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Improving the use of multidose drug dispensing systems: a focus on user experiences, safety, quality, and cost factors

Jorge Miguel Gonçalves Matos Pereira

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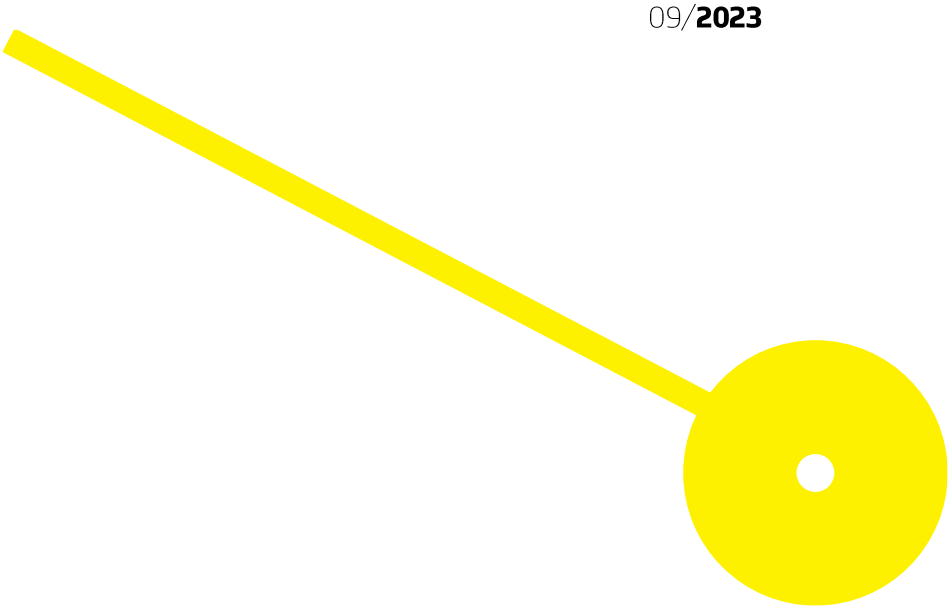

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Improving the use of multidose drug dispensing systems: a focus on user experiences, safety, quality, and cost factors

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Resumo

Introdução: O envelhecimento da população tem vindo a tornar-se mais notório, sobretudo nos países mais desenvolvidos, sendo considerado uma das transformações sociais mais significativas do século XXI. O comportamento de tomar medicamentos é algo extremamente complexo e individual, exigindo inúmeras estratégias multifatoriais para melhorar a adesão à terapêutica. A não adesão à terapêutica ocorre quando os doentes não tomam os seus medicamentos de acordo com as indicações médicas, o que pode levar a uma má qualidade de vida e a um aumento das hospitalizações. Nos últimos anos, tem-se dado bastante atenção à evolução do papel dos farmacêuticos e dos técnicos de farmácia na prestação de cuidados de saúde. Os técnicos de farmácia podem promover o uso responsável do medicamento, assim como desempenhar um papel vital na promoção e implementação de programas de adesão baseados na comunidade. A Preparação Individualizada da Medicação surge como uma opção a ser considerada pelos doentes, suas famílias e profissionais de saúde que os acompanham. Este serviço tem como principais objetivos fornecer ao doente o medicamento certo, na dose certa e no momento certo. **Objetivo:** Identificar informações atuais relativas à implementação e utilização dos sistemas MDD, possíveis soluções que possam levar à sua melhoria, particularmente na população idosa. **Métodos:** Foi realizada uma *scoping review* da literatura com artigos recolhidos nas principais bases de dados, Pubmed e EBSCO. Estudos nos quais foi permitido avaliar resultados no que toca à experiência do utilizador, segurança destes sistemas de dispensa de medicação, intervenções de qualidade, inovações tecnológicas ou relativas ao pagamento pelos sistemas MDD foram incluídos. **Resultados**: Foi encontrado um total de 1857 referências relevantes. Destas, 1706 referências foram incluídas na fase de triagem de resumos e 71 foram escolhidas para revisão de artigos com texto completo. Quinze artigos foram selecionados para extração de dados e avaliação da qualidade. **Conclusões:** Os sistemas de MDD podem ser considerados como uma solução viável, mas em última instância esta decisão depende da situação individual de cada doente.

Palavras-chave: Multidose drug Dispensing systems; Dose administration aids; Polypharmacy; Medication adherence; Polypharmacy in older people;

Abstract

Introduction: Population ageing has become more noticeable, especially in more developed countries, and is considered one of the most significant social transformations of the 21st century. Medication-taking behavior is extremely complex and individual, requiring numerous multifactorial strategies to improve adherence. In recent years, considerable attention has focused on the evolving role of pharmacists and pharmacy technicians in the delivery of health care services. Pharmacy technicians can play a vital role in promotion, administration, and implementation of community-based adherence programs. Individualized Medication Preparation emerges as an option to be considered by patients, their families and the health professionals accompanying them. This service has as main objectives to provide the patient with the right medicine, in the right dose and at the right time. **Objective:** Identify current evidence regarding the implementation and use of MDD systems, possible solutions that could lead to its improvement, particularly in the elderly population. **Methods:** A scoping review of literature was conducted with collected articles in the main databases, Pubmed and EBSCO. Studies applying outcome measures that were associated with the appropriateness of user's experience, the safety of these dispensing systems, quality interventions, technological innovations or regarding the payment for MDD systems were included. **Results:** A total of 1857 relevant references were found. Of these, 1706 references were included in the abstract screening phase and 71 were chosen for full-text article review. Fifteen articles were shortlisted for data extraction and quality assessment. **Conclusion:** MDD systems can be considered as a viable solution but ultimately depends on the individual patient's situation.

