Chapter 16

Clinical Pharmacy Applied To Pediatrics: A Humanization Strategy On The Perception Of The Rational Use *Of Off*-Label Drugs

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Ana Márcia Silva Aguiar
Undergraduate student of the Pharmacy Course at Centro Universitário São Camilo-ES
E-mail: marciasilvamf70@gmail.com

Ana Julia Oggione Guerrera
Undergraduate student of the Pharmacy Course at Centro Universitário São Camilo-ES
E-mail: ajoggioniguerra@gmail.com

Bethania Ribeiro Almeida Santiliano
Professor-supervisor: Master. Professor at the São Camilo University Center-ES
E-mail: bethaniarlmeida@yahoo.com.br

ABSTRACT
Patient safety is one of the main research targets in various segments of the health field, so the clinical pharmacy has been contributing to patient-centered care to maximize therapy and minimize the risks of drug use. This study is a literature review that aimed to highlight the clinical pharmacy applied to pediatrics, as a humanization strategy on the policy of rational use of off-label drugs. As a methodological proposal, a clinical protocol was developed, from the perspective of clinical pharmacy in the use of off-label therapy in pediatrics, for use in hospital units, aimed at standardizing services, based on evidence. Finally, this research sought to highlight the role of the pharmacist in favor of the rational use of medicines, which from the clinical pharmacy is possible to mitigate possible problems related to medicines (PRMs), as well as to propose clinical pharmaceutical interventions, registered in the multi-professional medical records, in line with the optimization and conciliation of therapy aiming at the rational use of off-label drugs. Resulting in encouraging regional hospital establishments to develop clinical pharmacies, with the clinical pharmacist as a preceptor in the care process, encouraging the creation of clinical protocols, also promoting the pharmacovigilance service with the patient safety center in the hospital environment.

Keywords: Clinical Pharmacy, Off label drugs, Clinical protocols, Pediatrics, Rational Use of Medications.

1 INTRODUCTION

Currently, patient safety is one of the main research targets, in several segments within the health field, it has gained prominence among the factors that affect patient safety in recent years, the discussion about the occurrence of drug-related problems (DRPs) arising from mainly due to iatrogenesis and errors during the medication administration process (BOTELHO et al., 2021; CRUZ; BATISTA; MEURER, 2021).

In this context, a review of the prescriptions made, especially in the hospital environment, by clinical pharmacists, allows for identifying circumstances that generate negative drug results (NMR's), enabling preventive action against medication errors in drug therapy and contributing to patient safety (BOTELHO et al., 2021).

Considering that health systems are increasingly looking for cooperative and multidisciplinary work among health professionals, and that, in this sense, the clinical pharmacist is indispensable in monitoring the pharmacotherapy of patients, this service strives for the optimization of therapy, with a focus on medication reconciliation, making treatment safer, mainly by preventing DRPs resulting from prescription errors, drug interactions, discontinuation of treatment or even incorrect administration of drugs, which can lead to severe intoxication, with a risk of mortality (MALFARÁ, 2017).

According to Biasibetti (2020), there is a worldwide mobilization in favor of safety guidelines for pediatric care, therefore, encouraging studies that promote pediatric patient safety, based on multidisciplinary teamwork, is of paramount importance in guaranteeing completeness, complementarity, and continuity of care (BIASIBETTI et al., 2020).

At the national level, health care encompasses frequent discussions regarding the occurrence of drug-related problems (DRP's), which according to clinical pharmacy, are related to adverse drug reactions, affecting more and more hospitalized patients, which may result in their death. , therefore, it is estimated that about 70% of these events could be preventable and the pharmacist's interventions can provide direct benefits in terms of patient safety (BRASIL, 2019; BOTELHO et al., 2020).

It is worth noting that hospitalized pediatric patients are at greater risk of the use of medication, due to their inability to communicate complaints, lack of adequate pharmaceutical formulations, susceptibility, and incidents due to their anatomy and physiological characteristics, factors that can lead to the occurrence of AEs (Adverse Events) in the pediatric population, whose clinical pharmacy service helps to reduce the occurrence of these problems (BIASIBETTI et al., 2020).

