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REVIEW

Mapping of drug-related problems among older adults conciliating medical and pharmaceutical approaches

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Key summary points

Aim To analyze the process from the prescription of the drug to the health outcome, from a medical and pharmaceutical perspective, to prevent the occurrence of drug-related problems (DRPs) in older adults.

Findings A mapping of a logical process of drug use from the perspective of physicians, pharmacists, and patients has been established, but many fields remain unexplored (e.g. off-label use, substance use disorders, therapeutic failure), especially in some settings (e.g. home-dwelling) as little data is available in older adults.

Message Prevention of DRPs imperatively requires taking into account the opinions of all healthcare professionals as well as those of patients and their caregivers.

Abstract

Purpose To lay the fundamentals of drug-related problems (DRPs) in older adults, and to organize them according to a logical process conciliating medical and pharmaceutical approaches, to better identify the causes and consequences of DRPs.

Materials and methods A narrative overview.

Results The causes of DRPs may be intentional or unintentional. They lie in poor prescription, poor adherence, medication errors (MEs) and substance use disorders (SUD). Poor prescription encompasses sub-optimal or off-label drug choice; this choice is either intentional or unintentional, often within a polypharmacy context and not taking sufficiently into account the patient's clinical condition. Poor adherence is often the consequence of a complicated administration schedule. This review shows that MEs are not the most frequent causes of DRPs. SUD are little studied in older adults and needs to be more investigated because the use of psychoactive substances among older people is frequent. Prescribers, pharmacists, nurses, patients, and caregivers all play a role in different causes of DRPs. The potential deleterious outcomes of DRPs result from adverse drug reactions and therapeutic failures. These can lead to a negative benefit-risk ratio for a given treatment regimen.

Discussion/conclusion Interdisciplinary pharmacotherapy programs show significant clinical impacts in preventing or resolving adverse drug events and, suboptimal responses. New technologies also seem to be interesting solutions to prevent MEs. Better communication between healthcare professionals, patients and their caregivers would ensure greater safety and effectiveness of treatments.

Keywords Drug-related problems · Older adults · Compliance · Medication error · Prescription · Substance use disorders

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Background

Drug-related problems (DRPs) are defined as events or circumstances involving drug therapy that can induce a potential or real undesirable health outcome for a patient [1]. DRPs are frequent, costly, and often preventable [2]. Older people are at high risk of DRPs for several reasons. They suffer from multiple chronic diseases needing the use of several drugs [3–5]. Age-related changes in pharmacokinetics and pharmacodynamics modify the effects of drugs, often in a negative way [6]. Medical, economic, and social conditions are also significant factors influencing the use and effect of drugs in older adults [6]. Therefore, prescribing drugs to reach a positive benefit-risk ratio is challenging for both healthcare professionals and older patients. When given a drug, seniors may experience an adverse drug event and/or a treatment failure, which may result from a DRP, and thereby further deteriorate their health.

Many studies have reported frequencies, types, and risk factors of DRPs, especially in older adults [7, 8]. However, there is important heterogeneity in the types of DRPs reported, the tools used, and a general lack of clarity on the definition of DRPs and their associated issues. Moreover, healthcare professionals do not seem to speak the same language regarding prescribing and drug use [9]. Therefore, it is difficult to thoroughly understand the phenomenon of DRPs and identify corrective actions to improve medication use among older people. Considering and conciliating a medical and a pharmaceutical point of view might be a solution for an integrated and coordinated approach of DRPs.

The aim of this paper was to provide a narrative overview of DRPs in the older population to propose a mapping conciliating medical and pharmaceutical approaches.

Overview and mapping of DRPs

Nearly twenty classification systems have been developed for the identification of DRPs, which makes it difficult to compare the results [10]. The definitions and the concepts around DRPs are varied and confusing and some issues are never addressed.

The most consensual definition and classification of DRPs have been established by the pharmacists' working group of the Pharmaceutical Care Network Europe (PCNE). It defines DRP as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [11]. The last version, published in 2020, is composed of five domains: Problems, Causes, Planned Interventions, Acceptance of the intervention proposals, and Status of the problem (outcome of the intervention) [11].

Avoiding DRPs: the physician approach

For the physician, good prescribing must follow a rigorous stepwise process:

(1) to define the patient's problem (a good diagnostic),
(2) to specify the therapeutic objective (preventive, curative, symptomatic or palliative),
(3) to choose a suitable drug in adequacy with both the patient's condition and preferences. The chosen drug should fulfill two conditions: being both effective and safe for the patient's problem (a positive benefit/risk ratio), and also appropriate for the specific patient, i.e. complying with contra-indications (drug–drug interaction, drug–disease interaction or drug–condition interaction), dosage schedules, duration of treatment and pharmaceutical forms.
(4) to provide the patient with clear information and instructions to better obtain treatment adherence and prevent medication error, and
(5) to monitor outcomes such as effectiveness and safety.

