Chapter 19

Adverse reactions of analgesic and anti-inflammatory drugs in chronic pain

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Marcelo Alves Teixeira
Pharmacy Course. Federal University of Piauí

Hilris Rocha e Silva
Pharmacy Course. Federal University of Piauí

Lubna Karine Beserra Santos
Graduate Program in Pharmaceutical Sciences
Federal University of Piauí

Carla Solange de Melo Escórcio Dourado
Graduate Program in Pharmaceutical Sciences
Federal University of Piauí

ABSTRACT
Objective: To know the potential adverse reactions of analgesic and anti-inflammatory drugs in individuals with chronic pain. Methods: An integrative review was conducted using the descriptors "chronic pain", "side effects and adverse drug reactions", "anti-inflammatory drugs" and "analgesics", accompanied by the Boolean operands AND and OR in the PubMed and Virtual Health Library databases. Results: The studies pointed out that women and the elderly are the most affected by chronic pain, moreover analgesics and anti-inflammatory drugs the most used drugs in this condition, and that anti-inflammatory drugs account for numerous adverse reactions, especially those related to the gastrointestinal system and hepatotoxicity. Conclusion: It was evidenced that anti-inflammatory drugs were responsible for the main adverse drug reactions, including hepatotoxicity and gastrointestinal injury, especially in the elderly. As short term measures it is suggested the realization of awareness actions of professionals and patients regarding the proper management of pain, the maximum doses and the dangerous use of these drugs without medical indication and/or pharmaceutical guidance, in order to achieve a rational use of medicines.

Keywords: Chronic pain, Nonsteroidal anti-inflammatory drugs, Medications, Analgesics.

1 INTRODUCTION

Pain is an unpleasant sensory and emotional experience, associated with subjective and individual factors, which may involve cultural, psychological, physical, cognitive and neurological mechanisms. This process can cause several symptoms, such as changes in sleep, appetite and libido, decreased ability to concentrate, manifestations of irritability, loss of motivation to perform family, professional and social activities (SILVA et al., 2011; KRELING et al., 2016).

Pain is considered as a disease by the International Classification of Diseases, receiving ICD-11 (WILLIAMS et al., 2016), representing a major health problem, being in developed countries seen as one of the most disabling conditions, with incidence in the world between 5.4% and 33.2% in periods of 1 to 6 years of follow-up, reaching 33% of the adult population (TREEDE et al., 2015; LEUNG et al., 2016; LARSSON et al., 2017). The prevalence of CD is high even in the Brazilian population, as found by Aguiar (et al., 2021) in his systematic review, identifying a prevalence of 45.59%, being a major cause of leaves, retirements and low productivity.

One of the most prescribed treatments is pharmacological therapy, being fundamental to subsidize the assistance playing an important role in the relief of suffering, allowing a complete and successful pain management. The following are involved in the drug treatment of CD: analgesics, opioids or not, non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants and myorelaxants (MASCARENHAS et al., 2014; AGUIAR et al., 2021). The use of these pharmacological classes is recommended according to the Analgesic Ladder of the World Health Organization (WHO), on the first rung the analgesics should be used, on the second the analgesics associated with weak opioids and on the third rung the analgesics associated with strong opioids. At all levels anti-inflammatory drugs can be used in association with the classes mentioned. In addition to the ladder, the Clinical Protocol for Therapeutic Guidelines on Chronic Pain (PCDT CD) is also available to guide prescribers and patients on the treatment of CD, being among the classes cited analgesics, such as Dipyrone and Paracetamol, and anti-inflammatory drugs, such as ibuprofen and acetylsalicylic acid (GARCIA et al., 2013).

Considering that anti-inflammatory drugs and analgesics are among the main drug classes used in the treatment of CD, and that in addition, in a survey conducted by the Federal Pharmacy Council (2019) data revealed that analgesics/antipyretics accounted for (50%) of drug consumption in Brazil, being the most incident, followed by muscle relaxants (24%), anti-inflammatory drugs and corticosteroids (21%). The literature also highlights this use, where 33.4% of the population uses analgesic medications for pain relief (VASCONCELOS; ARAÚJO, 2018).