Clinical pharmacy is understood as patient-centered care that aims to maximize treatment efficacy and minimize the risks of drug use (GOMES, 2011). The clinical pharmacy service is in the process of advancing in Brazil, and every day, the need for the inclusion of the clinical pharmacist in the health teams becomes more evident, given the worrying incidence of DRPs triggered even by off-label therapy (CRUZ; BATISTA; MEURER, 2021).

Most drugs administered to children are off-label, that is, they are drugs prescribed with the use of the product in a situation different from that oriented by the regulatory agency in the country, with dosages that differ according to age, dose, indication or route of administration (DIEL, 2020).

Thus, considering that drug-related problems are common in the pediatric population in hospitalized patients, especially due to iatrogenic causes, this study aimed to highlight clinical pharmacy applied to pediatrics, as a humanization strategy on the policy of the rational use of off-duty drugs. label, contributing to the optimization of therapy and medication reconciliation, highlighting the importance of inserting the pharmaceutical professional into the multidisciplinary hospital team, through the provision of clinical pharmacy services, proving to be fundamental in preventing adverse events and guaranteeing the safety of pediatric patients in care during their hospitalization.

2 METHODOLOGY

The study consists of a bibliographic review, carried out from March to November 2021, consisting of two stages. In the first stage, a search was carried out in the bibliographic database, which is the most important part of the evaluation, since it is from there that these studies were identified based on the information collected and methods selected in the electronic databases: LILACS, SCIELO, MEDLINE and PUBMED, BVS, using the following descriptors: “Pharmaceutical care”; "pharmaceutical attention"; “therapeutic interventions”; "medicines"; “off-label use”, “pharmacovigilance”.

The second stage consisted of the critical analysis of the articles based on the information collected, in which the information of each study is rigorously organized using the following inclusion and exclusion criteria, aiming at the elaboration of a protocol aimed at drug therapy in pediatrics, within the scope of the hospital, focusing on the rational use of off-label drugs.

As inclusion criteria, original articles were used, whose themes were in line with the approach to off-label therapy in pediatrics associated with clinical pharmacy in pediatrics, written in Spanish, English, and Portuguese.

As for the exclusion criteria, conditions of insufficient data, the impossibility of access to the complete work, works published more than 5 (five) years ago, except for literary works and current legislation, as well as articles that do not contain subjects related to the researched descriptors were removed.

Thus, the elaboration process of the care protocol was concluded from the extraction and analysis of the data obtained, which from a thorough reading, of the 208 articles evaluated and selected 24 articles, as well as, were still discussed according to current legislation and media relevant governmental/institutional institutions, striving for the rational policy of Brazilian pharmaceutical assistance.

3 RESULTS AND DISCUSSION

In the post-world war period, with the expansion of the pharmaceutical industry, the pharmaceutical professional began to alienate themselves from the health team, later in the 1960s in the United States, with the advent of clinical pharmacy, pharmacists returned to participate in the team of health and contribute with their knowledge for the optimization of drug treatment (ALBUQUERQUE et al., 2021).

In Brazil, the first implementation of clinical pharmacy services took place only in 1979, until the beginning of the 21st century, the activities of pharmacists in hospitals were limited to the administrative areas of medication control and financial management of resources, with clinical pharmacy services this reality began to change later with the Unified Health System (SUS) and other health systems began to have a more personalized and patient-oriented view (BRASIL, 2019).

According to Bonfin (2018) based on the clinical pharmacy committee of the Association of Hospital Pharmacists of the USA, the duties of the Clinical pharmacist include:

> Clinical pharmacists can carry out activities such as pharmaceutical anamnesis, consultation, pharmaceutical monitoring, medication reconciliation, prescription/prescription analysis, dose adjustment, dosage adjustment, evaluation of drug interactions, drug incompatibility, analysis of the main laboratory tests and evolution in 7 medical records, elaboration of clinical protocols, patient orientation and the patient care team (BONFIM, 2018).

