. van Balveren JA, Verboeket-van de Venne WPHG, Erdem-Eraslan L, et al. Impact of interactions between drugs and laboratory test results on diagnostic test interpretation - a systematic review. Clin Chem Lab Med. 2018;56(12):2004-2009. DOI: 10.1515/cclm-2018-0900.
3. Ferreira BC, Dos Santos KL, Rudolph SC, et al. Estudo dos medicamentos utilizados pelos pacientes atendidos em laboratório de análises clínicas e suas interferências em testes laboratoriais: uma revisão de literatura. Rev Eletrônica de Farmácia. 2009;4(1): 33-43. DOI: 10.5216/ref.v6i1.5859
4. Yao H, Rayburn ER, Shi Q, et al. FDA-approved drugs that interfere with laboratory tests: A systematic search of US drug labels. Crit Rev Clin Lab Sci. Crit Rev Clin Lab Sci. 2017; 54(1):1–17. DOI: 10.1080/10408363.2016.1191425.
5. Dos Santos SLF, Borges RN, Barros KBNT. Drugs that interfere with the results of laboratory tests: an integrative review of the literature. RBAC. 2018;50(2):105-10. DOI: 10.21877/2448-3877.201800581.
6. Ferreira AF, Rocha CP, Vieira LM, et al. Alterações hematológicas induzidas por medicamentos convencionais e alternativos. Rev Brasileira de Farmácia. 2013;(94):94-101.
7. Cosci F, Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. Psychother Psychosom. 2020 Sep 1;89(5):283-306.

DOI: 10.1159/000506868.