Keywords: Multidose drug Dispensing systems; Dose administration aids; Polypharmacy; Medication adherence; Polypharmacy in older people;

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List of Abreviations

API– Active pharmaceutical ingredient;

CDSS– Clinical decision support system;

DAA– Dose Administration Aids;

DRP– Drug Related Problems;

EES– Electronic Expert Support;

eMMS– electronic medication management systems;

GP– General Practitioner;

IDU– Potentially inappropriate drug use;

MCCAs– Multi-compartment Compliance Aids;

MDD– Multidose Drug Dispensing;

NH– Nursing Home;

QII– Quality Improve Intervention;

RACF– Regional Age Care Facility;

SPDR– Swedish Prescribed Drug Register;

List of Tables:

1. Introduction:

The world population is increasing, with figures above 7 billion people already being counted at this point (United Nations, 2019). At the same time, population ageing has become more noticeable, especially in more developed countries, and is considered one of the most significant social transformations of the 21st century (Kanasi et al., 2016; Newgard & Sharpless, 2013) . This increase in the elderly population is related, among other factors, to better health care that has as a consequence an increase in the average life expectancy, also occurring a declining in fertility rates (Newgard & Sharpless, 2013; Velazquez-Berumen et al., 2015). Declining fertility and increasing longevity led to rising numbers of older people as well as a continuously growing share of the elderly in the population (Velazquez-Berumen et al., 2015).

Data from the United Nations show that the number of elderly people aged 60 years or more in the world population will increase significantly by 2050, and that Portugal, in particular, will be one of the countries with a higher percentage of the world's ageing population (United Nations Department of Economic and Social Affairs, 2019; Velazquez-Berumen et al., 2015). Aging is closely linked to a broad array of risk factors that are associated with chronic disease and declining health (S. R. Smith et al., 2006).

Global improvements in medical care, the ageing of the population and increased provision of public health interventions such as vaccination have caused changes in the types of disease that affect populations. In the past, infectious diseases were the primary causes of mortality; now, the primary causes of global mortality are noncommunicable diseases such as cardiovascular disease and neoplastic disease (Velazquez-Berumen et al., 2015).

Faced with this global scenario, several challenges arise. There is an urgent need to find solutions to help the aging population. This part of the population which tends to live longer, with several chronic pathologies, are often users of multiple medications and, consequently, will need health care for longer, these individuals will have a growing and sustained need for a variety of prescription drug therapies thus posing new problems to health systems (Glass, Mangan, et al., 2009; Kanasi et al., 2016; Newgard & Sharpless, 2013; Roughead et al., 2003; S. R. Smith et al., 2006).

The presence of multiple chronic conditions increases the complexity of therapeutic management for both health professionals and patients, and impacts negatively on health outcomes (Masnoon et al., 2017). In order to keep their health under control, they often need to take medication to control certain pathologies, such as Diabetes Mellitus, Dyslipidemia and Cardiovascular Diseases (Newgard & Sharpless, 2013).

1.1. Polymedication and Polypharmacy

What is found is that many of these patients end up taking several medications at the same time, in a chronic manner, predisposing to polymedication (Kim & Parish, 2017). The term polymedication refers generically to the concomitant use of five or more drugs in an outpatient setting (Kim & Parish, 2017). Polymedication may lead to the inappropriate use of certain drugs, with the main consequences being the possible onset of adverse reactions and drug interactions, as well as economic costs. These can be decreased if measures are taken, and it may be a key point of intervention by pharmacy professionals (Kim & Parish, 2017; Najafzadeh et al., 2016).

Not only polymedication has become a concern but also polypharmacy in these patients, since in many cases they may experience difficulties managing their medications (Kwint et al., 2013). Polypharmacy is common in the older population with multimorbidity, as one or more medicines may be used to treat each condition (Masnoon et al., 2017). There are several factors that can contribute to that, such as (i) patients having multiple chronic diseases that may be managed by (ii) multiple prescribers and (iii) multiple pharmacies and involve the long-term use of medications for acute conditions; the lack of (iv) evidence-based guidelines specific to high-risk populations; (v) drug formularies and (vi) costs that change over time.

The volume of prescription medications on the market has increased, however Health Care professionals are sometimes overwhelmed and this might hinder provide poor monitoring and follow-up. Moreover, we cannot forget the fact that common dosage of a medication may not be the optimal dosage for a patient, owing to pharmacogenomics and age-related changes in physiology (Szymanski, 2008). These polymedicated patients, also present increased difficulties in adherence and compliance with the therapeutic scheme indicated by their physician (Kwint et al., 2013; Naderi et al., 2012).

The term "adherence" refers to a patient's behavior of understanding the recommendations from their providers and taking medications correctly (Fallis et al., 2013; Kadia & Schroeder,

2015). Medication-taking behavior is extremely complex and individual, requiring numerous multifactorial strategies to improve adherence (Zelko et al., 2016). Medication nonadherence occurs when patients do not take their medications as directed by physicians, which can lead to overall poor quality of life and increased hospitalizations (Kadia & Schroeder, 2015). It has been described as a very common and costly complication that may result from gaps in care, not identified by health care providers (Hersberger et al., 2013; Kadia & Schroeder, 2015; Lemstra et al., 2018). A gap in care can be defined as the failure to translate and utilize medical knowledge effectively by physicians and patients (Kadia & Schroeder, 2015; Suzanne, 2011).The extent to which patients are adherent to their medications is simultaneously affected by multiple factors based on patient and provider barriers. Twenty-five percent to 50% of patients then stop their medications within 1 year of treatment initiation, which, in the worst-case scenario, leads to hospitalizations (ACPM, 2011; Kadia & Schroeder, 2015).

Medication non-adherence is high among older patients, those from culturally and linguistically diverse backgrounds, low socioeconomic backgrounds and low educational status (M. Smith et al., 2010; Toh et al., 2010). Nonadherence to chronic medications leads to worsening of therapeutic outcomes for patients (Lemstra et al., 2018). This results in an increase in morbidity and mortality rates (Kadia & Schroeder, 2015). Thus, medication nonadherence is a growing concern for the health care system, professionals, and payers because of the ample evidence that nonadherence leads to adverse events and higher costs of therapy (Faisal et al., 2021; Kadia & Schroeder, 2015; Mangan et al., 2013). By addressing these issues, the pharmacy team can improve adherence, for instance home visits by pharmacists or pharmacy technicians can provide an opportunity to identify the nature of poor medication adherence giving an opportunity to improve adherence, ultimately providing cost saving opportunities to their patients (Kadia & Schroeder, 2015; Toh et al., 2010).