Still, on the assignments, the pharmacist uses clinical methods of patient care, within the Pharmaceutical Care area there is the pharmacotherapeutic follow-up understood as part of the clinical pharmacy, involving interviews with the patient being necessary to use tools that contribute to a continuous systematic process and documented (ALBUQUERQUE et al., 2021).

In Brazil, for document records, among the methods used are SOAP (AMORIN et.al., 2019); PWDT (SANTOS et.al., 2020); TOM (CSHUNDERLICK; ZAMBERLAM, 2021); Dáder (OLIVEIRA, 2020).

The Dáder method includes the study of medication use and its relation to the patient's health problems, interviews are used to obtain recorded information and allow a detailed analysis of the situation to prepare a pharmacotherapeutic action plan (OLIVEIRA, 2020). The PWDT (Pharmacist's Work of Drug Therapy) method was developed to record clinical activities, and questions related to drugs can be classified according to indications, efficacy, safety, and performance of PWDT activities (SANTOS et.al., 2020).

However, the TOM (Therapeutic Outcome Monitoring) method, used to support pharmacists' activities in practice, is derived from the PWDT and includes the following steps: information gathering, identification of objectives, assessment, development of the treatment plan, the evolution of the evaluation, review of problem-solving and update of the action plan (CSHUNDERLICK; ZAMBERLAM, 2021).

The most used SOAP, SOAP (Subjective, Objective, Evaluation, and Plan) refers to a method, each letter composes data on the evolution of patient care, it contains a record of information about medications and their relationship with the disease, based on the Subjective and Objective information in the Evaluation phase, the pharmacist can identify DRP's and thus provides subsidy in the elaboration of a therapeutic plan (AMORIM et al., 2019).

In this sense, the method of monitoring drug therapy first begins with the collection of general information from the patient, such as the reason for the care, medications used and medical history, and current habits. After this stage, if the drug is suitable for use, evaluates its effectiveness and determines its safety, and even with the existence of a pharmaceutical care form, a specific and adequate form is required to record the activities (OLIVEIRA, 2020).

According to Botelho (2021), a clinical pharmacist is responsible for the user's needs related to the drug, through the detection, prevention, and resolution of DRP, it is a process of reviewing pharmacotherapy, which aims to identify DRP, to provide the patient with humanized care and benefit from the desired therapeutic effects (BOTELHO et al., 2021).

In this context, for the performance of clinical pharmacy, it is essential to know the main laboratory tests: biochemical and microbiological, tend to the results and possibilities of interference, both from drugs and from the patient's clinical condition (BONFIN, 2018).

The evolution of the medical record carried out by the clinical pharmacist is also a necessary activity, according to Resolution No. 555, of 2011, of the Federal Council of Pharmacy (CFF), which regulates the registration, custody, and management of information resulting from the practice of pharmaceutical assistance in health services, being the responsibility of the pharmacist, this attribution is highlighted in Resolution No. 585, of 2013, of the CFF (BRASIL, 2011; BRASIL, 2013).

It is worth mentioning that the clinical pharmacist has an indispensable role in the elaboration of clinical protocols whenever a prescription is identified with incompatibilities between drugs or procedures, which may cause DRP's, pharmaceutical interventions must be elaborated through protocols, preserving the patient's safety, continuing with its proper guidance (BRASIL, 2015).

Regarding this thought, considering the positive results regarding the participation of the clinical pharmacist in health promotion, as well as in the prevention of adverse events, intervening and contributing to the safe prescription of drugs for off-label therapy (OLIVEIRA et al., 2020), this study will then discuss the importance of clinical pharmacy in off-label therapy and its rational use.