The management of therapy in older adults is often difficult because polypharmacy complicates the achievement of a good prescribing. Optimization of drug therapy is an important outcome of the comprehensive geriatric assessment (CGA) [12], thanks to a multi-dimensional and multidisciplinary process using medication review using tools (ex: Beers criteria and other explicit criteria, MAI or other implicit criteria). Medication reviews allow reduction of polypharmacy, detection of drug overuse, underuse or misuse, and adaptation of the mode of administration to the capabilities of older patients to facilitate adherence [13].

Avoiding DRPs: the pharmacist approach

Clinical pharmacists play an important role in hospitals, nursing homes, and primary care settings to identify and resolve DRPs. They are qualified to detect potential or real problems, which for themselves are adverse drug events and therapeutic failures according to the PCNE classification [11]. Then, the possible causes of these problems rest on drug selection, drug form, dose selection, treatment duration, dispensing, drug use process, and on the patients themselves. From this pharmaceutical analysis, the clinical pharmacist will propose possible solutions at the drug level for the prescriber and/or the patient. This approach completes the intervention of the physician in order both to optimize drug treatment and to improve patient health outcomes.

Avoiding DRPs: the roles of patients and caregivers

Patients and caregivers have a central role in identifying and resolving many DRPs. For example, caregivers may ensure optimal preparation and administration of medications in older adults with cognitive impairment or loss of autonomy [14, 15]. Similarly, in long-term residential care and during hospitalization, medication administration should not be considered a simple process of the 5-Rs (right patient, drug, route, time, and dose), in a patient-centered environment, medication administration involves many partners, including patients, to ensure a safe medication use [16]. In Canada, a quality improvement initiative recognized the critical importance of empowering patients and caregivers to help prevent medication errors (MEs) during transitions of care and produced a list of "5 Questions to Ask about Your Medications" [17]. Furthermore, patients and caregivers can provide essential information for medication monitoring or perform such monitoring themselves (e.g. glycemic control or blood pressure), which can allow medications to be adjusted more quickly to reach targets or avoid adverse events [18]. Hence, engaging patients and caregivers in medication management, adopting a patient-centered care strategy, could lead to safer outcomes [19].

Avoiding DRPs: identification of causes

The causes resulting in DRPs belong to the medical decisions and actions undertaken during prescription, preparation, application, and monitoring. These actions involve physicians, pharmacists, nurses, patients, and their caregivers. At times, no cause for a DRP seems to be identifiable. A thorough and systematic approach can help to identify the origin of this DRP, combining the approaches of the prescriber and the pharmacist, and considering them from the point of view of intentionality (Fig. 1).

Unintentional failures in the drug process are MEs [20]. They can be preventable. The implication of a physician, a pharmacist or a nurse is often mentioned but seldom that of the patient and their caregivers. Patients who do not follow the instructions and advices of health professionals can make unintentional errors as they may forget or be unable to understand instructions properly. Logistic problems, such as unavailable drugs and mislabelling are some examples of unintentional MEs.

In contrast, intentional failures can be encountered in the following situations. Suboptimal drug prescribing is a situation leading to poor quality of care; it involves three forms: overuse (unnecessary or ineffective drug), underuse (omission of a necessary medication) and misuse (inappropriate drug in relation to the patient's conditions) [21]. These situations result from poor reasoning on the part of the prescriber leading to the following problems: wrong drug choice, inappropriate dose or therapy duration,