1.2. The Role of Pharmacist And Pharmacy Technician

In recent years, considerable attention has focused on the evolving role of pharmacists and pharmacy technicians in the delivery of health care services (Jesus et al., 2012; Oliveira RP & Jesus A, 2022; Poole et al., 2003). They are well-trained health professionals, yet they are often underused (M. Smith et al., 2010). Both can advise patients on the prescriptions and over-the-counter drugs they take (use, effect, potential adverse effects) and how to take them (e.g. use of an inhaler) (Rollason & Vogt, 2003). They can play important roles in optimizing therapeutic outcomes and promoting safe, cost-effective medication use for patients in medical homes (M. Smith et al., 2010). Increasing numbers of pharmacists and pharmacy technicians now regularly determine and monitor drug therapies, resolve and prevent potential drug-related problems, conduct and interpret drug-related laboratory tests, provide drug counseling and education, administer drugs, and provide immunization services (Poole et al., 2003).

Both the pharmacist and the pharmacy technician can work with patients, family members or caregivers, and the medical home team to develop an accurate, comprehensive active medication profile that includes current, recently discontinued, or changed medications. These professionals can also evaluate regimens for potential drug interactions, allergies, dosage adjustments, adverse events, therapeutic duplication, cost-effective therapies, and adherence trends (M. Smith et al., 2010). Community pharmacists and pharmacy technicians are well placed in the health care chain to play an active role in supporting patients' adherence to medication (Rollason & Vogt, 2003). Pharmacists and pharmacy technicians also have the opportunity to reinforce information already provided by other healthcare professionals and monitor adherence at subsequent patients' visits to the pharmacy (Mansoor et al., 2014).

Pharmacy technicians can promote the responsible use of medicines and play a vital role in promotion, administration, and implementation of community-based adherence programs. Their collaborative and interpersonal skills make them an important part of the pharmacy team for execution of the program (Mansoor et al., 2014). The teamwork of pharmacists and pharmacy technicians has shown successful results in addressing nonadherence and creating cost saving opportunities through pharmacy-based adherence programs (Mansoor et al., 2014).

1.3. Multidose Drug Dispensing Systems

An increasing number of these patients are receiving their medication in Multidose Drug Dispensing (MDD) systems, which can be also called Multi-compartment Compliance Aids (MCCAs) or Dose Administration Aids (DAAs), due to the benefits in terms of health outcomes and cost of health care (Glass, Haywood, et al., 2009; Glass, Mangan, et al., 2009). Although we could normalize one designation or acronym, for the purpose of this dissertation, we will always refer to the designation used in the articles cited.

In view of this, Individualized Medication Preparation emerges as an option to be considered by patients, their families and the health professionals accompanying them (Josendal et al., 2021; Kim & Parish, 2017; Mertens et al., 2018).

Individualized Medication Preparation consists of a pharmaceutical service that focuses on the organization of the patient's medication, according to the physician's prescription, and that allows optimizing the proper use of medications, through their repackaging in blister or bag-type packages, with exceptions, such as medications such as liquids and effervescent tablets (Hersberger et al., 2013; Jøsendal et al., 2022; Sjöberg et al., 2012). This service has as main objectives to provide the patient with the right medicine, in the right dose and at the right time (Gilmartin, Marriott, et al., 2013; Josendal et al., 2021). It is a service that implies constant communication and coordination between the various health professionals, but with numerous advantages for the patient in terms of safety and convenience, which can improve therapeutic adherence and thus achieve better disease control (Josendal et al., 2021; Wekre et al., 2011).

These types of preparations are often recommended in the management of chronic disease, to improve the adherence to multiple medications and thus health outcomes for patients (Ma et al., 2022). The provision of a MDD service through community pharmacies is expected to reduce medication-related hospitalization and adverse events through improved medication management (Glass, Mangan, et al., 2009). Whereas the use of these systems has grown, concerns about its packaging accuracy, particularly at a large scale, and consequently possible incident rates is something that should be considered (Carruthers et al., 2008; Gilmartin, Hussainy, et al., 2013).

In line with the growth in the use of these systems, technological innovations have emerged in recent years that could be useful to patients adherence, however the impact of its

implementation and on the dispensing of medication is something that still needs to be explored (Faisal et al., 2021; Rantanen et al., 2017).

There are also some concerns related with the safety and stability of the medicines once they are out of the manufacturer's packaging (Haywood et al., 2011; Redmayne et al., 2015).

Manufacturers' packaging is designed to protect drug products from environmental factors encountered during storage, such as light, air (oxygen, carbon dioxide, other gases) and moisture while ensuring limited interactions between the product and the packaging material (Drovandi et al., 2017; Glass, Mangan, et al., 2009; Haywood et al., 2011). However, this does not guarantee the stability of the active pharmaceutical ingredient (API) and the drug product on removal and repackaging into a MDD (Glass, Mangan, et al., 2009; Haywood et al., 2011; Redmayne et al., 2015). Varying stability has also been demonstrated for different brands of medications that contain the same API (Ma et al., 2022). Although the stability of a dosage form is often seen to be the responsibility of the manufacturer, this does not include removal from the original packaging (Albert et al., 2017; Glass, Mangan, et al., 2009; Redmayne et al., 2015).

In electing to repackage a drug product into a MDD, pharmacists and pharmacy technicians must consider the implications on drug stability of the transfer to a nonmanufacturer pack (Glass, Mangan, et al., 2009). The shelf-life of a drug product may be affected by the intrinsic stability of the API and interactions between the API and the excipients (Glass, Haywood, et al., 2009; Glass, Mangan, et al., 2009). Instability can lead to (i) loss of potency due to the degradation of the API, (ii) accumulation of potentially toxic degradation products causing adverse reactions in patients and (iii) changes in the physical appearance of a product that may affect patient compliance through loss of confidence in the medication (Glass, Haywood, et al., 2009; Glass, Mangan, et al., 2009). In addition to chemical decomposition by hydrolysis, oxidation, isomerization, polymerization or photochemical degradation of the API and / or excipients, physical changes in tablet hardness, friability, disintegration or dissolution rate may lead to altered bioavailability and thus therapeutic efficacy of the drug product (Glass, Haywood, et al., 2009; Glass, Mangan, et al., 2009).

2. Objectives

The research question is "What is the current evidence on the implementation and utilization of MDD systems, and what potential solutions exist for improving these systems, specifically, related to user experience, safety assessment methods, quality improvement interventions, technological support, and payment for the service.?"