3.1 MEDICINES *OFF LABEL*

Off-label use is defined as use outside the indication authorized by a national regulatory agency, in the case of Brazil it is a national regulatory agency ANVISA, off-label does not have a sufficient scientific basis, and its purpose is different from the instructions on the package leaflet, age, route of administration, dosage and frequency of use, are different (DIEL, 2020).

It is known that the prescription of drugs in pediatrics follows the same criteria used for adults, although there are more particularities and often insufficient evidence to guarantee risks and benefits, among these criteria the choice of appropriate pharmacotherapy, is an important factor in the rational use of drugs (OLIVEIRA, 2020).

This type of use is more common in some clinical situations, such as oncology, and in specific populations, such as children, the elderly, and pregnant women, given the blockage or even the improbability of conducting clinical trials with these groups. and Drug Administration (FDA), which encourages the inclusion of children in clinical research, have been expanding studies on the safety and efficiency of drugs for children, as well as political strategies for reducing risks and pharmacovigilance proposals to be implemented during the cycle of drug life (VIEIRA, 2017).

However, despite the evidence that aims to improve the standardization of medications in Pediatrics, there is still little information about the amplification of the use of off-label medications in children, which makes it difficult to monitor adverse drug reactions (ADRs), appearing in their notifications, according to pharmacovigilance protocols, associated with the implementation of clinical pharmacy service, are fundamental (ZANELLA LAZARETTO, 2020).

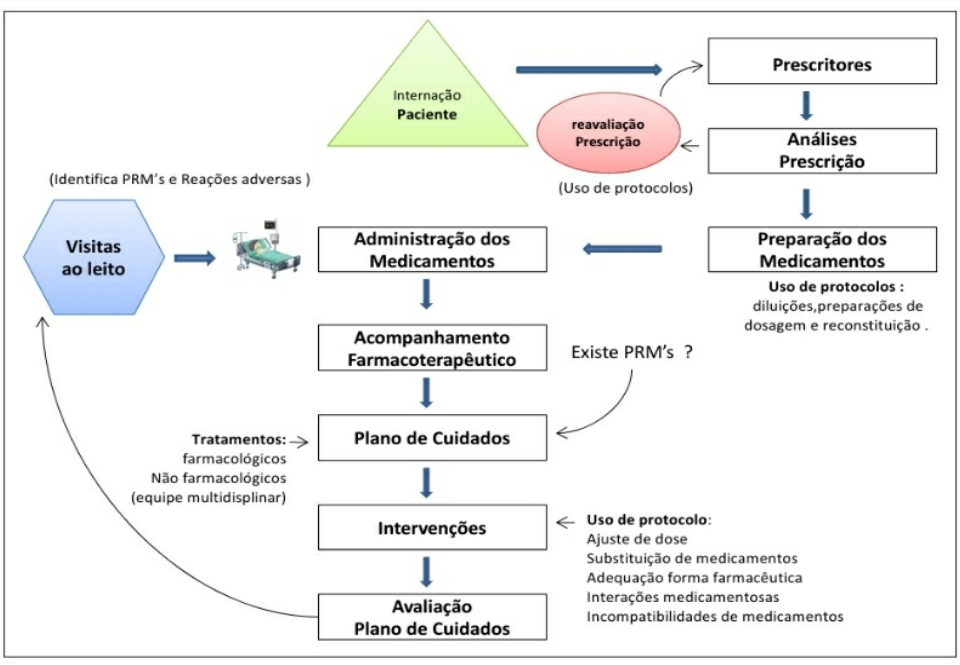
3.2 ROLE OF THE CLINICAL PHARMACIST IN THE PREPARATION OF OFF-LABEL THERAPY IN THE HOSPITAL SETTING

Drug therapy is one of the most common interventions in health care (MEDEIROS; OLIVEIRA, 2020). According to national norms (RDC 214/2006) the preparation and dispensing of medicines for hospital use are the exclusive responsibility of the pharmacist (BRASIL, 2006). But, although it is the responsibility of the pharmaceutical professional, data show that only 7.2% of hospital pharmacies fractionate the medications for dispensing, whose manipulation/dilution often occurs in nursing stations, exempt from the supervision of the pharmaceutical professional (CHAVES et al., 2018).

