

HOSPITALIZATION DUE TO COMPLICATIONS FROM THE USE OF ANALGESICS, ANTIPYRETICS AND ANTI-INFLAMMATORIES IN BRAZIL BETWEEN 2007 AND 2021

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Abstract: Introduction: Non - opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are among the most used drugs in the world, and are often used without a medical prescription. **Objective:** To describe the epidemiological profile of hospitalizations due to adverse effects due to the use of analgesics, antipyretics and anti-inflammatories in Brazil between 2007 and 2021. **Methodology:** This is a descriptive observational study, whose data were collected through the DataSUS platform. Collection started from the Hospital Information System (SIH), through hospital morbidity data by place of residence between January 2007 and December 2021. **Results and Discussion:** There were 688 hospitalizations due to adverse effects from the use of analgesics, antipyretics and anti-inflammatories. The most affected region was the southeast with 44.33% of all cases in the country. The national average age group most affected is represented by two peaks: from one to four years of age and from 20 to 29. Although there is no difference between the number of hospitalizations of men and women, the female rate was approximately 25 %. The general mortality rate was 2.47 among hospitalized patients, however, this rate varied between private and public services, the latter being 70% higher. **Conclusion:** Greater awareness policies on the proper and rational use of medicines must be implemented. In addition, further investigation by the hospital team must be encouraged, in order to promote lower rates of adverse reactions in those patients who have had episodes of suspected complications before. **Keywords:** Analgesics, Antipyretics, Anti-inflammatories, Adverse effects, Hospitalizations.

INTRODUCTION

Pain is a prevalent symptom in the daily lives of a large portion of the Brazilian population. It is estimated that on average 30% of the population complains or suffers from some type of pain. A study carried out in the Unified Health System showed that the prevalence of chronic pain ranged from 30% to 50%. Another study found a headache rate in 10% of all cases treated at the Basic Health Care Unit, with 80% of patients reporting headache in the previous year. ¹

A study carried out at a pain clinic in a large city in southern Brazil showed that the most prevalent pain was low back pain (21.1%), followed by pain in the lower limbs (15.8%), neck pain (13.2%), pain in the upper limbs (12.3%), generalized pain (9.6%), headache (7.0%) and orofacial pain (5.3%), with 15.8% of the patients referring location pain in the abdomen, thorax and hemibody. ^{two}

It is clear, therefore, that an appropriate treatment is necessary for each type of pain. And, for this to happen, it is necessary to understand the characteristics of pain, such as severity and its nature – acute pain versus chronic pain or nociceptive pain versus neuropathic pain. Proper treatment requires an understanding of the most effective medications available on the market today, as well as their advantages and disadvantages. ³

Although several classes of drugs are used to treat pain, three categories in particular – acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids – are used most frequently worldwide. ³ Each of these drugs is associated with different adverse events and with varying degrees of effectiveness. In general, acetaminophen is the least potent, while NSAIDs and opioids offer stronger analgesic effects. ⁴

Paracetamol is among the most used analgesic medications in the Brazilian population along with Metamizol, popularly

known as dipyrone. According to a survey recently released by IQVA, which appears in Interfarma's 2019 Guide, analgesics stand out among the ten drugs that have earned the most in the Brazilian market. At the top of the list, an analgesic that works for different types of pain leads, Dorflex, composed of sodium dipyrone monohydrate, orphenadrine citrate and caffeine, therefore, it does not usually cause drowsiness in patients. ⁵ Despite its routine use and not requiring a prescription to be obtained from a pharmacy, the use of acetaminophen can cause acute liver failure if used excessively. ⁴

Associated with analgesics, NSAIDs are one of the most commonly used groups of drugs. Many patients, particularly those with arthritis, are daily users of NSAIDs. ⁶ Among several NSAIDs, diclofenac is the most commonly used NSAID worldwide. ⁷ They are a diverse group of compounds that have analgesic, antipyretic, and anti-inflammatory effects. ⁸ Most NSAIDs are acidic compounds with relatively high bioavailability. They are highly bound to plasma proteins and are metabolized by the liver. ^{6,9} Most patients take therapeutic doses of these drugs for short periods and generally tolerate them well. ¹⁰ In addition to their analgesic, anti-inflammatory, and antipyretic efficacies, NSAIDs also offer protection against a number of critical disorders, including cancer and heart attacks. ¹¹ However, data from multiple placebo-controlled trials and meta-analysis studies have shown numerous adverse effects of NSAIDs in gastrointestinal, cardiovascular, hepatic, renal, cerebral and pulmonary complications.