The research question outlined above can be broken down into the following specific objectives:

- Explore the user experience in using MDDs, focusing on aspects such as ease of interaction, satisfaction, and any challenges faced.
- Investigate the perspectives of health professionals regarding the implementation and usage of MDDs, including their perceptions of effectiveness, challenges encountered, and suggestions for improvement.
- Assess the safety protocols and practices implemented in the preparation MDDs, with a focus on identifying potential risks, errors, and strategies to enhance safety in medication dispensing.
- Evaluate the impact of a specific Quality Improvement Interventions (QII) in the preparation of MDDs, aiming to enhance the accuracy, efficiency, and overall quality of the medication dispensing process.
- Investigate the role of technology in the preparation and use of MDDs, examining how technological advancements contribute to the efficiency, accuracy, and user-friendliness of these devices.
- Assess the integration of MDDs with other healthcare technologies, exploring potential synergies and challenges in incorporating technology into the medication dispensing process.
- Examine the existing payment models for MDD services, considering both the perspectives of healthcare providers and users, to understand the financial implications and barriers associated with the adoption of MDDs.

- Investigate potential strategies for optimizing the payment structure for MDD services, aiming to ensure sustainability, affordability, and accessibility for diverse patient populations.

These specific research objectives provide a focused and systematic approach to exploring key aspects related to the use of MDDs, encompassing user experiences, safety assessments, quality improvement interventions, technological integration, and financial considerations.

3. Methods

A scoping review of literature was conducted with collected articles in the main databases, Pubmed and EBSCO. No limits were applied to the publishing year, the initial search was completed in November 2022 and then updated with studies and cross-references throughout the research work. For EBSCO, the following subsets+ were selected: Academic Search Complete, eBook Academic Collection (EBSCOhost), eBook Collection (EBSCOhost), eBook University Press Collection (EBSCOhost), eBook Open Access (OA) Collection (EBSCOhost), Library, Information Science & Technology Abstracts.

The query for PUBmed was defined as:

- Pubmed:(((multidose dispensing system[Title/Abstract]) OR (multi drug dispensing system[Title/Abstract])) OR (dose administration aids[Title/Abstract]) OR (medication therapy management[Title/Abstract])

The query for EBSCO was defined as

- EBSCO search complete:AB multi-dose dispensing systems OR AB multidrug dispensing systems OR AB dose administration aids OR AB medication therapy management

The search strategy followed a PICO strategy:

- Patients: (patients from primary healthcare or nursing homes);
- Intervention: (use of MDD/MCA/DAAs);
- Comparison: (usual care/not using MDD/MCCAs/DAA; not required);
- Outcomes: (appropriateness of medication use regarding users experience of MDD systems, their safety and quality interventions created, technological innovations and costs).

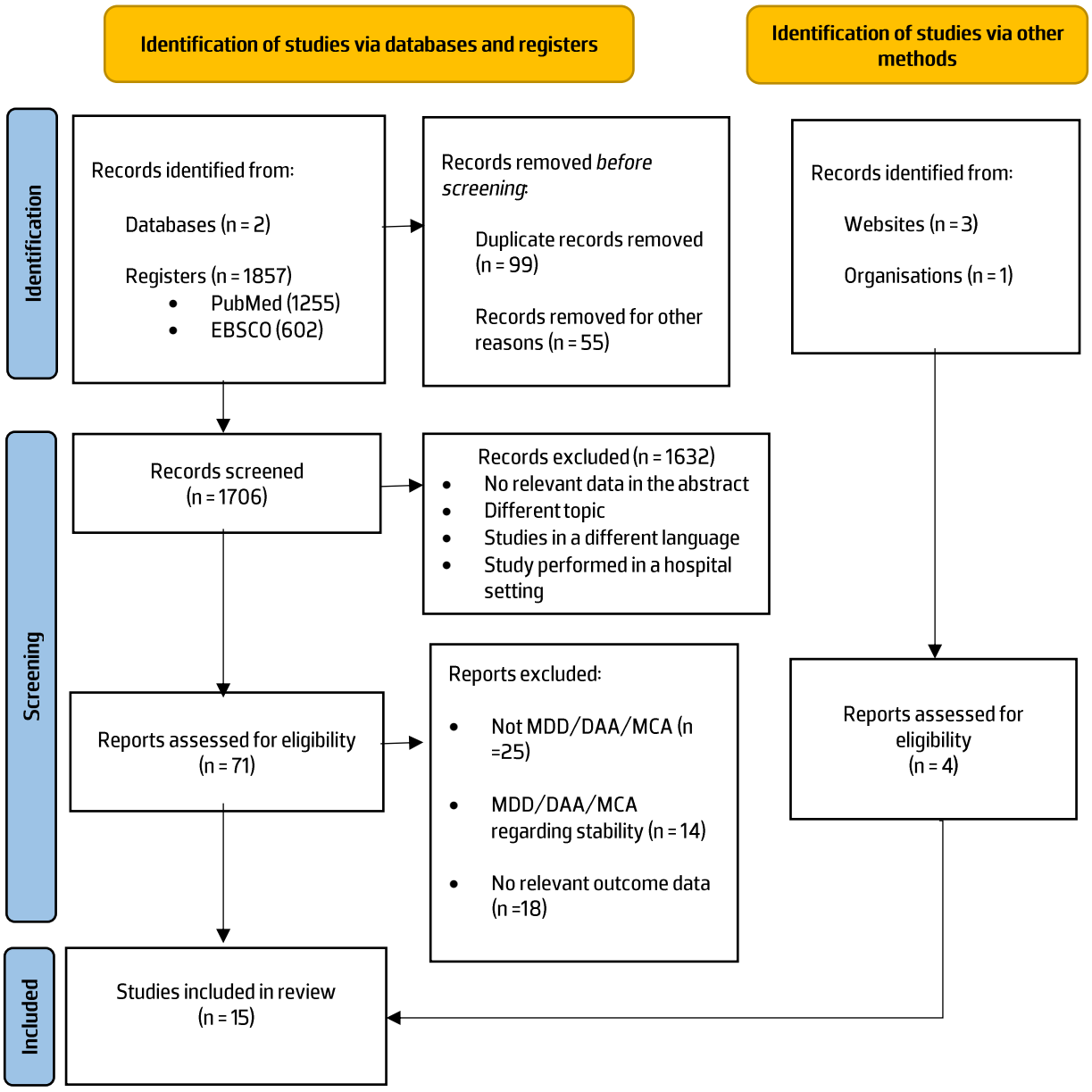
Once the bibliographical research had been completed, the analysis was carried out. Initially, based solely on the title and abstract, in order to make a pre-selection of the most relevant and targeted evidence to the review topic.