From this perspective, the work: "Pharmaceutical Care in Health Care" made available by Profar®, prepared by the Federal Council of Pharmacy, allows the clinical pharmacist to guide the construction of a pharmaceutical care manual, including pediatrics, promoting technical support and didactic material, with instructions for preparing and administering medications and pharmacotherapeutic follow-up (CFF, 2016).

There are countless challenges encountered in drug therapies for pediatric patients, among them the limitation of data on the safety and efficacy of drugs; the lack of adequate commercial pharmaceutical form; dose calculation based on weight or body mass index; performing complex calculations in the preparation of dilutions; whose early detection of DRPs and issuing of pharmaceutical interventions prove to be crucial in this process of effectiveness and quality of life for the individual, especially in children (pediatrics) (ZANELLA LAZARETTO, 2020). In this context, it proposes a flowchart containing the processes of clinical pharmacy in the Hospital environment (figure 1).

Figure 1 - Flowchart of clinical pharmacy processes in a hospital setting



Source: The authors (2021)

Subtitle: bedside visits

medication administration

pharmacotherapeutic follow-up

care plan

interventions

Assessment

care plan

Treatments:

Pharmacological

Non-pharmacological (multidisciplinary team)

patient hospitalization

Reassessment / Prescription

use of protocol

dose adjustment

Substitution of medications

Pharmaceutical form adequacy

Drug interactions

Incompatibility of medications

presticotes

Prescription analyzes

medication preparation

Use of protocols: dilutions, dosage preparations, and reconstitution

Pharmaceutical care in off-label therapy, starting from this stage of analysis of the prescription still in the dispensing, must be carried out by the clinical pharmacist, the procedures must follow the following parameters: correct dosage; right way; reconstitution/dilution; infusion time; prescription/interaction/dosage of antimicrobials; possible replacement of medications (OLIVEIRA, 2020).

In the preparation of medicines, hospitals seek to develop standardized methods. In this administration process, the nine right items of verification for the safe administration of off-label medicines must be followed: right patient; right medicine; right dose; right way; right time; right record; right approach; right guidance; right pharmaceutical form; right monitoring (ZANELLA LAZARETTO, 2020).

During bedside visits, the pharmacist should keep the patient's medical record updated with related information, events, signs, and symptoms and seek to identify whether the patient or family member has any complaints related to drug treatment, noting possible drug-related problems and the need for pharmacotherapeutic follow-up, It is also extremely important to continuously evaluate the pharmacotherapeutic plan (MEDEIROS; OLIVEIRA, 2020).

In interventions that include discontinuing the use of certain drugs, pharmacists should contact prescribing professionals to communicate identified needs and request intervention assistance as a behavior to plan, record and execute with users and health professionals to resolve or prevent interference or problems. that may interfere with medication as part of the medication monitoring process (ALBUQUERQUE et al., 2021).

The pharmacist has an important role as a member of the multidisciplinary team, contributing to therapeutic resolutions in patient care, applying their knowledge and ensuring the rational use of medicines, evaluating drug therapy for the appropriate use and cost-effectiveness of medicines from the pharmacy clinic with bedside visits and pharmacotherapeutic follow-up (MIYAGI; LAM; GIRDWOOD, 2020). In this opportunity, they are parameters for identifying adverse reactions, and it is important to recommend the use of pharmacovigilance services, as underreporting proves to be important in clinical pharmacy (OLIVEIRA, 2020).

3.3 PHARMACOVIGILANCE AND CLINICAL PHARMACY

For the National Health Surveillance Agency (ANVISA), pharmacovigilance is a science with activities related to the identification, evaluation, understanding, and prevention of adverse reactions or any problems related to drug use (Brasil, 2019). However, since Decree nº 3.961 in 2001, pharmacovigilance is a tool to spontaneously notify any suspected adverse reactions or other problems caused by drugs, such as quality deviations, loss of efficacy, misuse, administration errors, abuse, and poisoning (BRASIL, 2001).