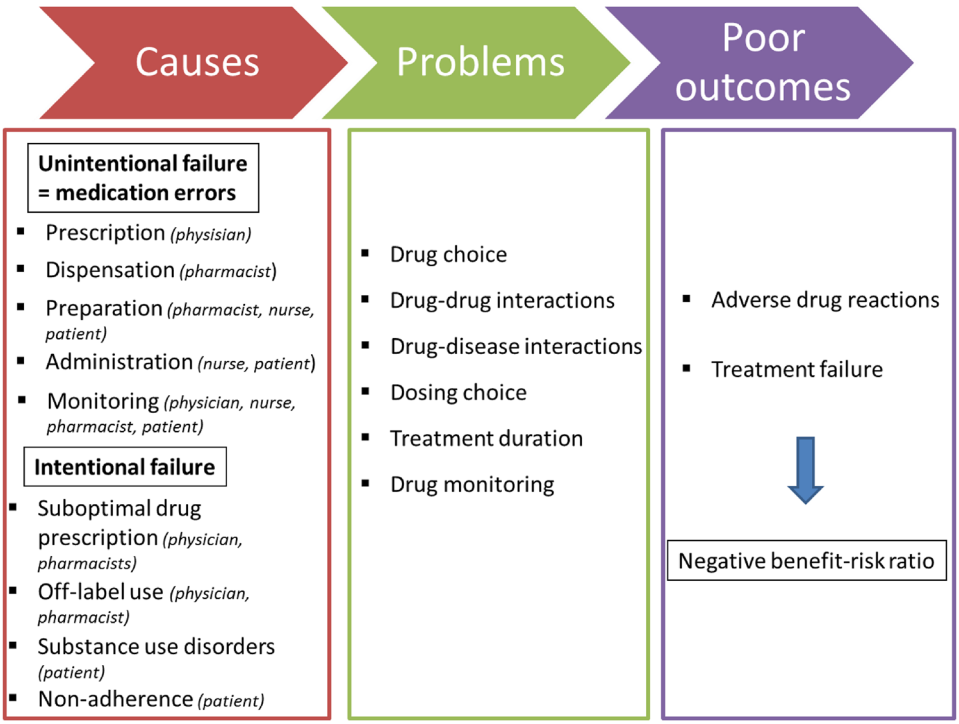

Fig. 1 Mapping of drug-related problems based on medical and pharmaceutical approaches and the involvement level of each actor (physician, pharmacist, nurse and patient)

incorrect drug interaction analysis, and inadequate monitoring. A suboptimal drug prescription can be considered as a frontier situation with ME, but failure to verify the drug suitability or to assess the patient's conditions to adapt a prescription can hardly be attributed to an unintentional situation [22]. Off-label use is another frequently observed situation that must be distinguished from suboptimal drug use. Off-label use concerns a healthcare professional who intentionally selects drugs for medical purposes outside their marketing authorized conditions [23]. This is a common situation in pediatrics due to a lack of clinical trials in this age group. This argument is also valid for older adults who are under-represented in clinical trials [24]. For example, dosages recommended for young or middle-age adults are not necessarily suitable for older adults, and information is not always available or explicit when a physician needs prescribing for an older patient. The medical and legal consequences of an off-label prescription deserve special attention in this situation which may affect patient safety. The substance use disorders (SUD) of certain prescribed drugs—opioids, central nervous system depressants, and stimulants—can lead to a variety of adverse health effects, including addiction. Due to the frequency of psychoactive substance prescription among the older population, SUD needs a special interest among DRPs. Surprisingly, SUD is not mentioned among DRPs. Finally, non-adherence is defined as an intentional behavior of the patient not to follow the instructions or not to refill the prescription [25]. Non-adherence could be a cause of treatment failure and adverse effects.

Avoiding DRPs: the conciliation of medical and pharmacist approaches

This process analysis carried out at the physician, pharmacist, nurses and patient-level were conducted to identify the causes and consequences of medication problems (Fig. 1).

Whereas pharmacists consider an ADR or a therapeutic failure as a problem according to the PCEN classification, physicians consider these events as the consequence of a problem in the process of drug choice or use. Indeed, an ADR or a therapeutic failure, either potential or real, can only be the result of a problem in the prescription process or in the use of drugs by patients, pharmacists or nurses. The causes of these problems are the results of unintentional or intentional failures, which involve physicians, pharmacists, nurses, patients or caregivers at different levels of intervention.

Drug-related problems among older adults

From this mapping on DRPs conciliating medical and pharmaceutical approaches, the analysis of a DRP would conduct to study three situations: (1) poor outcomes (adverse drug reactions, therapeutic failures), (2) problems conducting to poor outcomes, (3) causes explaining the problems. A brief review of each situation is reported in the geriatric field.

Causes explaining the problems

Medication errors

A medication error (ME) is defined as "a failure in the treatment process (prescription, dispensation, preparation, administration, and monitoring) that leads to, or has the potential to lead to harm to the patient" [20].

Polypharmacy in older adults with multimorbidity is a known risk factor of ME [26]. Nguyen et al. showed a relationship between age and ME with a maximal risk around 75 years [27]. Moreover, social isolation, placement in nursing home, or hospitalization play an important role in the occurrence of ME in older adults; the care transition between these different places also increases this risk [28]. In 2006, the notion of a positive culture of error and the importance of reporting ME appeared during the first meeting of the International Network of Safe Medication Practice Centers [29]. Some working groups and authors have focused on ME in older adults and have proposed preventive solutions [30–32].