In the case of more acute and severe pain, opioids are the most used classes, and even in these situations they must be indicated. Although subjective, pain can be measured through scores on the visual analogue scale. From at least 7, severe pain, such as in the

post-surgical setting and other situations where NSAIDs, acetaminophen or other treatments provide inadequate pain relief, is that opioids are recommended as they are associated with serious side effects including depression breathing, motor and cognitive impairment, sedation and development of tolerance. In addition, prolonged use of opioids can result in the development of an increased sensitivity to pain known as opioid-induced hyperalgesia.¹²

Poisoning due to the use of any medication from the three classes is not uncommon and these are situations in which the patient needs to be treated urgently, as it can quickly cause target organ damage if not managed. Between 2010 and 2017, 565,271 cases of poisoning were reported in Brazil. Of these, 298,976 had the drug as the most frequent toxic agent, corresponding to 52.8% of all occurrences. The predominance of poisoning by a drug agent accidentally caused is equivalent to 42,968 (36.3%) cases. Self-medication motivated 17,923 cases of intoxication (15.15%). The other cases were due to therapeutic use (13,084 or 11.06%), common use (10,750 or 9.1%), abuse (7,451 or 6.3%) and administration error (6,888 or 5.82%).¹³

Although there are contraindications, complications and adverse effects can occur regardless of the medical care provided. This study seeks to describe the epidemiological profile of hospitalizations due to adverse effects due to the use of analgesics, antipyretics and anti-inflammatories in Brazil between 2007 and 2021.

METHODOLOGY

This is a descriptive observational study, whose objective is to understand the epidemiological distribution of hospitalizations due to adverse effects caused by analgesics, antipyretics and

anti-inflammatories in Brazil. Data were collected by the DataSUS platform, through information collected by the Notifiable Diseases Information System (SINAN). The collection started from the Hospital Information System (SIH), through hospital morbidity data by place of hospitalization between January 2007 and December 2021. The information was characterized by regions of Brazil according to hospitalizations by year of attendance. The indicators used were: gender, age, color/race, cost per hospitalization, type of network used by patients (public or private), deaths and mortality rates.

Considering that the information is publicly accessible and does not identify collective or individual data, this research did not need to be submitted to the local Research Ethics Committee (CEP), even though it considered the ethical principles contained in the Resolution of the National Health Council 466 /2012.

RESULTS AND DISCUSSION

Access to pharmacies and ease of acquisition of medicines promote an increase in the consumption of medicines by the Brazilian population. In Brazil, according to data from the Federal Council of Pharmacy, there is one pharmacy for every 2,700 inhabitants.¹⁴ Furthermore, data from the Federal Council of Medicine indicate that 77% of Brazilians use medication without any medical advice and, what is worse, according to estimates by the World Health Organization (WHO), around 50% of users do so. use of medication incorrectly.^{15,16}

In order to prescribe a medication, it is necessary to know the appropriate dosage and drug for each type of patient. All medications have contraindications that need to be checked in advance in order to mitigate possible complications and adverse effects.⁴

Region	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
TOTAL	3	49	67	56	52	46	41	61	42	44	41	49	53	46	38	688
North region	-	1	3	-	3	2	1	-	2	2	1	-	3	4	1	23
Northeast Region	-	16	27	17	19	18	19	20	15	8	10	6	12	12	20	219
Southeast region	2	27	26	35	24	19	18	31	14	24	18	20	24	13	10	305
South region	1	5	11	2	4	6	2	8	7	8	12	16	4	11	3	100
Midwest region	-	-	-	2	2	1	1	2	4	2	-	7	10	6	4	41

Table 1.0 Number of patients hospitalized for complications due to the use of analgesics, antipyretics and anti-inflammatories between 2007 and 2021.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022.

Region	Minor 1 year	1 to 4 years	5 to 9 years old	10 to 14 years	15 to 19 years old	20 to 29 years old	30 to 39 years	40 to 49 years old	50 to 59 years old	60 to 69 years	70 to 79 years old	80 years and over	Total
TOTAL	34	91	54	44	58	90	76	78	63	49	30	21	688
North region	3	3	-	-	2	7	3	1	2	-	1	1	23
Northeast Region	16	41	32	14	16	13	23	25	15	10	9	5	219
Southeast region	12	26	16	21	26	43	42	34	30	25	16	14	305
South region	3	11	5	6	9	20	7	15	11	10	2	1	100
Midwest region	-	10	1	3	5	7	1	3	5	4	2	-	41

Table 2.0 Number of patients by age group among hospitalizations due to complications from the use of analgesics, antipyretics and anti-inflammatories between 2007 and 2021.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022.