Rayaan software was used, a free of charge sofware that helps expedite the initial screening of abstracts and titles using a process of semi-automation while incorporating a high level of usability (Ouzzani et al., 2016).

Studies applying outcome measures that were associated with the appropriateness of medication use, having in consideration users experience (patients or healthcare professionals), or studies about the use of MDD systems involving medication safety were included. Studies regarding quality interventions or technological interventions, possible costs or any other type of economic evaluation of MDD were also included. Only studies in English and Portuguese were included. Articles that addressed a different topic, presented no relevant data, written in a different language or performed in a hospital setting were excluded. Systematic reviews or meta-analyses were not included.

Having in consideration the theme of this review the articles found were screened. After the identification of duplicates articles were sequentially screened, first by title, then by abstract and finally full text. Prior to this the duplicates were excluded. Articles were screened by two independent reviewers and a consensus was sought for any discrepancy through discussions at the end of each screening.

3.1. Flow Diagram of articles included in the review



4. Results

A total of 1857 relevant references were found, with 1753 references remaining after software removal of duplicates and other articles that had a different theme. Of these, 1706 references were included in the abstract screening phase, and of those 71 were chosen for full-text article review. Fifteen articles were finally shortlisted for data extraction and quality assessment, taking into account the established objectives and their relevance regarding the subject. Studies selected, ranged from 2008 to 2022, and have very distinct number of participants, as seen in Tabe 1.

Table1: Number of participants in each study.

Reference	*Number of Participants n=*
(Carruthers et al., 2008)	2480
(Johnell & Fastbom, 2008)	731105
(Wekre et al., 2011)	24
(Wallerstedt et al., 2013)	30,922
(Gilmartin, Hussainy, et al., 2013)	1757
(Gilmartin, Marriott, et al., 2013)	435
(Tora et al., 2014)	180059
(Miranda & Costa, 2014)	267
(Elliott et al., 2016)	88
(Gilmartin et al., 2016)	983
(Rantanen et al., 2017)	17+27
(Mertens et al., 2019a)	250
(Mertens et al., 2019b)	62
(Faisal et al., 2021)	5
(Tukukino et al., 2022)	151

Most of the studies were undertaken either in Europe or Australia, as can be seen in Table 2. Six studies were conducted in the Nordic countries, five were in Australia, two were from the Netherlands, one in Portugal and one in Canada. The study design and the setting of the intervention were also very different.

Despite the heterogeneity present in the selected studies, ranging from the size of the sample, study design to the topics covered, these were included due to the importance of the information presented, such as some of the technological innovations for instance.

Table 2: Summary of included studies.

Reference	*Design*	*Setting*	*Country*
(Carruthers et al., 2008)	Audit	RACFs	Australia
(Johnell & Fastbom, 2008)	Cross-sectional Study	SPDR	Sweden
(Wekre et al., 2011)	Qualitative Study	Primary Health Care	Norway
(Wallerstedt et al., 2013)	Longitudinal Analysis	Primary Health Care	Sweden
(Gilmartin, Hussainy, et al., 2013)	Cross-sectional Observational Study	NH	Australia
(Gilmartin, Marriott, et al., 2013)	QIIs	14 Pharmacies and 45 NHs	Australia
(Tora et al., 2014)	A Register Study	NH	Sweden
(Miranda & Costa, 2014)	Cross-sectional Study	3 Pharmacies	Portugal
(Elliott et al., 2016)	Audit	RACF's	Australia
(Gilmartin et al., 2016)	QIIs	45 RACF's	Australia
(Rantanen et al., 2017)	Observational Study	Phase 1: NH Phase 2: Home care Patients	Finland
(Mertens et al., 2019a)	Cross-sectional Study	8 Pharmacies	The Netherlands
(Mertens et al., 2019b)	Cross-sectional Study	3 Pharmacies	The Netherlands
(Faisal et al., 2021)	Mixed-Method Study	Primary Health Care	Canada
(Tukukino et al., 2022)	Descriptive Study	Primary Health Care	Sweden

Caption: DAA (Dose Administration Aid); MDD (Multidose Drug Dispensing); NH (Nursing Home); QII (Quality Improve Intervention); RACF (Regional Age Care Facility); SPDR (Swedish Prescribed Drug Register);

Some of the selected articles were more focused regarding experiences of users and health professionals, others more about the safety in preparation of these systems and possible interventions to improve it´s execution, some examples of the technology developed in the last years and the possibility of payment for these type of services.

Thus, in order to facilitate the articles screening, considering the objectives previously established for this systematic review, it was decided to analyze the results according the specifics of each article as presented in Table 3 , which will be further developed in discussion.

Table 3: Summary of topics of Interest.

Topics of Interest	*Articles that focused the topic*
Experiences of users and health professionals concerning the use of MDDs;	(Mertens et al., 2019b; Wekre et al., 2011)
Safety Assessment in the Preparation of DAA/MDD;	(Carruthers et al., 2008; Gilmartin, Hussainy, et al., 2013; Johnell & Fastbom, 2008; Mertens et al., 2019a; Wallerstedt et al., 2013)
Introduction of a quality improvement intervention (QII) in the preparation of MDDs;	(Gilmartin et al., 2016; Gilmartin, Marriott, et al., 2013)
Use of technology in the preparation/use of MDDs;	(Elliott et al., 2016; Faisal et al., 2021; Tora et al., 2014; Tukukino et al., 2022)
Payment for the preparation of the MDD service;	(Miranda & Costa, 2014)

5. Discussion

In accordance with the study objectives and considering outcomes measured in the retrieved articles, we will proceed with a detailed discussion on each topic.