Medication errors in ambulatory older patients Living alone at home without any care service seems to be a risk factor for ME [33]. In a study conducted in more than 30,000 people aged 80 years and more, two-thirds of the adverse effects or potential adverse effects detected were related to patients' errors [34]. The majority occurred by not modifying the medication follow-up when advised to do so by clinicians, not administering the right medication and right dose at the right time, and not following clinical advice about medication use. This suggests that older people do not know enough about the medication they take or have a poor understanding of the medical objective of their medications [35, 36]. Increased patient knowledge about their medications could decrease the risk of ME. Yet, some medication errors occurring at home are not related to patients, especially for those who have their medications managed by a nurse or another caregiver at home. Patients can have multiple prescribers and thus several prescriptions delivered in multiple pharmacies;

in addition, home care nurses have a less direct relationship with patient's practitioners and pharmacies [37, 38]. Finally, there are few articles dealing with ME at home, probably due to the difficulty of identifying and collecting data. Therefore, other studies are still needed to correctly identify ME occurring at home.

Medication errors in older patient living in long-term residential care Older people living in long-term residential care are potentially at increased risk of ME than most other groups because the majority of residents have complex health needs. Institutional risk factors including characteristics and processes are yet seldom investigated. Almost 70% of residents have suffered from at least one ME during prescription, monitoring, administration or dispensation (1.9 errors per resident) [38]. The administration seems to be one of the most affected steps [39]. This may be explained by the fact that drug administration is only one of the numerous tasks nurses have to carry out. On the other hand, in some residences, nurses prepare treatments, but the administration is handled by care assistants who do not have the necessary knowledge to prevent a potential ME or anticipate the potential seriousness of clinical consequences. A systematic review showed that a wrong dose is the most common type of error, followed by dose omission and overdose, especially during care transition, which seems to be a key step in ME occurrence risk [28].

Medication errors in older patients during care transition Transition of care represents a vulnerable situation for older patients and can lead to ME. Medication conciliation is a process used to identify and prevent MEs at care transition points in hospitals. A study carried out in a 38-bed acute geriatric unit (200 patients) revealed1.58 ME per patient [40]. One third of them were considered serious or even life-threatening [40].

Therapeutic interchange is another risk factor of ME at hospital admission, by forcing a switch from the patient's home medication to a different medication in the same class that is on the hospital formulary [41]. The proportion of ME at discharge from hospital seems to be usually lower than that on admission [42]. An added problem is the absence of medication justification for changes on the discharge prescription. This could be considered by the family physician as an error and thus therapeutic modifications may not be followed. This is all the more critical in frail older patients who require multiple hospitalizations, with a delay when writing discharge paper [43, 44].

Medication errors in older patients during hospitalization As in the previous situations, MEs are more frequent during hospitalization in older than in young adults [45]. The frequency of ME ranges from 17.5 to 76.7% in older inpatients, with an average ME between 1.4 and 2.2 per patient [40, 45–47]. A large part of MEs were drug omissions, followed by dose or frequency discordances during the administration stage [40, 45–47]. However, other pathologies which are specific to older adults greatly increase the risk of ME. For example, two-thirds of patients with cognitive impairment presented at least one DRP; ineffective or inappropriate drug and unnecessary drug therapy are the most common DRPs [48]. On the contrary, in a palliative care unit, where the average age is high, the most common error is represented by the lack of necessary concomitant drug [49].

Contribution of technologies to avoid MEs Some studies propose using QR code and Web services for older ambulatory patients, but this requires the use of a smartphone, which is uncomfortable for most older Europeans [50]. Moreover, this technology is of no help for patients with neurocognitive disorders. For patients with nursing service or hospitalized, new technologies must be put to the service of a caregiver. An automated drug distribution system has already been tested in a short-stay geriatric unit with promising results on the reduction of ME [51]. A recent systematic review focusing on older people assessed the impact of smart medication systems in daily use; these devices seemed to prevent ME occurrence in older adults [52]. Selected studies were conducted in people's homes, in nursing homes or in a short-stay older people's home. Medication systems that were studied included electronic pillboxes, automated home medication dispensers, and automated medication dispensing systems (QR code). Overall, these devices can prevent MEs in older people. However, caution is still warranted, as a study showed that 96% of technology-induced prescription errors were MEs caused by human–machine interaction [53].

Suboptimal drug prescribing

As discussed previously, suboptimal drug prescribing encompasses three situations: overuse, underuse and misuse. Although many studies focus on potentially inappropriate medications (PIMs) referring only to drug selection, it is also appropriate to include situations leading to inappropriate interactions, underdosage or overdosage, treatments of too short or too long duration, and wrong monitoring leading to treatment failures and/or ADRs.