Given the above, the management, technical, administrative, and clinical activities of a hospital pharmacy must be organized according to the complexity of the hospital's operation, whose purpose is to guarantee the safe and reasonable use of prescribed drugs through preventive actions. and educational, in addition to being responsible for all the needs for medicines and therapeutic supplies, and other products for the health of hospitalized patients (ZANELLA ZANELATO, 2020).

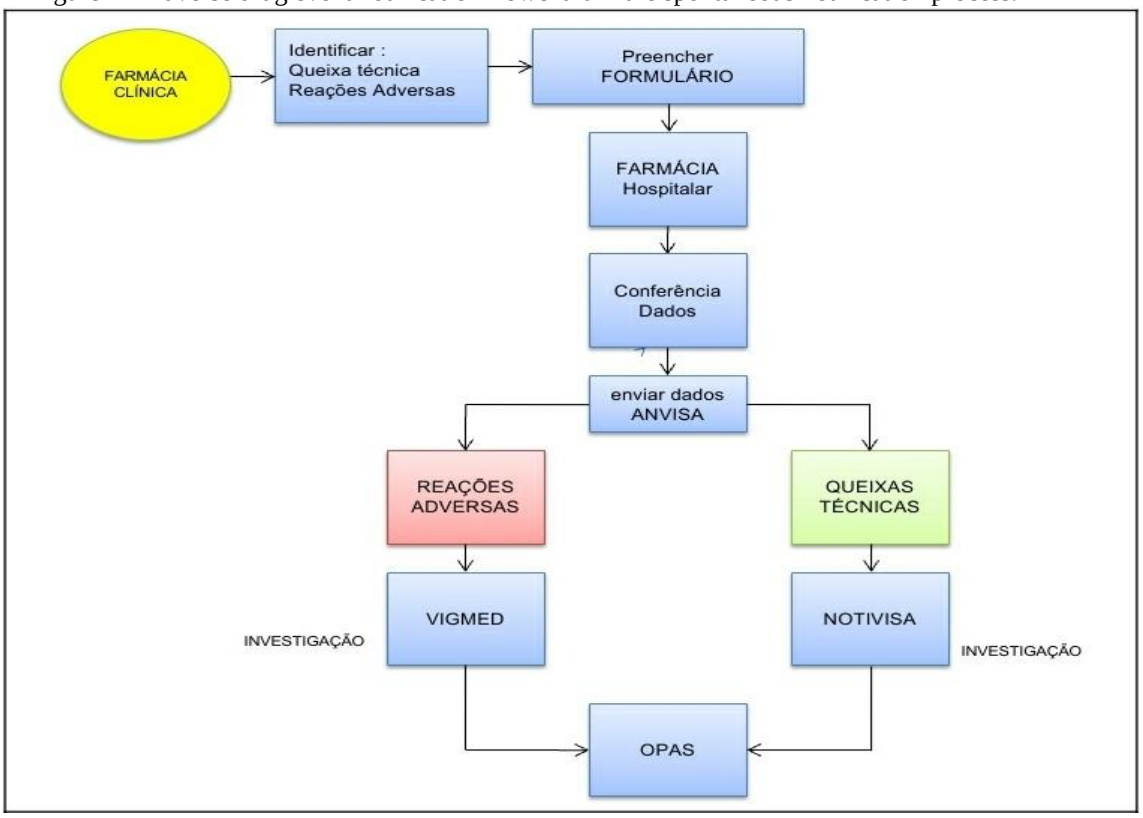
In this opportunity, from the use of the pharmacovigilance program, the pharmacy professional promotes the safety of the medicines in the treatment of the pediatric patient, this is an important aspect due to the scarcity of research for this public, it is up to the pharmacist to detect adverse reactions of the patient and notify them (MEDEIROS; OLIVEIRA, 2020).