Therefore, taking into consideration the profile of analgesic and anti-inflammatory drug consumption by Brazilians, the fact that CD is a highly prevalent disease worldwide, and that the drug classes mentioned are on the list of drugs for treatment, the objective of this integrative review is to know the potential adverse reactions of analgesic and anti-inflammatory drugs in chronic pain, seeking to identify the epidemiological profile of these users and the most commonly used drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs)

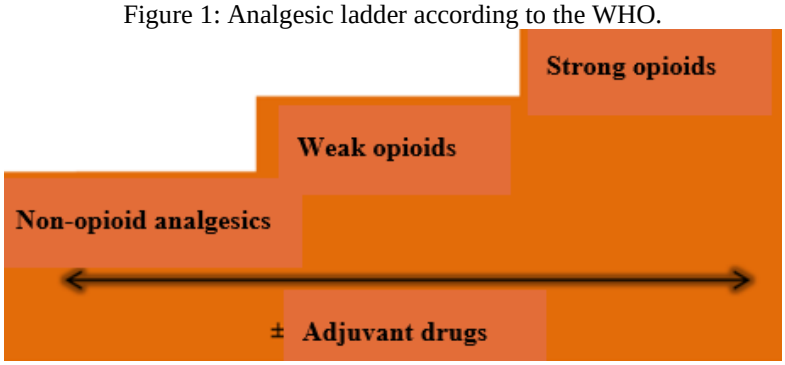
NSAIDs are the most commonly used drugs in clinical practice. Their mechanism of action is the inhibition of cyclooxygenase enzyme type 1 (COX-1) and type 2 (COX-2) with consequent reduction of prostaglandin synthesis and sensitization of nerve endings in peripheral tissues, a common site of pain and inflammation. They have analgesic, antipyretic, anti-inflammatory and antithrombotic properties (WANNMACHER; FERREIRA, 2011).

The COX-1 isoform is constitutively expressed in most tissues, including platelets and stomach, and is involved in signaling between cells and tissue homeostasis. COX-2 is induced mainly in inflammatory cells, when these are activated during inflammation, and tends to facilitate the inflammatory response (COUTINHO et al., 2009). COX are essential enzymes for the conversion of arachidonic acid into prostaglandins, and most NSAIDs inhibit the activity of both COX isoforms, resulting in direct suppression

of the formation of pro-inflammatory mediators such as thromboxane and prostaglandins (SAHOTA et al., 2014; KADIISKAA et al., 2005).

NSAIDs are primarily indicated for mild to moderate pain (Figure 1), and in the elderly are commonly used for inflammatory processes such as osteoarthritis or rheumatoid arthritis. However, for patients in whom paracetamol does not provide adequate analgesia, or when a greater anti-inflammatory effect is required, the use of NSAIDs should be considered. The main drugs that represent this class are ibuprofen, diclofenac sodium, ketoprofen, etodolac, and piroxicam, among others. However, the American Geriatrics Society suggests that NSAIDs be avoided if possible in the elderly (JONES, 2001; O'Neil et al., 2012).

Figure 1: Analgesic ladder according to the WHO.



Source: Adapted from VARRASSI et al., 2010.

The main adverse effects of NSAIDs are interference with platelet aggregation, which may increase the potential for bleeding and consequent hemorrhage; gastrointestinal effects, including dyspepsia and gastric ulcerations; nephrotoxicity, including reversible renal failure, acute nephritis, and a predisposition to cause acute tubular necrosis (WANNMACHER; FERREIRA, 2011).

Opioid analgesics

The term opioid is attributed to any substance, either endogenous or synthetic, that presents, to a varying degree, properties similar to morphine (BALTIERI et al., 2004). However, its rewarding properties can lead to addiction, causing the individual to develop tolerance and dependence (BICCA et al., 2012). Tolerance refers to the reduction in effect after prolonged drug administration that results in a loss of potency of the drug (CAHILL et al., 2016), requiring an increase in dose to achieve the desired effect. On the other hand, dependence arises when the absence of the opioid leads to withdrawal signs and symptoms, so the scientific challenge is to maintain analgesic potency while limiting the development of tolerance and dependence (FIELDS et al., 2015).

Opioids are indicated for the treatment of acute, moderate, or severe pain that does not respond to less potent analgesics. The main representatives of this class are morphine, tramadol, and methadone. They act on specific receptors (mu, kappa, delta, epsilon) located in the central nervous system and peripheral

organs that, when activated, interfere with the transmission of pain impulses. For patients with chronic pain, the decision to use long-term opioid therapy should be carefully planned, taking into consideration the risk-benefit to the patient versus the possible Adverse Drug Reactions (ADRs) that the treatment may cause (CHOU et al., 2009).