Prescribing inappropriateness can be assessed by explicit indicators which can be applied with little or no clinical judgment. In clinical practice, these explicit criteria can only provide guidance on the suitability of the drug chosen and require taking into account the patient's clinical conditions to judge the real inappropriateness of prescribing. Implicit

criteria are more appropriate, as based on clinical judgment, but these tools are time-consuming. Implicit criteria assess prescribing appropriateness from several elements: indication, dose, adequate directions, drug–drug interactions, drug–disease interactions, duplication, duration, monitoring, and costs. Few mixed tools exist combining both implicit and explicit criteria to further optimize prescriptions in older adults [54, 55].

In a European community-dwelling setting, the estimated PIM prevalence was 22.6% (95% CI 19.2–26.7%) [56]. In nursing homes, the prevalence of PIM use was estimated at 43.2% (95% CI 37.3–49.1%) [57]. PIM prevalence increased over time; prescribed medication number was reported as the main risk factor for PIM use [57]. In residential long-term care facilities, the percentage of residents using at least one PIM was 46.5% (range from 18.5 to 82.6%) according to Beers' criteria, 61.1% (range from 23.7 to 79.8%) according to STOPP criteria and 48.6% (range from 30.5 to 74.0%) according to START criteria (underuse measure) [58]. Regardless, older people are at high risk of using PIM, in all settings and countries, making it a major public health concern.

Some studies showed a positive relationship between inappropriate prescribing and mortality, use of health-care services, adverse drug events, and quality of life, whereas others reported mixed or negative results [59]. These discrepancies may be explained by the choice of more or less rigorous methods assessing the causal link between inappropriate drugs and outcomes (e.g. mortality, morbidity, adverse drug events, quality of life). Studies using causality assessment were less conclusive on negative outcomes after PIM prescribing [60].

Off–label use

Off-label use is defined as prescribing drugs either for unregistered therapeutic indications or age groups or using unregistered dose or methods of administrations [23]. As older adults with several co-existing medical conditions are poorly represented in clinical trials, there is no good clinical data to support the indication, and possible adverse reactions are probably not detected in this age group. Therefore, the summary of product characteristics (SPC) often reports this sentence: "not studied in elderly patients or lack of sufficient data in elderly patients". A prescription for an older patient may then be considered as outside the marketing authorization. In the UK, a study has shown that 84% of patients admitted in geriatric medicine wards received off-label drugs [61]. Most of the studies on off-label use in the older population concern antipsychotics, antidepressants, and anticonvulsants [62]. For example, Patel et al.identified that 41% of pharmacy claims for anticonvulsants were off-label (3% by psychiatrists versus 46% by other specialists) [63]. Some factors are associated with off-label prescribing such as advancing age, institutionalization, cognitive impairment, and prescriber characteristics [62]. Off-label prescribing can be deleterious. In a study based on a pharmacovigilance database, off-label use induced adverse drug reactions in 20% of patients aged over 65 years and non-compliance with contra-indications was the main factor involved [64].

If a drug does not have an indication covered by marketing authorization, but if there is good clinical proof in this indication, its use may be appropriate. The case of bevacizumab demonstrates the difficulty of regulating off-label use. Bevacizumab is an antibody directed against vascular endothelial growth factor (VEGF inhibitor), only approved for the systemic treatment of cancers (e.g. metastatic colorectal cancer) since 2004 [65]. After experimental studies, series of clinical cases, and several randomized controlled trials, the safety and efficacy of bevacizumab in the treatment of ophthalmic diseases, particularly in age-related macular degeneration (AMD) by intravitreal administration were demonstrated [65]. Therefore, bevacizumab has been widely prescribed off-label in many countries. On the other hand, ranibizumab was approved for AMD only, but its cost was around 50 times higher than that of bevacizumab [66]. Numerous clinical trials subsequently showed that ranibizumab and bevacizumab have similar efficacy and safety, but bevacizumab has never been labeled for AMD. In Europe, Bro et al. explain that government institutions and national ophthalmologic societies had diverging opinions on the use of off-label bevacizumab and failed to find a consensus position [67]. The question of responsibility for off-label therapy remains unanswered.

Even if off-label prescribing is common in older adults, such a practice is not necessarily wrong if it might provide significant benefits for the patient. However, some precautions must be taken. Off-label prescribing is possible if no acceptable alternative with approved indication is available and if patient characteristics allow this prescription. The physician must inform the patient of the reasons and the potential risks associated with the off-label prescription of a drug. Close monitoring for on-label prescription is mandatory. Finally, adverse effects must be reported early and thoroughly to pharmacovigilance in order to highlight the drug safety in off-label use.

In Europe, a Geriatric Expert Group was set-up in 2011 to provide scientific advice to the European Medicines Agency on issues related to older adults. A reflection paper has been produced to characterize the baseline frailty status of older patients enrolled in clinical trials whatever their age. The aim is to ensure that clinical trial populations are representative of the users of the medicine, as the benefit-risk balance in older patients may depend on their physical frailty status [68].