In Brazil, between 2007 and 2021, there were 688 hospitalizations due to adverse effects from the use of analgesics, antipyretics and anti-inflammatories **Table 1.0**. The most affected region was the southeast with 44.33% of all cases in the country. The second most affected region was the Northeast with 31.8% of cases, followed by the South, Midwest and North regions, respectively.

Between the analyzed period of this study, considering the causes of exogenous intoxication by medication due to habitual, accidental, therapeutic use, by medical prescription, administration error, self-medication and abuse, there were 195,844 cases notified to the Information System for Notifiable Diseases (SINAN) **Table 2.0**. The main causes were accidental and self-medication, which represented 60.5% of cases. Furthermore, the rate of intoxication has been increasing practically every year since 2007. This confirms the lack of knowledge on the part of the population to use medications correctly.

The national average age group most affected is represented by two peaks: from one to four years of age and from 20 to 29 **Table 3.0**. While in the Northeast the age group most affected is between one and nine years old, in the Southeast the population with the highest rates of hospitalization is between 20

and 39. Furthermore, during this period, there was no difference between the number of hospitalizations of men (48.1%) and women (51.9%) **Table 4.0**, as well as the days spent in hospital between the groups, 3.6 and 3.3, respectively. However, when analyzing the mortality rate, the mortality rate of women (2.8%) was higher than that of men (2.11%) by approximately 25%.

The cost of hospitalization for hospitalized patients is relatively high and varies according to the different regions and age groups affected. The national average cost is R\$ 493.50, ranging from R\$ 366.43 in the South region, which has the lowest amount spent per hospitalization/inhabitant, to R\$ 537.88 in the Southeast region, which has the lowest average cost. face **Table 5.0**. Regarding age groups, from 1 to 4 years old, the average cost is R\$191.26. In the case of the population over 80 years old, this value rises to R\$ 1,119.76, six times more.

The cost of hospitalization is directly related to the severity of the condition and the cost of medications. NSAIDs are broadly categorized into: selective cyclooxygenase (COX)-2 inhibitors (COXIBs) and non-selective NSAIDs. Non-selective NSAIDs are responsible for the greatest number of gastrointestinal and renal side effects.

Region/Gender	Masculine	Female	Total
TOTAL	331	357	688
North region	14	9	23
Northeast Region	118	101	219
Southeast region	137	168	305
South region	42	58	100
Midwest region	20	21	41

Table 4.0 Distribution by sex among hospitalizations due to complications caused by the use of analgesics, antipyretics and anti-inflammatories between 2007 and 2021.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022.

Year Notification	Usual Use	Accidental	Therapeutic Use	Doctor's Prescription	Administration Error	Self-Medication	Abuse	Total
TOTAL	23,905	80,089	24,442	1,043	12,704	38,363	15,298	195,844
2007	278	1,387	349	43	189	475	211	2,932
2008	404	1,956	511	37	256	647	365	4,176
2009	571	2,320	637	35	281	921	417	5,182
2010	604	2,619	863	61	430	1,064	479	6,120
2011	927	3,536	1,006	43	608	1,348	644	8,112
2012	1,104	4,583	1,309	67	661	1,864	850	10,438
2013	1,319	6,082	1,655	71	883	2,201	907	13,118
2014	1,589	5,960	2,074	103	871	2,629	1,030	14,256
2015	1,546	5,751	1,845	56	964	2,662	973	13,797
2016	1,561	6,464	1,703	112	1,136	2,724	1,064	14,764
2017	2,146	8,118	2,713	110	1,363	3,513	1,538	19,501
2018	2,656	8,548	3,021	82	1,449	4,416	1,677	21,849
2019	3,371	8,727	3,334	80	1,556	5,322	1,987	24,377
2020	2,752	7,066	1,854	64	1,004	4,225	1,554	18,519
2021	3,077	6,972	1,568	79	1,053	4,352	1,602	18,703

Table 3.0 Number of notifications registered for exogenous drug intoxication in Brazil between 2007 and 2021.

Source: Ministry of Health/SVS - Information System for Notifiable Diseases - Sinan Net.

Still, there is a class of super selective NSAIDs, such as: Celecoxib, Eterocoxib and Parecoxib. However, these are responsible for increasing the risk of cardiovascular events.