However, the risk of ADR is higher when starting opioid therapy or after a dose increase, indicating the need for monitoring. Thus, the main ADRs are nausea, vomiting, constipation, cognitive impairment, delirium, and harm such as falls and fractures. In addition, studies have pointed out that opioids may increase the risk of cardiovascular events, pneumonia, and hospitalization. These potential risks must be weighed against the effectiveness the drug may have in reducing severe or moderate pain. In general, opioids with long half-lives should be avoided in the elderly who have never previously used other opioids (O'Neil et al., 2012).

2 METHOD

This is an integrative literature review study that aims to synthesize all the results obtained in a systematic, orderly and comprehensive way on the proposed theme or subject. Such synthesis enables the grouping of knowledge on a particular subject and highlight the points that need improvement in studies and future publications (ERCOLE et al., 2014).

Data collection and analysis were performed following the steps for the integrative review process, which are: 1) identification of the theme and elaboration of the guiding question; 2) literature search or sampling with the establishment of criteria for inclusion and exclusion of studies; 3) definition of the information to be extracted from the selected studies/study categorization; 4) critical analysis of the studies included in the integrative review; 5) discussion of the results and, 6) presentation of the review/knowledge synthesis. For this phase we used the variation of the acronym PICO, a proposition of the evidence-based practice (EBP), this represents an acronym for Patient, Intervention, Comparison/Control and Outcomes. For variation, the acronym PICO is adopted, being *P* (population), I (Interest) and CO (Context). Thus, we considered for this research the Population (people with chronic pain), Intervention (use of anti-inflammatory drugs and analgesics), and Context (potential adverse reactions), aiming to answer the following question: What are the potential adverse reactions of anti-inflammatory drugs and analgesics in people with chronic pain?

The electronic search was conducted using the PubMed and Virtual Health Library (VHL) databases from September to October 2021. The descriptors used were: "chronic pain," "drug side effects and adverse reactions," "anti-inflammatory agents," and "analgesics," and their respective terms in English, ″chronic pain,″ ″drug side effects and adverse reactions," ″anti-inflammatory agents," and ″analgesics,″ all being Health Sciences Descriptors (DeCS) or Medical Subject Headings (MeSH) and used with the Boolean operator AND and OR.

The inclusion criteria used for the selection of the sample were articles from national and international journals, texts available in full, with a time frame of 2011 to 2021, which addressed adverse reactions to anti-inflammatory drugs and analgesics in chronic pain. The exclusion criteria were repeated articles and publications that did not fit the purpose of the study. A selective and more in-depth reading of the articles was made in their entirety and, based on this reading, the irrelevant research to the theme of the study and those that were repeated were excluded, leaving, in the end, five articles.

To organize the information from the studies, a data collection instrument was used, which included the following items: author, year of study development, type of study, objective, methodology, results, and conclusions. For the analysis of the studies included in the integrative review we used tables and graphs with detailed information from each article, thus allowing their subsequent analysis and discussion.

3 RESULTS AND DISCUSSION

Studies have found that analgesics and NSAIDs are among the most commonly used drugs by the population mainly for pain relief (SANTOS et al., 2018; GAMA; SECOLI, 2020) three of the five studies that make up this review, pointed out that women represent the majority of users of analgesics and anti-inflammatory drugs (RIANON et al., 2015; BARROS et al., 2019; ROLLASON et al., 2020) (Table 1). Such finding corroborates with a study conducted in Brazil, in which 45.7% of the interviewed population (n = 420) were carriers of CD, being the female gender (72.3%) the most affected (GAMA; SECOLI, 2020). They are more often afflicted by headaches, muscle pain and chronic pain diseases, such as migraine, moreover, since very young they live with painful crises, such as those of the menstrual period, using more medications in numerous stages of life, mainly NSAIDs and / or analgesics (DONATI et al., 2016). Rianon et al. (2015) punctuated this well when they showed in their study that they are 1.79 times more likely to get an NSAID prescription for CD compared to men. It is also noteworthy that women are the most likely to seek health services, seeking it 1.9 times more compared to men. Being female is also a predictor of more seeking health care, being measured with a magnitude of 2.43 times compared to males (PEGARO et al., 2019).