Substance use disorders

"Drug abuse" and "drug misuse" are terms often used to evoke a psychoactive substance use disorder (SUD). It is a topic generally associated with young people (teenagers or young adults) who are often perceived as marginalized, although this cliché has been changing in recent years [69, 70]. Conversely, in the older population little attention has been paid to SUDs. In particular, "baby boomers" are distinct compared with past generations as they came of age during the 1960s and 1970s, a period of changing attitudes toward drug and alcohol use [69]. With the worldwide aging of the population characterized by a large influx of "baby boomers", it is particularly relevant to identify SUD.

Substance use among older adults is often underestimated. Addictive behaviors are often associated with hidden characteristics that are difficult to detect by usual approaches [71]. Available data originate mainly from North America and relate to the damaging use of psychoactive drugs, alcohol and, much less frequently, illegal substances [69, 70]. In a review, Wu et al. showed that 25% of US older adults have used psychoactive medications with abuse potential in 2012 [71]. Medications with abuse potential the most frequently used were opioids (propoxyphene, hydrocodone, oxycodone, and codeine) and benzodiazepines, often after a justified medical prescription [71]. In the USA in 2004, more than half a million visits to the emergency departments involved nonmedical use of pharmaceuticals [72]. Opioids and benzodiazepines were the two most cited medications among adults aged 55 years and over (33% and 21%, respectively). Most of the visits involved the use of other substances (mainly alcohol).

A study conducted using this multidimensional approach based on data from the French Addictovigilance Network has shown that psychoactive substances involved in problematic use (apart alcohol) among subjects aged 65 and over in France were mainly medications from two drug classes: benzodiazepines and benzodiazepine-like (in particular zolpidem and zopiclone) and opioid analgesics (in particular fentanyl, oxycodone and tramadol) [73]. These medications are often used long-term, leading to difficulties in stopping consumption, mainly due to withdrawal syndrome. These drugs are sometimes used at high doses, illegally acquired (hidden consumption, falsified prescriptions) and/or used in the search for a positive or euphoric effect. It is not so surprising to identify these two drug classes among the psychoactive substances most frequently associated with problematic use by older adults [74]. Other medications, such as tianeptine, methadone or gabapentin, may sometimes be used in a problematic manner. Here again, exposure is often of long duration, with the search for a positive effect. The use of psychoactive substances in older adults is associated with numerous potentially fatal health problems, in particular, confusion, falls, respiratory distress, hallucinations, but also addiction which may require treatment in specialized centers. More rarely, the use of non-medicine substances such as poppers, cocaine, cannabis, ketamine or new psychoactive substances (e.g. synthetic cathinones) has also been pointed out. Such use may be chronic, recreational or experimental. In particular, a series of cases of space-cakes use (cakes with cannabis) in subjects over 68 years of age has been reported [73].

With population ageing, psychoactive substance uses may become a real public health problem in the future. The first step is to identify problematic substance use, which can lead to potentially serious health consequences. Older substance users may not present with the same symptoms as their younger counterparts and, therefore, may be more difficult to identify. Both the general practitioner and the pharmacist play an important role in the prevention, identification, and management of addiction in the geriatric population [75, 76].

Non-adherence

Medication adherence is defined as the extent to which prescribed medications are taken according to the dosage and frequency recommended by the healthcare professionals [25]. Poor adherence may have a major impact on clinical outcomes, contributing to worsening of diseases, increased health care costs and even death [77]. Between 30 and 50% of patients with chronic diseases do not take their medications as prescribed, but few studies have reported this medication adherence problem in older patients [78].

In fact, it is important to distinguish two types of non-adherent patient behaviors: unintentional or intentional. Unintentional non-adherence is a situation where patients fail to follow a recommended therapeutic scheme without doing so consciously. These are involuntary omissions and the inability to follow treatment instructions due to lack of understanding (e.g. cognitive impairment) or physical problems (e.g. visual impairment, osteoarthritis, etc.). From our point of view, this situation should be classified as a patient ME. On the contrary, intentional non-adherence occurs when a patient consciously elects not to follow the measures recommended by a healthcare professional; it represents between 33 and 75% of non-adherence situations [79]. The main reasons put forward by patients are the absence of symptoms, the delay between taking the drug and its effect, the fear of adverse effects, the administration schedule complexity, the poor understanding of the medication, and a poor patient-practitioner relationship [80]. Involvement of the patient to make the treatment goals understood, simplification of the treatment regimen adapted to the patient's lifestyle, information about the potential adverse effects, and involvement of the caregivers have been suggested to

enhance adherence [81]. Combined behavioral and educational interventions in older patients with polypharmacy do not always lead to improved adherence and clinical outcomes when comparing an intervention (pharmaceutical care) and a control group [82]. However, pharmacists can help improve adherence in older people, including helping to establish a good relationship between healthcare professionals who work together [8].