The most common side effect of NSAIDs are mild gastrointestinal adverse effects (GAE) characterized by dyspepsia, heartburn and nausea.¹⁷ Most of these SAE are limited to the upper gastrointestinal (GI) tract. They are readily noticed by the patient and are easily diagnosed in clinical practice. However, there are more severe SAEs that occur in the more distal segments of the GI tract. In contrast to the upper GI complications that are often patient-noticed, the lower GI side effects of NSAIDs are not readily detectable, so efforts are limited to control these effects.¹⁸

This detrimental effect of NSAIDs can result in serious conditions ranging from minor injuries to lumen stenosis, a condition called diaphragmatic disease.^{19,20} All NSAIDs can cause distal SAE, but with variable intensity.^{21,22} Even low-dose ASA regimens are not excluded from this side effect.^{23,24} It is important to note that the risk of distal GI toxicity from NSAIDs appears to increase with formulations that are designed for gut delivery; for example, enteric coating and sustained release.^{25,26}

It is estimated that 1-5% of NSAID users may develop adverse renal effects.⁶ Both acute and chronic renal failure can be caused by NSAIDs.²⁷ Various forms of renal failure caused by NSAIDs have been observed, including acute deterioration of renal function, renal papillary necrosis, acute interstitial nephritis, hyperkalemia, and sodium and fluid retention.^{28,29} The acute form of these side effects is dose/duration dependent and generally reversible. However, they sometimes result in chronic kidney failure. Indeed, it seems that a history of acute renal failure makes the patient more prone to the chronic version of the complication.¹⁰

Among the cardiovascular conditions associated with NSAIDs, acute myocardial infarction is the most studied, perhaps because it is the most lethal and the most common. Most studies have reported the risk associated with all NSAIDs of varying intensity, dose and duration.³⁰

In addition to adverse effects related to the mechanisms of drug action, allergic reactions and cases of anaphylaxis may occur. The prevalence of adverse drug reactions is not known, but it is estimated that 7% of the general population and up to 20% of hospitalized patients have hypersensitivity reactions to drugs. In Brazil, the highest rate of identified reactions is associated with the use of NSAIDs.³¹

It is known that in the black population, the consequences of hypertension, be it kidney disease, cardiovascular disease, cerebrovascular disease, appear more aggressively. However, there was no higher prevalence of blacks or browns among those hospitalized for adverse effects **Table 6.0**. The white population represented 33.3% of the cases and, excluding those without racial information, this figure rises to 49%.

When evaluating the overall mortality rate, the age group with the highest number of cases was 50 to 59 years old, representing 29.4% of deaths. The overall mortality rate was 2.47 among hospitalized patients, however, this rate varied between public and private care. Patients treated in the public network had a 70% higher mortality rate **Table 7.0**. There were no deaths from adverse effects in the North region during the study period.

Based on these data, it is clear that greater awareness policies about the adequate and rational use of medicines must be implemented. In addition, further investigation by the hospital team must be encouraged, in order to promote lower rates of adverse reactions in those patients who

Region	Minor 1 year	1 to 4 years old	5 to 9 years old	10 to 14 years	15 to 19 years old	20 to 29 years old	30 to 39 years old	40 to 49 Years	50 to 59 years old	60 to 69 years old	70 to 79 years old	80 years and more	Total
TOTAL	275.43	191.26	876.31	247.84	273.82	506.68	878.09	409.94	585.41	412.22	458.13	1,119.76	493.5
North region	662.55	172.27	136.95	1,214.95	148.61	136.95	338.01	...	906.21	972.97	627
Northeast Region	208.99	151.98	1,216.84	167.86	243.02	273.81	413.02	539.18	177.21	628.13	333.85	2,438.66	481.41
Southeast region	279.56	209.2	413.01	246.71	314.19	471.29	1,160.66	375.5	848.39	418.97	508.65	675.42	537.88
South region	226.09	193.73	345.26	384.52	244.06	275.47	1,136.14	210.47	662.89	234.38	227.77	892.74	366.43
Midwest region	...	308.62	47.27	355.68	270.75	1,108.95	88.7	811.65	160.67	274.94	619.56	...	462.99

Table 5.0 Average cost of hospitalization per complication of analgesics, antipyretics and anti-inflammatories between 2007 and 2021 according to each age group in reais (R\$).

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022.