5.1- User's experiences (patients and health professionals);

There have been some studies regarding patient's and health personnel experiences, and also opinions about the use of MDD systems. When it comes to health professionals, Wekre et al (2011), detailed in their study that health professionals agreed that this system requires a more frequent communication between all professionals, which may lead to better handling of drugs and fewer dispensing errors, which ultimately can be considered an argument in favor of the use of these systems (Wekre et al., 2011). However, if a communication problem exists, for example any update of the medication regimen should be transmitted as soon as possible, otherwise patients may experience drug related problems (DRP) (Wekre et al., 2011).

On the other hand, Mertens et al (2019) sought to explore patient's experiences with MDD systems. Their results show the importance of shared decision making between physicians and patients. It was reported that those patients were the ones that rated their experience with MDD system with a higher grade, in contrast with cases in which patients started MDD system without their consent (Mertens et al., 2019b). The authors also point out that prior to this system, other measures should be taken in consideration (simplification of the drug regimen; use of drug reminder charts and/or use of reminder alarms; use of pill boxes), when faced with a situation where patients do not take their medication correctly or are starting to lose their management capacity (Mertens et al., 2019b). If none of the above proved to be useful than an MDD system can be considered.

5.2- Safety Assessment;

There's a growing concern about the safety of medication preparation of MDD's systems. These systems have individual doses of a day or week supply of drugs arranged according to the dosage schedule for the day and before they are given to the patient several health personnel are

involved in its preparation mainly the general practitioner (GP) that prescribe them, the pharmacy staff that prepare them and the nurses that give them to patients, so the probability of error exists.

Having that in mind, Carruthers et al (2008) study had the premise to audit DAAs in RACFs, which is a place where older people can live when they need ongoing help or health care and can no longer live at home (Carruthers et al., 2008). The rate of incidents in DAA packaging was high (4.3%), considering the 297 incidents detected from 6972 packs of medication of the 2480 residents that participated in this study (Carruthers et al., 2008). These incidents can be explained by several reasons such as medication missing from the package (99); medication wrongly dispensed (12); incorrect labelling (32); medication dispensed by the pharmacies that was already ceased by the GP (7); incorrect instructions of dosage (37); (vi) medications not delivered to the RACF (13) (Carruthers et al., 2008). These results show the need to improve the safety and awareness for all health professionals, about the use and preparation of these systems.

Another study had the same goal, however, this time they were trying to evaluate the safety of DAAs in NH. Currently a large proportion NH population have their medicines repacked into DAAs, which enlightens the need to audit the safety of this preparations (Gilmartin, Hussainy, et al., 2013). The authors ended up with a similarly high rate of incidents, in this case 684 incidents occurred in 457 DAAs from a total of 3959 that were audited of the 1757 residents (Gilmartin, Hussainy, et al., 2013). Some of the reasons to justify these incidents were unsuitable repacking according to pharmaceutical guidelines (50,1%); added medicine (9,8%); incorrect quantity repacked (5,4%); omitted medicine (5,3%); damaged medicine (5,1%) (Gilmartin, Hussainy, et al., 2013). The current findings indicate there is the potential for NH residents to receive inaccurate or unsuitably re-packed medicines, with the potential to lead to adverse health consequences if not first identified and rectified.

In Susanna M. Wallerstedt study, the objective was a bit different than the articles previously referred. In this case, patients were already users of MDD systems, the authors were trying to find out a possible association between the use of MDD systems and an increase use of drugs (Wallerstedt et al., 2013). The results showed that these patients were in fact taking more drugs than previously, having fewer drug changes in their treatment, happening the same during the follow-up (Wallerstedt et al., 2013). Nevertheless, we cannot assume instantly that the

increased use of drugs by these patients it's a direct consequence of the use of MDD systems. The authors have in consideration for example that some of the new drugs were indeed necessary for the patient, regarding his new health state (Wallerstedt et al., 2013). Also, these patients have a stricter control of their medicines in comparison with normal users, which ultimately may influence part of the results, something that should also be considered.

In Sweden a different approach was tried, in order to investigate if a possible association could exist between the use of MDD systems and potentially inappropriate drug use (IDU) (Johnell & Fastbom, 2008). The results indicate that multi-dose users may be more exposed to potential IDU (Johnell & Fastbom, 2008). This may partly be explained by the higher drug use in the multi-dose than the ordinary prescription users (Johnell & Fastbom, 2008). Also, these users are more susceptible to fewer renewal of prescriptions and less inclination to make changes to medication lists, which can influence potential IDU (Johnell & Fastbom, 2008). These conclusions highlight the need of an improved used of these systems, with a proper and constant communication between health professionals, otherwise it could lead to complications.

In the Netherlands the use of these systems is also growing, however little is known about drug regimen changes when MDD are used. With that premise in mind, Mertens et al (2019) aimed to investigate the frequency type, procedure followed, immediate necessity and time taken to make MDD adjustments (Mertens et al., 2019a). The results of the study show that a considerable part of MDD adjustments were effectuated immediately 135 (52%), 81 (31%) by adjusting the MDD system manually, 49 (19%) by temporarily dispensing the drug separately from the MDD system and 5 (2%) by ordering a new MDD system (Mertens et al., 2019a). Taking these results into account, pharmacists were of the opinion that almost half of adjustments could be deferred adjusted (Mertens et al., 2019a). These type of adjustments takes time and brings additional costs to the preparation of these systems, so they must weigh the pros and cons of immediate or deferred adjustment for every individual patient (Mertens et al., 2019a). Explicit agreements and timely communication between prescribers, patients and pharmacists about the reason and acuteness of immediate MDD adjustments might decrease the number of immediate MDD adjustments, resulting in improved dispensing efficacy as immediate adjustments took around twice the time compared to deferred adjustments.

4.3- Quality improvement interventions;

Taking into account previous studies on the safety of DAA/MDD preparation and use, something needed to be done to improve these outcomes. Julie Gilmartin and her colleagues created a quality improvement intervention (QII) in order to improve DAA medicine supply (Gilmartin, Marriott, et al., 2013). The intervention included several strategies like education sessions; guidelines or protocols to direct the DAA supply service; additional DAA medicine checking by the community pharmacist and pharmacy technicians at the NH; stamps or bookmarks to be used in medicine records and to increase awareness of medication regimen changes; logbooks and stickers to record inter-professional communication regarding medication regimens; medicine identification sheets to facilitate DAA checking (Gilmartin, Marriott, et al., 2013). This study provides health professionals with practical suggestions to improve their DAA medicine supply service. Respondents believed the intervention had the potential to improve pharmacy medicine supply, or medicine administration involving DAAs in NH (Gilmartin, Marriott, et al., 2013). The QII evaluated in this study can also provide a basis for community pharmacies who are striving to improve their DAA medicine supply service.