8. Oliveira JR, Varallo FR, Jirón M, Ferreira IM, Siani-Morello MR, Lopes VD, Pereira LR. Descrição do consumo de psicofármacos na atenção primária à saúde de Ribeirão Preto, São Paulo, Brasil. Cadernos de Saúde Pública. 2021; Jan 11;37:e00060520. DOI: 10.1590/0102-311X00060520.
9. Katanić J, Stanimirov B, Sekeruš V, Đanić M, Pavlović N, Mikov M, Stankov K. Drug interference with biochemical laboratory tests. Biochemia Medica. 2023; 33(2):020601. DOI: 10.11613/BM.2023.020601.
10. Boas práticas de farmacovigilância para as Américas [Internet]. Organização Pan-Americana da Saúde (Rede PAHRF Documento Técnico Nº 5). Available from: https://iris.paho.org/handle/10665.2/28455.
11. Bulário Eletrônico [Internet]. Agência Nacional de Vigilância Sanitária. Available from: https://www.gov.br/anvisa/pt-br/sistemas/bulario-eletronico. Accessed on: 05/18/2023.
12. Drug Information [Internet]. Uptodate. Available from: https://www.uptodate.com/contents/search.
13. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf . 1999;20(2):109-17. DOI: 10.2165/00002018-199920020-00002.
14. Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. Neurological Sciences. 2014 Jul;35:983-93. DOI: 10.1007/s10072-014-1701-0.
15. Castellanos-Sinco HB, Ramos-Peñafiel CO, Santoyo-Sánchez A, et al. Megaloblastic anaemia: Folic acid and vitamin B12 metabolism. Rev. Medica del Hosp. Gen. de Mex. 2015;78(3):135-143. DOI: 10.1016/j.hgmx.2015.07.001.
16. Qahtani SAA. Drug-induced megaloblastic, aplastic, and hemolytic anemias: current concepts of pathophysiology and treatment. Int J Clin Exp Med. 2018; 11(6): 5501-5512.
17. Pagno AR, Gross CB, Gewehr DM, et al. Drug therapy, potential interactions and iatrogenesis as factors related to frailty in the elderly. Rev. bras. geriatr. gerontol. 2018; 21(05): 610-619. DOI: 10.1590/1981-22562018021.180085.
18. Monitorização da segurança de medicamentos: diretrizes para criação e funcionamento de um Centro de Farmacovigilância [Internet]. Organização Mundial da Saúde. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/seguranca.pdf. Accessed on: 05/18/2023.
19. Rocha FL, Hara C, Paprocki J. Doença mental e estigma. Rev Med Minas Gerais. 2015; 25(4): 590-596. DOI: 10.5935/2238-3182.20150127.
20. Amorim KPC, Garrafa V, De Melo AD, et al. Participantes de ensaios clínicos em oncologia: perfil e aspectos envolvidos nas suas decisões.Trab. educ. saúde. 2018; 16(3): 1381-1402. DOI: 10.1590/1981-7746-sol00139.
21. Tolou-Ghamari Z, Zare M, Habibabadi JM, Najafi MR. Antiepileptic drugs: a consideration of clinical and biochemical outcome in patients with epilepsy. International journal of preventive medicine. 2013 May;4(Suppl 2):S330.
22. Verrotti A, Scaparrotta A, Grosso S, et al. Anticonvulsant drugs and hematological disease. Neurol Sci . 2014;35(7):983-93. DOI: 10.1007/s10072-014-1701-0.
23. Balda MV, Garay OU, Papale RM, et al.Clozapine-associated neutropenia and agranulocytosis in Argentina (2007-2012). Int Clin Psychopharmacol . 2015;30(2):109-14. DOI: 10.1097/YIC.0000000000000060.
24. Padda J, Khalid K, Syam M, Kakani V, Tonpouwo GK, Dhakal R, Padda S, Cooper AC, Jean-Charles G. Association of Anemia With Epilepsy and Antiepileptic Drugs. Cureus. 2021 Nov 7;13(11). DOI: 10.7759/cureus.19334.
25. Curtis BR. Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. Hematology Am Soc Hematol Educ Program. 2017;2017(1):187-193. DOI: 10.1182/asheducation-2017.1.187.
26. Wolf JM, Wolf LM. Uma revisão sobre a terapêutica anticoagulante oral no manejo da trombose. Rev. Saúde e Biol. 2017; 12(1): 66-78.
27. Vukotić NT, Đorđević J, Pejić S, et al. Arch Toxicol. 2021; 95(3): 767–789. DOI: 10.1007/s00204-020-02963-4.
28. MacAllister SL, Young C, Guzdek A. Molecular cytotoxic mechanisms of chlorpromazine in isolated rat hepatocytes. Can J Physiol Pharmacol . 2013; 91(1): 56-63. DOI: 10.1139/cjpp-2012-0223.
29. Telles-Correia D, Barbosa A, Cortez-Pinto H, et al. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. World J Gastrointest Pharmacol Ther. 2017 Feb 6; 8(1): 26–38. DOI: 10.4292/wjgpt.v8.i1.26.
30. Chou AIW, Lu M, Shen WW. Hepatotoxicity induced by clozapine: a case report and review of literature. Neuropsychiatr Dis Treat. 2014; 10: 1585–1587. DOI: 10.2147/NDT.S67654.
31. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, Watkins PB, Navarro V, Barnhart H, Gu J. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology. 2015 Jun 1;148(7):1340-52. DOI: 10.1053/j.gastro.2015.03.006.
32. Das A, Guarda LA, Allen LG. Liver injury associated with quetiapine: an illustrative case report. Journal of clinical psychopharmacology. 2017 Oct 1;37(5):623-5. DOI: 10.1097/JCP.0000000000000749.
33. Druschky K, Toto S, Bleich S, Baumgärtner J, Engel RR, Grohmann R, Maier HB, Neyazi A, Rudolph YJ, Rüther E, Schwörer H. Severe drug-induced liver injury in patients under treatment with antipsychotic drugs: Data from the AMSP study. The World Journal of Biological Psychiatry. 2021 May 28;22(5):373-86. DOI: 10.1080/15622975.2020.1819565.
34. Baeza I, de la Serna E, Calvo-Escalona R, Merchan-Naranjo J, Rodriguez-Latorre P, Martínez-Cantarero MC, Andrés P, Alda JA, Munoz-Samons D, Ilzarbe D, Arango C. One-year prospective study of liver function tests in children and adolescents on second-generation antipsychotics: is there a link with metabolic syndrome? Journal of Child and Adolescent Psychopharmacology. 2018 Sep 1;28(7):463-73. DOI: 10.1089/cap.2017.0117.
35. Vidaurre J, Gedela S, Yarosz S. Antiepileptic drugs and liver disease. Pediatric Neurology. 2017 Dec 1;77:23-36. DOI: 10.1016/j.pediatrneurol.2017.09.013.

36. Meseguer ES, Elizalde MU, Borobia AM, Ramírez E. Valproic acid-induced liver injury: A case-control study from a prospective pharmacovigilance program in a tertiary hospital. Journal of Clinical Medicine. 2021 Mar 10;10(6):1153. DOI: 10.3390/jcm10061153.

37. Sasaki E, Iida A, Oda S, et al. Pathogenetic analyses of carbamazepine-induced liver injury in F344 rats focused on immune- and inflammation-related factors. Exp. Toxicol. Pathol. 2016; 68(1): 27-38. DOI: 10.1016/j.etp.2015.09.004.

38. Andrade RJ, Aithal GP, Björnsson ES, Kaplowitz N, Kullak-Ublick GA, Larrey D, Karlsen TH, European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. Journal of hepatology. 2019 Jun 1;70(6):1222-61. DOI: 10.1016/j.jhep.2019.02.014.