Region	White	Black	Brown	Yellow	No Information	Total
TOTAL	229	27	202	9	221	688
North region	1	-	8	-	14	23
Northeast Region	11	2	119	1	86	219
Southeast region	142	22	59	3	79	305
South region	72	2	5	4	17	100
Midwest region	3	1	11	1	25	41

Table 6.0 Distribution by color/race among hospitalizations due to complications caused by the use of analgesics, antipyretics and anti-inflammatories between 2007 and 2021.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022.

Region	Public	Private	Ignored	Mortality Rate
TOTAL	2.98	1.75	2.48	2.47
Northeast Region	3.06	2	4.23	3.2
Southeast region	3.03	1.08	1.77	1.97
South region	4.55	4.55	1.79	3
Midwest region	-	-	3.23	2.44

Table 7.0 Mortality rate by type of health service among hospitalizations due to complications caused by the use of analgesics, antipyretics and anti-inflammatories between 2007 and 2021 according to the regions of Brazil.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022.

have had episodes of suspected complications before.

CONCLUSION

Non - opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are among the most used and/or prescribed drugs in the world, mainly because they have a symptomatic effect on inflammatory diseases or processes. However, these are medications that can cause allergies, hepatotoxicity, gastrointestinal, renal and cardiovascular impairment. In Brazil, between 2007 and 2021, there were 688 hospitalizations due to adverse effects from the use of analgesics, antipyretics and anti-inflammatories. The most affected region was the southeast with 44.33% of all cases in the country.

The national average age group most affected is represented by two peaks: from one to four years of age and from 20 to 29. Furthermore, during this period, there was no difference between the number of hospitalizations of men, although, when analyzing the rate of mortality, the rate in women was higher than in men by approximately 25%. When evaluating the overall mortality rate, the age group with the highest number of cases was 50 to 59 years old, representing 29.4% of deaths. The overall mortality rate was 2.47 among hospitalized

patients, however, this rate varied between public and private care. Patients treated in the public network had a 70% higher mortality rate.

CONFLICT OF INTERESTS

None.

FINANCING

Researchers.

REFERENCES

1. Dor no Brazil – SBED [Internet]. [cited 2023 Jan 25]. Available from: <https://sbed.org.br/duvidas-frequentes-2/dor-no-Brazil/#:~:text=Em%20geral%2C%20pelos%20dados%20Brazileiros>
2. Cipriano A, Almeida DB de, Vall J. Perfil do paciente com dor crônica atendido em um ambulatório de dor de uma grande cidade do sul do Brazil. *Rev dor* [Internet]. 2011; 12(4).
3. Nalamachu, S. An Overview of Pain Management: The Clinical Efficacy and Value of Treatment [Internet]. *AJMC*. 2013 Available from: https://www.ajmc.com/view/a467_nov13_nalamachu_s261
4. Brunton, L.L. Goodman & Gilman: As Bases Farmacológicas da Terapêutica. 12ª ed. Rio de Janeiro: McGraw-Hill, 2012.
5. Ribeiro W. 10 medicamentos que mais faturaram com vendas no Brazil [Internet]. *ictq.com.br*. [cited 2023 Jan 25]. Available from: <https://ictq.com.br/varejo-farmaceutico/1072-10-medicamentos-que-mais-faturaram-com-vendas-no-Brazil/#:~:text=1%20%2D%20Dorflex>
6. Harirforoosh S, Jamali F. Renal adverse effects of non-steroidal anti-inflammatory drugs. *Expert Opin Drug Saf*. 2009;8(6):669-81.
7. McGettigan P, Henry D. Use of non-steroidal antiinflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS medicine*. 2013 Feb;10(2):e1001388
8. Vane JR. The fight against rheumatism: from willow bark to COX-1 sparing drugs. *J Physiol Pharmacol*. 2000 Dec;51(4 Pt 1):573-86.
9. Knights KM, Winner LK, Elliot DJ, Bowalgaha K, Miners JO. Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDPglucuronosyltransferases: inhibition by NSAIDs. *Brit J Clin Pharmacol*. 2009 Sep;68(3):402-12.
10. Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. *Am J Kidney Dis*. 1996 Jul;28(1 Suppl 1):S56-62.
11. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. 2020 Oct;180:114147.
12. Departamento de Trabalho e Indústrias do Estado de Washington. Diretriz para prescrição de opioides para tratamento da dor em trabalhadores acidentados. Site do Departamento de Trabalho e Indústrias do Estado de Washington. www.lni.wa.gov/claimsins/Files/OMD/MedTreat/FINALOpioidGuideline010713.pdf. Publicado em 1º de julho de 2013. Acessado em 25 de janeiro de 2023.
13. Andrade SM de, Cunha MA, Holanda EC, Coutinho GSL, Verde RMCL, Oliveira EH de. Caracterização do perfil das intoxicações medicamentosas por automedicação no Brazil, durante o período de 2010 a 2017. *Research, Society and Development*. 2020 May 10;9(7):e236973952.
14. Conselho Federal de Farmácia - Brazil - Notícia: 18/02/2020 - A desigualdade no consumo de medicamentos [Internet]. www.cff.org.br. [cited 2023 Jan 24]. Available from: <https://www.cff.org.br/noticia.php?id=5658&titulo=A+desigualdade+no+consumo+de+medicamentos#:~:text=No%20Brazil%2C%20existe%20uma%20farm%C3%A1cia>
15. OS RISCOS DA AUTOMEDICAÇÃO AUMENTARAM COM A PANDEMIA [Internet]. copass-saude.com.br. Available from: <https://copass-saude.com.br/posts/os-riscos-da-automedicacao-aumentaram-com-a-pandemia>
16. Conselho Nacional de Saúde [Internet]. www.conselho.saude.gov.br. Available from: http://www.conselho.saude.gov.br/ultimas_noticias/2005/medicamentos.htm
17. Sostres C, Gargallo CJ, Arroyo MT, Lanás A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract Res Clin Gastroenterol*. 2010;24(2):121-32.
18. Davies NM, Jamali F. Pharmacological protection of NSAID-induced intestinal permeability in the rat: effect of tempo and metronidazole as potential free radical scavengers. *Human Exp Toxicol*. 1997 Jul;16(7):345-9.