The same authors decided to explore whether this intervention was also feasible in the context of RACFs. They target DAA medicine supply service provided to their residents with a similar intervention (education session, stickers, bookmarks, template documents articles, posters and guidelines) (Gilmartin et al., 2016). The DAAs, containing regularly packed medicines, were compared with the current, prescriber-prepared and updated medicine chart held at the RACF. The overall DAA incident rate increased significantly from 11.5% pre-intervention to 21.0% of all DAAs audited post-intervention (Gilmartin et al., 2016). The higher incident rate may reflect the generic nature of the intervention and its overall lack of specificity for particular types of incidents. These findings emphasize the need that QII to be designed for specific local contexts, taking into account the possibility of certain types of incidents. This study has highlighted the importance of ongoing and wide-scale evaluation of established medicine supply services provided to residents of RACF.

4.4- Techonological support;

There are some new and innovative solutions in the multidose dispensing services scenario, however, implementation of these interventions within the workflow of a community pharmacy can be considered a challenge.

Having that in mind Faisal et al (2021) pretended to explore which factors affected the implementation of a real-time adherence-monitoring, multidose-dispensing system in community pharmacies. They had to they disposal the smart adherence technology system, which is essentially a smart multidose blister package and a web-based portal to monitor the patient's medication intake remotely (Faisal et al., 2021). When a cavity is broken to access the medications, the telecommunications device records the medication intake event and uploads the data to a cloud-based software portal. This allows to observe patient medication schedules, set up notifications and obtain a report on patient medication adherence. The system can also generate reminders which can be sent as text to a mobile phone or an email address. The study participants valued the availability of real-time medication in take data and perceived that it could be a useful tool to aid in clinical decision making related to therapy (Faisal et al., 2021). Although it was perceived as an easy-to-use system, some of the requirements necessary (initial setup and staff training) can be considered barriers. The need of a larger space and specific storage locations for the smart blister package was also something that pharmacy staff referred as a potential barrier.

Other example of a possible technology that could be used to improve the medication adherence for elderly patients is the one presented in Pekka Rantanen study. It was examined the safety and usability of Evondos E300® Medicine Dispensing Robot with Multidose Sachets, an integrated advanced robotic device and telecare system (Rantanen et al., 2017). This was a two-phase study, phase I took place in a NH mainly to test for possible robotic malfunctions that could jeopardize patients safety, phase II involved a less controlled setting, this case home care patients (Rantanen et al., 2017). When the patient presses the device's dispenser button, the device delivers a sachet containing the medicine(s). If a patient misses a sachet or happens a systems malfunction, the telecare system passes that information to the home care unit for action (Rantanen et al., 2017). Thus, no medication doses were missed, the patients still received

their medicines. In this trial the home care patients were satisfied with the device and willing to use a robotic system, and the nurses' opinions were positive.

Over recent years, some RACFs implemented electronic medication management systems (eMMS), in which electronic medication administration charts are used instead of a paper chart for the purpose of medicine administration (Elliott et al., 2016). These hybrid paper–electronic medication management systems, in which GP prescribers' orders are transcribed into an electronic system by pharmacy technicians and pharmacists to create medication administration charts, are increasingly replacing paper-based medication management systems in RACFs. With that in mind Elliot et al. (2016) investigated possible discrepancies between GPs paper medication orders and pharmacy-prepared electronic medication administration charts, back-up paper charts and DAA, as well as delays between prescribing, charting and administration (Elliott et al., 2016). Almost half of the identified discrepancies were caused by pharmacy data entry discrepancies, or failure to update the eMMS when there was a change (resulting from either RACF staff failing to notify the pharmacy of medicine changes or failure of the pharmacy to correctly enter the data into the eMMS). Although this study only involved one pharmacy and one RACF, it highlights some of the risks associated with hybrid paper electronic medication management systems, which is why improvements are needed to properly manage patients' medication.

Given the fact that patients are using more and more medicines, the risks of drug interactions are consequently increasing, including in MDD systems. Even though the pharmacy staff whenever is preparing these systems should check for possible interactions, they can happen. With that in mind, Tukukino and colleagues decided to study *Janusmed®,* a decision support integrated into medical records that provides recommendations for managing interactions, to check for possible medication alerts in patients using MDD systems (Tukukino et al., 2022). From the 26 (79%) out of 33 patients using multi-dose drug dispensing, most of the alerts that appeared can be managed by dose adjustments or separated intake (Tukukino et al., 2022). As a decision support tool, it had the intended effect, that is, to affect GPs behavior. However, as these alerts and recommendations continue to appear although the drug treatment is adequately managed, physicians may disregard them, thereby increasing the risk that important alerts are overlooked in a time-strained practice. To avoid information overload, one

may hypothesize that the interaction alert system could benefit from increased integration with clinical data.

Drug Related Problems (DRP) due to inappropriate drug use or inappropriate doses are common in the population using MDD systems. They may cause suffering for patients and substantial costs for society. With these assumptions Hammar Tora and his colleagues decided to use the clinical decision support system (CDSS) Electronic Expert Support (EES) to detect possible DRPs in patients with MDD systems (Tora et al., 2014). The results show that potential DRPs were detected in the majority of patients with MDD, on average two alerts per patient (Tora et al., 2014). Despite having a higher number of drugs, patients with the highest age received a lower number of alerts compared with younger patients (Tora et al., 2014). These results can be partly explained considering that elderly have an increased risk of cardiovascular disease comparing with patients ≤64 years. However, is of great importance to monitor patients with MDD of all ages for potential DRPs related to age, dose or drug combinations. A CDSS such as EES might be a useful tool in health care and pharmacies, but more research is needed on clinical relevance of alerts and actual patient outcomes.