Problems inducing poor outcomes

The proposed mapping in Fig. 1 retains six problems leading to adverse drug reactions or therapeutic failures. Possible causes include drug choice, interactions, dosing choice, treatment duration, and drug monitoring.

In 2020, Placido et al. published a systematic review on the frequency, types, and risk factors of DRPs in home-dwelling older adults [83]. The median of DRPs per patient was 3 (IQR 2.3–6.0). The main causes were drug choice (51.4%) and dose selection (11.6%). Among drug choice issues, suboptimal drug prescriptions (inappropriate medications, underprescribing) were the main causes. As for risk factors of DRPs, they include polypharmacy and the most frequently prescribed drugs for cardiovascular, metabolic, digestive, and nervous disorders. Given the small number of articles (13) found in this review, it becomes urgent to develop strategies to improve medication use in the home-dwelling older population.

In France, 40% of prescriptions in community pharmacies could potentially induce interactions, 29% present issues of drug selection, and 12% of dosing [84]. In this study, 78% of pharmaceutical interventions proposed to the prescriber were accepted, more easily for dosing choice and interaction problems than for the relevance of the drug chosen [84]. Therefore, the complementarity prescriber-pharmacist duo may improve drug safety in older patients, but there remains a difference in judgment on the choice of drugs. More DRPs were detected among older adults receiving home nursing care compared to older patients living in nursing homes in Norway [85]. Similar to the French study in community pharmacies, the overall acceptance to change prescriptions was high (70%), without significant difference between the nursing home and home nursing care [85].

In conclusion, drug selection, dosing choice, and interactions are the principal problems observed in older patients. In the case of a drug selection problem, it is not easy to establish whether it is intentional (drug misuse) or unintentional (medication error). However, the important refusal rate to change a drug suggests an intentional cause. More and better information on the reasons for choosing a drug would allow the pharmacist's intervention to be targeted with pertinence, the aim of which is to help the prescriber to optimize the prescription.

Poor outcomes of DRPs for older adults

Adverse drug reactions

An adverse drug event (ADE) occurs during treatment but does not necessarily have a causal relationship to the drug, whereas an adverse drug reaction (ADR) is directly related to the drug after assessed causality [86, 87]. The doctor wants essentially to avoid or treat any direct adverse consequence of a drug in a patient. The pharmacist can act before or after the occurrence of a real consequence in the patient. Therefore, with the scope of the reconciliation approach on the concept of DRP, the occurrence of an ADR should be avoided or addressed.

Based on a literature review, the mean prevalence of ADRs in older adults leading to hospitalization was estimated at 10.0% (95% CI 5.1–16.8%), and the prevalence of ADRs occurring during hospitalization at 11.5% (95% CI 0–27.7%) [88]. Overall, the prevalence of ADRs in older adults in the acute care setting ranged from 5.8 to 46.3% with a mean of 11% (95% CI 5.1–16.8%) [88]. ADR-related mortality in hospitalized adults ranged from 0.14 to 4.7%, with a greater risk in those aged 75 years and more [88]. This large variation in the ADR prevalence is due to the choice of ADR definition, and to the differences in the methods used both to detect ADRs and to evaluate causality. Cardiovascular and neuropsychiatric drugs are the main medication classes associated with ADRs. Other medications such as nonsteroidal anti-inflammatory drugs, antibiotics, antidiabetics, and drugs with anticholinergic proprieties are also mentioned [88]. Falls, orthostatic hypotension, delirium, renal failure, and bleeding are the most frequently reported ADRs occurring in older adults [6]. Beijer et al. estimated in a meta-analysis that older adults had a four times higher risk of suffering from an ADR than the younger adult population [89]. Chan et al. identified that more than 50% of ADRs leading to hospitalization are preventable [90]. The main risk factors are female sex, multimorbidity, polypharmacy, renal failure, hypoalbuminemia due to malnutrition, and anorexia [6]. In clinical practice, ADR detection is often difficult as patients frequently present with non-specific symptoms. Thus, the involvement of medication in the occurrence of new clinical problems should be systematically considered among the etiologies in older adults. Failing to identify an ADR may result in a prescribing cascade, with the prescription of a new drug to treat the ADR instead of stopping the culprit drug [91], further contributing to polypharmacy and ADR risks. Tools for ADR detection have been developed, amongst others the GerontoNet ADR risk scale that showed a good validity to identify specific subpopulations of older inpatients at increased risk of ADRs [92].