It is also pointed out that the greater search for health services by women is attributed by studies to characteristics of the conformation of masculinity itself, such as the position they occupy in the gender hierarchy, being, rather, a strategy for not being equal to women, exercising the dominant role, to whom the power in gender relations belongs, and family provider, associating the search for health care with fragility, identifying these places as belonging to women, children, and the elderly (NASCIMENTO; GOMES, 2008; OLIFFE, 2009; LEVORATO et al., 2014).

Table 1. Characterization of the studies on the use of analgesic and anti-inflammatory drugs by people with CD.

Authors	Title	Year	Type of study	Goal	Main results
Rollason et al.	Evaluation of Phenotypic and Genotypic Variations of Drug Metabolizing Enzymes and Transporters in Chronic Pain Patients Facing Adverse Drug Reactions or Non-Response to Analgesics: A Retrospective Study	2020	Retrospective	Assess whether the extent of ADR or non-response to analgesic treatment is related to a variation in cytochrome P450 (CYP), P-glycoprotein (P-gp) or Catechol O-Methyl-transferases (COMT) activity	145 ADRs were identified with a 40% probability that the reaction is linked to the metabolic state. Modification of cytochromes was observed in the existence of ADRs.
Rianon et al.	Persistent nonmalignant pain management using nonsteroidal anti-inflammatory drugs in older patients and use of inappropriate djuvante medications	2015	Transversal	Describe national prescribing trends with determinants of NSAID prescribing for the treatment of noncancer pain among patients aged 65 years and older in U.S. outpatient settings using National Ambulatory Medical Care Survey (NAMCS) data from 2000 to 2007	89% of consultations recorded prescription of NSAIDs by physicians, with the majority being women (68%), and a mean age of 75.4 years. Reported ADRs included gastrointestinal bleeding, cardiovascular events, and renal toxicity.
Neumann-Podczaska et al.	Analgesic use among nursing home residents, with and without dementia, in Poland	2016	Transversal	Assessing analgesic use among nursing home residents and delineating the associations between pain management and cognitive functions	28.8% of participants received analgesic treatment. It was identified that some participants were taking 2 NSAIDs/times. NSAIDs can both induce and exacerbate hypertension, and result in the "prescribed cascade"
Nagai et al.	Characterization of the Adverse Effects Induced by Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs Based on the Analysis of the Japanese Adverse Drug Event Report	2017	Retrospective	Examine ADRs induced by acetaminophen and NSAIDs as reported to the JADER database.	For acetaminophen, toxic epidermal necrolysis (NET), oculomucocutaneous syndrome, and Stevens-Johnson syndrome were identified as the most severe. For NSAIDs gastric ulcer hemorrhage and gastric ulcer were the most reported. Most ADRs were classified as liver disorders or skin disorders.

	Database (JADER)				
Donati et al.	Risk of acute and serious liver injury associated to nimesulide and239 ther NSAIDs: data from drug-induced liver injury case-control study in Italy	2016	Control case	Estimating the risk of acute and severe liver injury associated with the use of nimesulide and other NSAIDs	Nimesulide and ibuprofen have been associated with a statistically significant increased risk of liver damage. Increased risk of liver injury related to time of exposure to nimesulide and paracetamol. Small risk of acute and severe liver injury in NSAID users. Nimesulide and ibuprofen have been associated with a higher risk of hepatotoxicity than other NSAIDs.

Source: Research data.

As for age, only one article did not outline this parameter (KNAUTH et al., 2012), while Rolasson et al. (2020) delimited the study in the age range of 1 to 99 years, finding a mean age of 55 years, Rianon et al. (2015) and Neumann-Podczaska et al. (2016) included individuals over 60 years of age, finding a mean of 75.4 years and a median of 83 years. Donati et al. (2016), included in their research individuals from the age of 18 years, and mean age of 52.8 years (Table 1). When we observed data from other studies, we noticed that older people were the ones who consumed the most NSAIDs and analgesics. Moreover, the higher consumption in this age group can be associated with the health-disease process, in which chronic noncommunicable diseases (NCDs) are one of the main causes of the aging process, occurring mainly in the elderly and contributing significantly to the onset of pain complaints, which explains the higher consumption of these drugs in this age group (NEUMANN-PODCZASKA et al., 2016).