4.5- Payment for the preparation of the DAA/MDD service;

MDD systems are increasing in use, however there is a cost associated with preparing this type of system. Given the current funding model for pharmacies, both in the public and private sectors, regardless of the fact that these type of systems are funded by the government in some countries, others which isn't. It is necessary to study the public perspective and assess the patient's willingness to pay for this service so that it can be successfully implemented in the community pharmacy context.

With these principles in mind Inês Miranda carried out a study, collecting information through a questionnaire in community pharmacy (Miranda & Costa, 2014). Analyzing the answers, the majority of respondents considered the service useful, not only for themselves, but in some cases to a relative or acquaintance. It was found that the service is most often perceived as useful among individuals with behaviors considered non-adherent, which suggests that these users are a priority target group for implementing the service (Miranda & Costa, 2014). The main

reason given for considering it fair to pay for the service was the perception that it is a task that requires more work for the pharmacy and its staff (Miranda & Costa, 2014). A more recent study with a similar approach, also investigated the possibility to pay for the DAA and its preparation. In this case, a structured online questionnaire was used and the results showed that the majority of respondents also stated that they were willing to pay for this service, even more so if it was for a relative (Reis et al., 2023).

Both studies suggested that the implementation of a DAA system may be feasible in community pharmacy, given the large proportion of respondents who consider it a useful service for themselves and, above all, for others, since they recognize it as a possible tool for promoting adherence. In addition, a significant proportion of potential users is willing to pay for the service, though perhaps not enough to cover all its costs or the time spent preparing these systems.

Usually, MDD systems are useful to improve medication adherence, but they also have some disadvantages. As presented in some of the articles patients knowledge seems to diminish; not all medication can be dispensed via MDD systems; dispensing via MDD system compared with manual dispensing is more expensive; patients with a reduced manual dexterity or reduced vision alternatives should be considered; this type of systems to be properly used requires constant communication between GPs, pharmacy staff and the patients. These arguments should be taken in consideration before starting the use of these systems, we cannot rely solely in start using these systems and stop the necessary follow-up of these patients if we want to keep them safe and prevent possible complications.

Some interesting technology options appeared in the last years, however it's feasibility at a large scale and associated costs may pose as barriers to implement these measures in the community context.

6. Limitations

The existing literature on multidose drug delivery systems can be considered relatively scarce. It is recognized that these type of devices have the potential to improve medication safety, not only by the fact that it reduces discrepancies in the medication and can be considered convenient and easy to use.

Taking into account the terms adopted to search for articles in this review, considering a different equation research or a better use of mesh terms could be of use. This is something that could be improved, in order to obtain possible articles with more solid evidence in regards to the research objectives.

Some papers have been published in recent years, however in the selected articles each author uses a different approach regarding this matter, which can influence in part some of their results, making it hard to establish solid conclusions regarding some aspects associated with the use of these systems.

Therefore, it can be considered a challenge to implement some of the presented solutions of these devices and assess possible benefits. Having in consideration the context, it may not be directly applicable, especially when each country presents differences in terms of pharmacy size, scale, volume and regulations. In some cases, this system may also not be suitable thanks to technical challenges as the technology necessary by the user and the pharmacy that prepares the multidose system, the extra work the lack of a financial remuneration.

In future studies, it would be essential to estimate costs and benefits from different stakeholder points of view. These stakeholders should include healthcare decision-makers and providers, patients and relatives, community pharmacies, and public insurance. Further research applying relevant study designs, methods, and outcome measures is needed to provide more solid evidence for MDD systems, in terms of medication safety, appropriateness of medication use, and costs.

The scoping review methodology adopted followed standard best practice. However, as with all searches it is possible that some papers were missed either through the search process.

7. Future perspectives

It is safe to say that a still limited number of controlled studies have explored MDD in primary healthcare. Further evidence is needed to draw solid conclusions on MDD's outcomes and their safety in certain conditions. Another point to be considered in future studies should focus the stability of the medicines in these dispensing systems (Glass, Mangan, et al., 2009; Ma et al., 2022). There's a need to have in consideration if these systems are still safe to use under certain conditions, such as differences in temperature and humidity that varies in each country, especially aggravated in the last years thanks to global warming.

Few works were developed regarding that subject, one of the most recent having in consideration not only the stability but also which brand, and consequently the excipients used, was more suited to be repackaged (Ma et al., 2022).

8. Conclusion

The mission of the pharmacy professional is to contribute to the improvement of public health by ensuring the safe, effective and appropriate use of medicines. Medication-taking behavior is complex and involves components of the patient, the doctor and the process. Conversations about medicines should begin by listening to patients' concerns, preferences and goals of care. After listening to patients' needs, professionals can incorporate evidence-based knowledge about medicines to make decisions.

Increasing adherence can have a greater effect on health than improving a specific medical therapy. Simple cost-effective interventions to reduce non-adherence are therefore sought in order to improve public health and reduce avoidable expenditure on healthcare systems. Multidose drug dispensing systems have as a purpose to proportionate the right medicine, in the right dose and at the right time.

Regarding this review and the defined objectives, it was possible to obtain some valid insights. Concerning user's experience, health professional or mere patient, though the sample of articles is small, it can be concluded that the various players consider it to be a system that can improve adherence to therapy, properly used allows for fewer dispensing errors and safer handling of medicines. Constant communication and teamwork are essential for its proper use, also involving patients in decision-making process is something that should be considered by the different professionals during the process of implementation or subsequent use.

When it comes to the safety of this system, taking into account the incident rate presented in the selected articles, it is clear from the results and some of the testimonies that despite its growth in the community, the creation of tools or procedures to make these systems more secure is beneficial, although they need to be adequate according each reality. About technological innovations in the area, some options have emerged that could be differentiating for patients and pharmacy professionals, allowing them to have more information which ultimately can be used to improve medication adherence and the patients safety for instance. Some of the obstacles recognized with implementing these innovations are initial set up, staff training, costs associated and lack of an adequate financial remuneration considering the extra work.

With respect to payment for this service, even if the selected articles related to this objective is limited, the information analyzed showed that the population perceives this system

as useful, especially among individuals that presented non adherence behaviors, showing willingness to pay for the service considering the context of community pharmacies.

Further studies are required in order to get more solid conclusions regarding some aspects of the use of multidose drug dispensing systems. MDD systems can be considered as a viable solution, but ultimately this decision depends on the individual situation of each patient.

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