ANVISA uses two information systems for the notification and monitoring of inconsistencies and injuries inherent to the use of medicines, with VigMed indicated for records related to adverse events and NOTIVISA for the recording of notifications of technical complaints provided for by the Ordinance of the

Ministry of Health of No. 1660, homologated on July 22, 2009, called NOTIVISA (National System of Notifications for Health Surveillance).

It is a computerized system that allows registering and notifying technical complaints about medicines and health products and adverse events (BRASIL, 2009; DUTRA, 2020). The present protocol proposes a flowchart aimed at intensifying the reporting of adverse events in the process of spontaneous reporting (Figure 2).

Figure 2 - Adverse drug event notification flowchart in the spontaneous notification process.



Source: The authors (2021)

Subtitle: CLINICAL PHARMACY - Identity: Technical complaint / Adverse reactions

Fill in the FORM - Hospital PHARMACY / Data checking / Send ANVISA data

ADVERSE REACTIONS

VIGMED / TECHNICAL COMPLAINTS

NOTIVISA

OPAS

Investigation

It should be noted that the records can be completed by health professionals, in a specific form, printed, and forwarded to the local health surveillance service, for analysis and investigation by the technicians and subsequent active and subsequent forwarding to ANVISA is one of the most common

methods and interventions fast and effective measures related to pharmacovigilance (MOTA; VIGO; KUCHENBECKER, 2019).

Through pharmacovigilance, by monitoring reports of adverse events or any drug-related problems, the performance of drugs available on the market can be monitored and measures must be taken to minimize possible damage (DUTRA, 2020).

3.4 CLINICAL PROTOCOLS IN OFF-LABEL THERAPY

The national commission for the incorporation of technologies in the SUS (CONITEC) is responsible for integrating SUS technologies such as technical procedures, health services, equipment, and medicines, being responsible for evaluating scientific evidence, generating an investigation process considering scientific research and clinical consequences, cost and effectiveness after this process generate a report favorable or against the incorporation of technology in the SUS (BRASIL, 2019).

It should be noted that the development of protocols and clinical guidelines have received investments from the SUS in recent years, however, few are still applied in health units, especially in hospitals, consisting of the standardization of services with quality and scientific evidence (BRASIL, 2017).

Therefore, considering the pharmaceutical professional's relationship between the medicine and the patient, reports the importance of his performance in the hospital environment, due to the clinical characteristics of the patient, the complexity of the medicines used, and the great daily variation of the prescriptions, it requires a very pharmacotherapeutic evaluation In detail, pharmacists can monitor and establish protocols for the administration of target drugs, this therapeutic process, using protocols, is a quality indicator and one of the essential steps in the care process (CERQUEIRA, 2018).

Given this context, the Federal Council of Pharmacy (CFF) created the Support Program for Pharmaceutical Care in Health Care (Profar), which has been providing a collection of clinical practice guides. These guides provide the basis for the pharmacist to select the best approach to pharmaceutical care in healthcare and clinical practice (CFF, 2019).

Thus, considering the frequent use in off-label therapy and its preparations, Zanella Lazaretto's research (2020) presents solid medicines used in a Brazilian pediatric hospital, and their preparations, based on this study, proposes the construction of a table, which it lists the drugs used in the hospital environment, the formulations that suffer the most modifications in preparation (Table 1).

Table 1. List of oral medications most used in the pediatric hospital with the most frequent changes in their preparation.