Similarly, the study by Rianon et al. (2015) 89.6% of the elderly had prescription medications for the treatment of CD. The authors reported that analgesics were the most commonly mentioned category of medication during outpatient visits, and NSAIDs the most commonly prescribed type for adults over 65 years of age. Furthermore, 18% to 40% of adults aged 65 years and older received at least one prescription for an NSAID/year. Accordingly, Salcher et al. (2018) highlighted that 49.2% of the elderly who participated in their study were using some pain medication, with NSAIDs being the most commonly used, accounting for 95.7%. And a study conducted in Brazil evaluating the profile of drugs used by self-medication by the elderly, described that the most consumed drugs were from the musculoskeletal system, corresponding to muscle relaxants of central action and NSAIDs (OLIVEIRA et al., 2010).

Dealing specifically with some medications, paracetamol (acetaminophen), as directly reported by Rollason et al. (2020) and Nagai et al. (2017), as well as naproxen and diclofenac, and ibuprofen, directly mentioned in three studies by Rianon et al. (2015), are quite sought after by people, since, depending on the dose they are over-the-counter (OTC) medications and do not require a prescription (SALCHER et al., 2018). Paracetamol (acetaminophen) acts in the treatment of CD as an analgesic adjunct to anti-inflammatory therapy, through inhibition of COX-1 and COX-2 enzymes in peripheral tissues. Its use

associated with tramadol shows good response in individuals with no improvement with NSAID use alone (NAGAI et al., 2017) .

With regard to opioid analgesics, tramadol, morphine, buprenorphine, fentanyl, methadone, and codeine, which act by binding to opioid receptors distributed in the nervous system and peripheral tissues, and their analgesic effect triggered mainly by binding to mu (μ) receptors, their use requires more attention, and only if the benefits outweigh the risks, always giving preference to other safer options. Codeine should be preferred to tramadol because it has fewer adverse effects, and among the strong opioids morphine is the safest (GARCIA, 2013).

Regarding the form of use of medicines, this was mentioned only in one study, which identified in addition to regular use, the use in the form "if necessary", however, the literature shows that drugs should only be used for a short period of time, even in individuals without contraindications (NAGAI et al., 2017). Being the treatment time varied, depending on the need of each patient, taking into account the absence of effect in the maximum tolerated doses or the presence of uncontrollable side effects as criteria for discontinuation of treatment (GARCIA, 2013). Nevertheless, it was identified that some participants took two NSAIDs at a time, however, there is no reason that justifies the duplication of any substances of the same therapeutic class, because the risk of side effects increases significantly without positive influence on the therapeutic effect (NAGAI et al., 2017). Moreover, there is also no superiority of one drug over another within the same class (ROSENBLUM et al., 2008).

Four of the five studies included in this review reported ADRs, the main ones being complaints of gastrointestinal occurrences and liver function damage (Table 2). It is noteworthy that the goal of treatment with analgesics and NSAIDs in CD is to improve quality of life by decreasing pain and minimizing the potential toxicity of the treatment, however, many individuals experience numerous ADRs throughout treatment, which are mainly observed in the elderly, the group most affected by CD, as demonstrated in the results of this review due to age-related physiological changes, multiple comorbidities, and polypharmacy (BARROS et al., 2019; RIANON et al., 2015; KNAUTH et al., 2012).

Table 2. Adverse reactions to analgesics and anti-inflammatory drugs according to studies included in the review.

Authors	Adverse Reactions
Rianon et al. (2015)	**Opioid analgesics**: delirium, gastrointestinal symptoms, respiratory depression, risk of falling. **NSAIDs:** gastrointestinal bleeding, cardiovascular events, and renal toxicity.
Neumann-Podczaska et al. (2016)	**NSAIDs:** can both induce and exacerbate hypertension
Nagai et al. (2017)	Stevens-Johnson syndrome, altered liver function, interstitial tubule nephritis, erythema multiforme, gastric ulcer hemorrhage and gastric ulcer, drug rash, acute kidney injury, toxic epidermal necrolysis.
Donati et al. (2016)	Acute and severe liver damage

Source: Research data.

Therefore, the increased occurrence of gastrointestinal ADRs is intrinsically related to the mechanism of action of NSAIDs, which by inhibiting COX and consequently prostaglandins, whose physiological action is to stimulate the production of mucus and bicarbonate in gastric epithelial cells, and reduce the production of hydrochloric acid in parietal cells, leave the gastrointestinal mucosa unprotected leading to the appearance of lesions (CHOU et al., 2007). On the other hand, the increased risk of bleeding (BARROS et al., 2019; KNAUTH et al., 2012) is mediated by inhibition of platelet function that occurs due to inhibition in COX-mediated thromboxane A2 production, reducing platelet aggregation capacity (CHOU et al., 2007).