19. Laine L, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther.* 2006 Sep 1;24(5):751-67.
20. De Petris G, Lopez JI. Histopathology of diaphragm disease of the small intestine: a study of 10 cases from a single institution. *Am J Clin Pathol.* 2008 Oct;130(4):518-25.
21. Laine L, Curtis SP, Langman M, Jensen DM, Cryer B, Kaur A, et al. Lower gastrointestinal events in a double-blind trial of the cyclo-oxygenase-2 selective inhibitor etoricoxib and the traditional nonsteroidal anti-inflammatory drug diclofenac. *Gastroenterology.* 2008 Nov;135(5):1517-25.
22. Lake H. Ibuprofen belly: A case of small bowel stricture due to non-steroidal anti-inflammatory drug abuse in the setting of codeine dependence. *Aust N Z J Psychiatry.* 2013; 47: 1210-1211.
23. Nadatani Y, Watanabe T, Tanigawa T, Sogawa M, Yamagami H, Shiba M, et al. Incidence and risk factors of gastrointestinal bleeding in patients on low-dose aspirin therapy after percutaneous coronary intervention in Japan. *Scand J Gastroenterol.* 2013 Mar;48(3):320-5.
24. Curtis JR, Lanus A, John A, Johnson DA, Schulman KL. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. *Arthritis Care Res.* 2012 Dec;64(12):1819- 28.
25. Davies NM. Sustained release and enteric coated NSAIDs: are they really GI safe? *J Pharm Pharm Sci.* 1999 Jan-Apr;2(1):5-14.
26. Davies NM, Jamali F. Influence of dosage form on the gastroenteropathy of flurbiprofen in the rat: evidence of shift in the toxicity site. *Pharm Res.* 1997 Nov;14(11):1597-600.
27. Musu M, Finco G, Antonucci R, Polati E, Sanna D, Evangelista M, et al. Acute nephrotoxicity of NSAID from the foetus to the adult. *Eur Review Med Pharmacol Sci.* 2011 Dec;15(12):1461-72.
28. Breyer MD, Harris RC. Cyclooxygenase 2 and the kidney. *Curr Opin Nephrol Hypertens.* 2001;10(1):89-98.
29. Whelton A, Hamilton CW. Nonsteroidal antiinflammatory drugs: effects on kidney function. *J Clin Pharmacol.* 1991;31(7):588-98.
30. Garcia Rodriguez LA, Tacconelli S, Patrignani P. Role of Dose Potency in the Prediction of Risk of Myocardial Infarction Associated with Nonsteroidal Anti-Inflammatory Drugs in the General Population. *J Am Coll Cardiol.* 2008;52(20):1628-36
31. ASBAI. Associação Brasileira de Alergia e Imunologia. Anafilaxia por medicamentos. 2017. [Internet]. Acesso em: 25 de janeiro de 2023. Disponível em: http://www.sbai.org.br/imageBank/asbai_anafilaxia_medicamentos.pdf