Therapeutic failures

A therapeutic failure is defined as an "unexpected failure of a drug to produce the intended effects as determined by previous scientific investigations" [93]. Hartigan-Go et al. proposed to consider a therapeutic failure as an ADR [94]. Therapeutic failures lead to disease persistence, which increases the length of hospital stay, hospital readmission, and disease costs. Few studies have assessed the prevalence of therapeutic failures, and notably in the older population. For older patients with polypharmacy in primary care, treatment failures occur in 11.7% of cases [95]. In nursing homes, fewer than 3% of DRPs are linked to therapeutic failures [96]. In long-term care hospitals, 29.5% of DRPs are caused by suboptimal responses to treatment or therapeutic failures [97].

This variation in the observed prevalence can be due to the use of different methodologies to estimate therapeutic failures. Some researchers have proposed various tools. Hallas et al. proposed an algorithm to determine the causes of therapeutic failures and thus identified that 3% of admissions in six medical wards of the same hospital were linked to therapeutic failures [98]. In another study conducted in the emergency departments of several Italian hospitals, 33% of admissions were due to treatment failures according to Hallas' algorithm [99]. Polypharmacy and advanced age increased the risk of therapeutic failure. More recently, another tool was developed by consensus using the Delphi method to include several factors related to therapeutic failures: pharmacokinetics, clinical condition, inappropriate medication, interaction, business competition (generics), manufacturing quality (counterfeiting, mislabeled products, supply disruption…), and idiopathic or non-established factors (resistance, tolerance, tachyphylaxis) [100]. Based on this algorithm, 2.6% of admissions in the intensive care unit of a tertiary-level care Bogota's hospital were due to therapeutic failures [101]. In 61% of cases, therapeutic failure occurred in patients aged 60 years and more.

Antiepileptic drugs seem to be frequently involved in hospital admissions for therapeutic failures (seizures) [101]. Finally, in the majority of cases, therapeutic failures are due to inappropriate drug use, including interactions, subtherapeutic dose, insufficient monitoring, and non-adherence [102, 103].

Interventions on DRPs in older adults

Different types of interventions have been studied to identify and resolve DRPs in older adults, such as pharmacist-led medication reviews, pharmacist home visits, CGAs, educational interventions, computerized decision support systems. In general, isolated interventions have not shown a beneficial effect on patient health outcomes. In contrast, multifaceted interventions, combining different techniques, have shown an improvement in patient care by reducing inappropriate prescribing, reducing ADRs, shortening length of stay in hospital and preventing MEs [104–106]. Recent evidence demonstrates the importance of medication reconciliation in the transitional care to prevent DRPs [107, 108]. Thus, an intervention could be based on the following key steps: medication reconciliation, medication review, counseling, and post-discharge follow-up.

Conclusion and perspectives

This article lays the fundamentals of DRPs and organizes them according to a logical process, conciliating medical and pharmaceutical approaches. This process analysis carried out at the level of the prescriber, the pharmacist, and the older patient leads to better identification of causes and consequences of DRPs.

Many articles have demonstrated that the major problems encountered by older adults are related to drug selection, dosing choice, and drug interactions. The proportion of consequences, either ADRs and/or therapeutic failures, varies. It is worth noting that MEs are not the most frequent causes of DRPs among this population, while most problems are induced by PIM prescribing.

Polypharmacy is the common risk factor of suboptimal drug prescribing, MEs, off-label use and non-adherence. The drug classes most often involved belong to the cardiovascular system, the nervous system, and the alimentary tract and metabolism. Off-label use is seldom studied in the older population; more research is needed to establish to what extent it contributes to DRPs.

SUD is surprisingly little studied in older adults. In current geriatric care, this problem is seldom tackled with older patients and their caregivers. It is obvious that little attention has been paid to SUD in the older population. The more drug abuse increases, the more vulnerable this population is to drug effects. SUD is a part of DRPs and needs to be more investigated because the use of psychoactive substances among older people may become a real public health problem in the future. Both the general practitioner and the pharmacist play an important role in the prevention, the identification, and the management of addiction in the geriatric population [109].

Most of published papers argue in favor of an interdisciplinary pharmacotherapy program, which has shown a high clinical impact in preventing or resolving ADRs, suboptimal responses and treatment failures. New technologies also seem to be interesting solutions to prevent MEs. A thorough review of drugs given to older patients should ensure the safety and effectiveness of treatments. The medication

review, together with better communication between healthcare professionals and patients, will optimize prescriptions for the benefit of older patients.

Authors' contributions MLL and VNTH designed the study and oversaw the management of all aspects of the study. All authors met the requirements for authorship as defined by the ICMJE; all authors made substantial contributions to drafting and revising the work, approved the final version submitted herein, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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