One of the studies in this review reported that of the 51 individuals who regularly took NSAIDs, 22 (33%) were diagnosed with hypertension, 14 (21.2%) with congestive heart failure, two (3%) with esophageal reflux, and one (1.5%) with renal failure, demonstrating the risk of using these drugs, since they can exacerbate symptoms of underlying diseases ((NAGAI et al., 2017). The increased level of systemic blood pressure is inherent to the mechanism of action of these drugs, because by reducing renal prostaglandins that are vasodilators in afferent arterioles, they decrease the glomerular filtration rate, leading to activation of the renin-angiotensin-aldosterone system, causing increased blood pressure and risk of renal failure (NAGAI et al., 2017; VARRASSI, 2010).

With regard to severe cutaneous ADRs and liver disorders these can appear due to idiosyncrasies despite correct dosing and administration (KNAUTH et al., 2012). In the study by Donati et al. (2016) nimesulide and ibuprofen were associated with a statistically significant increased risk of liver damage, and the chance of developing liver damage with paracetamol use was increased threefold. In addition, exposure to higher doses of nimesulide was associated with a six-fold increase in the risk of acute liver injury. For ibuprofen, on the other hand, a significant risk of severe, acute liver damage was observed, with the risk increasing with dose. The study concluded that there is a small risk of acute and severe liver injury in NSAID users, and that nimesulide and ibuprofen were associated with a higher risk of hepatotoxicity than other drugs in this class, with the exponential increase in risk of hepatotoxicity being related to longer duration of treatment and higher doses.

As for opioid analgesics, gastrointestinal problems are characterized mainly by constipation, which occurs in 40 to 90% of cases and can occur after a single dose. It is a dangerous symptom, because it is related to increased morbidity and mortality and worsened quality of life. It results from the activation of mu (μ) receptors in the gastrointestinal tract, acting directly on the enteric nervous system or reducing the parasympathetic autonomic flow. Although respiratory depression is a dangerous reaction, its occurrence is small, and there are few reports in the literature related to the chronic use of opioids, with tolerance developing in a few days. On the other hand, there is an increased risk in patients with sleep apnea, morbid obesity and chronic obstructive pulmonary disease (COPD), and they should be avoided in these patients or used when the benefits outweigh the risks (BURKE et al., 2012).

Rolasson et al. (2020) investigating 243 distinct evaluations involving the study of ADR or drug non-response, identified 145 ADRs to analgesics and NSAIDs in a usual therapeutic dosage, thus concluding that ADRs are likely to be linked to the metabolic status of the individual (genotype and phenotype) in 40% of the cases. Additionally, they also observed a modification of cytochromes in the existence of ADRs, such as CYP2C9 for diclofenac, identifying numerous adverse reactions due to this genotype. The probability of an association between an ADR and metabolic status was rated overall as intermediate to high in 38.8% of cases taking tramadol, 37.5% for morphine, 68.5% for codeine, and 28.6% for oxycodone. In this perspective, the authors highlighted some determining factors for such an association, such as: environmental, diet, smoking, alcohol consumption, as well as preexisting diseases. Codeine and tramadol also showed a marked decrease in analgesia and ADRs in people with a modified CYP phenotype. The authors further concluded that genotyping and/or phenotyping may determine the onset of ADRs in individuals and that therefore, evaluating both parameters is important for prescribing NSAIDs and analgesics in the management of CD (RIANON et al., 2015).

4 CONCLUSION

In conclusion, it was verified that most studies investigated the adverse reactions of analgesic and anti-inflammatory drugs in chronic pain, highlighting that the main ADRs caused hepatotoxicity or gastrointestinal injury, with NSAIDs being the ones that most caused these reactions, especially in the elderly . In theory, the researches did not analyze more deeply which are the causes related to the occurrence of ADRs other than those related to the mechanism of action of the drugs.

That said, it is necessary to take into account the physiology and peculiarities of each individual regarding the use of painkillers and anti-inflammatory drugs in the management of CD, in relation to the maximum doses and the risk of their use without medical indication and/or pharmaceutical guidance.

The limitation of this study is that it investigated only the adverse reactions of analgesics and anti-inflammatory drugs in chronic pain, and it is necessary to expand this review beyond this pharmacotherapeutic indication.

The study hopes to contribute to the development of new research on the importance of the use of painkillers and anti-inflammatory drugs and on the promotion of the rational use of medicines, in order to promote improvements in the development of strategies for this issue.

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