Medicamento	Grupo terapêutico	Posologia recomendada	Efeitos adversos
Metadona comprimido 10 mg	Opióides com potência analgésica	Dose inicial de 100 mcg por kg,a cada 12 cada 6 horas. A dose máxima 10 mg por dose. Nota-se que não há informação sobre a idade.	18% das crianças relataram sintomas como tontura fadiga e rubor.
Diazepam comprimido 5 mg	Benzodiazepínico	**1 a 11 meses:** 250 mcg por kg **1 a 4 anos:** 2,5 mg por kg **5 a 11 anos**: 5 mg por kg **12 a 17 anos:** 10 mg por kg A cada 12h, dose máxima 40 mg por dia	Disartria, dor de cabeça, Ataxia, tremores, tontura, sonolência.
Tacrolimo cápsula gelatinosa dura 1 mg	Imunossupressor	Iniciam de 50 a 150 mcg por kg duas vezes ao dia. Neonatos e crianças doses iniciais de 0,15 a 0,3 mcg 1 vez dia	Formigamento, coceira, herpes ulceras e dermatite rosácea.
Sulfametoxazol 400 mg + Trimetoprima 80 mg comprimido	Antimicrobiano	750 mg por m^2 de superfície corporal de sulfametoxazol e 150 mg por m^2 de superfície corporal de trimetoprima. (dados Micromedex).	Náuseas, vomito, diarréia Transaminases elevadas.
Besilato de Anlodipino comprimido 5 mg	Bloqueador dos canais de cálcio, ação prolongada,	**Um mês a 11 anos**; 100 mcg a 200 mcg por kg 1 vez ao dia dose máxima 400mcg. **12 a 17 anos**; 5 mcg 1 vez ao dia dose máxima, até 10 mcg ao dia	Tontura, fadiga, sonolência, edema, rubor, náusea, dor abdominal, dor de cabeça e palpitações.

Source: Adapted, ZANELLA LAZARETTO (2020).

When evaluating the data, it was found that tracollim does not require manipulation due to the low concentration in the solid form, sulfamethoxazole plus trimethoprim has a liquid form, and they are also available in oral suspension on the market (ZANELLA LAZARETTO, 2020). Understanding that solutions, oral suspensions, liquid forms, or dilutions of injectable drugs facilitate preparation, while the solid form lacks crushed or powdered tablet derivatives (BRASIL, 2017). In most Brazilian hospitals, pharmacy services do not have the essential tools to carry out unit dose manipulation for all drugs used (BIASIBETTI et al., 2021).

The drugs that undergo the most modification in preparation include amlodipine, diazepam, and methadone, it should be noted that the instruction leaflet for amlodipine states that diazepam cannot be broken down or can be divided into equal parts by chewing and the leaflet for methadone does not provide any modification of information (ROCHE, 2020). In this case, information about safe handling on the drug formulary is inconsistent. Thus, the clinical pharmacy contributes to the safe use of off-label therapy and should be standardized in care processes/protocols consistent with the necessary and safe therapy (SÁ; FERREIRA, 2020).

4 FINAL CONSIDERATIONS

Clinical pharmacy has been growing, with a positive impact on the number of interventions by the clinical pharmacist during the period considered, which can promote the rational use of medicines, increase patient safety and contribute to the reduction of costs associated with medical prescription.

Thus, this study sought to encourage regional hospital establishments, which have not yet developed clinical pharmacies, to implement it, with the pharmacist as a preceptor in the care process, taking responsibility for the patient/client's needs related to the medication, through the detection, prevention, and resolution of problems related to medication errors may be related to problems with communication, prescription, dispensing, and administration of medications, problems including labels, packaging, names, among others, to prevent DRPs, be the role of the clinical pharmacist to implement safe practices in medication administration.

However, it encourages the creation of multidisciplinary clinical protocols, so that there is standardization in procedures related to pathologies and medications according to each eventuality, with emphasis on off-label therapy, avoiding situations that compromise the health of the pediatric population and thus bring positive results to the hospital, guaranteeing the final quality in the work process, thus ensuring better care with reduced risks and increased chances of therapeutic success.

In this sense, the clinical pharmacist is committed to preventing and reducing medication errors, adverse drug reactions, drug interactions, and incompatibilities, in addition to promoting the correct and rational use of drugs, which contributes to improving patient safety and quality of care. assistance, in addition to reducing treatment costs, thus improving hospital efficiency.

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