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Opportunities for changes in the drug product design to enhance medication safety in older people: Evaluation of a national public portal for medication incidents

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Aims: Medication safety requires urgent attention in hospital pharmacy. This study evaluated the medication-related problems/errors as reported to the Dutch medication incident registry and disseminated for information to pharmacists. Through analysis by an expert panel we aimed to better understand which problems could have been mitigated by the drug product design. Additionally, the (wider) implications of the problems for current hospital/clinical practice were discussed.

Methods: Items were extracted from the public Portal for Patient Safety. Items were included if relevant for older people and connected with the drug product design and excluded if they should reasonably have been intercepted by compliance to routine controls or well-known professional standards in pharmaceutical care. To explore any underreporting of well-known incidents, it was investigated if different medication-related problems could be observed in a regional hospital practise over a 1-month period. For 6 included items (cases), the implications for hospital/clinical practise were discussed in an expert panel.

Results: In total, 307 items were identified in the Portal for Patient Safety; all but 14 were excluded. Six cases were added from daily hospital practice. These 20 cases commonly related to confusing product characteristics, packaging issues such as the lack of a single unit package for an oncolytic product, or incorrect or incomplete user instructions.

Conclusion: Medication registries provide important opportunities to evaluate real-world medication-related problems. However, underreporting of well-known problems should be considered. The product design can be used as an (additional) risk mitigation measure to support medication safety in hospital practice.

KEYWORDS

aged, aged 80 and over, drug labelling, hospital, medication errors, pharmaceutical, pharmaceutical preparations, pharmacy service, technology

1 | INTRODUCTION

Ageing is known for gradually impairing human organs and bodily functions leading to an increased risk for multiple chronic conditions, frailty, polypharmacy and difficulties managing medications.[1–3] Therefore, the older population (i.e. individuals >65 years) constitutes the main group of patients in ambulatory and hospital care.[3,4] In view of a worldwide increase in longevity, the percent of older people will

continue to increase.[5,6] This implies that the main group of patients in ambulatory and hospital care will grow older and will also require more complex medical and pharmaceutical care.[7–9]

Scientific evidence indicates that the prescription, procurement, preparation, dispensing, management and (self-)administration of medicines involve complex tasks that may cause medication-related problems (MRPs), which may result in patient harm.[10–13] For this study, an MRP was defined as an event or circumstance involving a drug therapy that actually or potentially interferes with the desired health outcomes. As such, the definition includes medication errors.[14] Scientific evidence also indicates that MRPs increase as a result of substitution policies, drug shortages or other supply issues and that they are most prevalent in older people on polypharmacy.[15–17] All this implies that hospital pharmacists should pay urgent attention to medication safety in older people.

In the Netherlands, pharmacists, medical doctors, general practitioners, nurses, midwifes and other workers in healthcare can report MRPs to the Portal for Patient Safety (PPS; earlier named Central Medication Incidents Registration).[18,19] PPS is a national medication incident registry that screens, analyses and evaluates MRPs and subsequently decides whether an alert should be disseminated to healthcare professionals. In addition, newsletters and any other relevant information are made publicly available on the PPS public internet portal (www.vim-digitaal.nl). Moreover, some incidents are discussed with the Dutch medicines evaluation board (MEB) to explore opportunities for product improvement such as those related to the formulation, strength, dosing device, packaging, product information or package label.[20] This approach is in line with the Swiss cheese model i.e. the understanding that risk mitigation measures in pharmaceutical care should best be adopted at multiple layers rather than only on the layer where the error occurred, or only the layer where the error should be prevented in the first place.[21]

The PPS has proven to be useful to evaluate MRPs as e.g. medication errors relating to anticoagulants, problems related to IT-matters, or problems related to automatic dose dispensing.[22–24] A systematic evaluation of any MRP relevant to older people and (potentially) connected with the drug product design has not yet been conducted. The primary aim of this study was to systematically evaluate the MRPs in the public PPS that are relevant to older people and for which specific characteristics in the drug product design provide opportunities to mitigate risk and hence promote medication safety. The secondary objective was to evaluate the likely implications of MRPs for current hospital/clinical practice.

2 | METHODS

2.1 | General information

2.1.1 | Definitions

See Table 1.

2.1.2 | Study design

(i) Database study in the public portal of a national medication incident registry (PPS). (ii) Cross-sectional observational study in a regional hospital practice. (iii) Expert opinion.

2.1.3 | Ethical considerations

This study did not require ethical approval in the Netherlands. The public PPS does not contain specific patient information. The MRPs observed in daily hospital practice were recorded without any reference to a specific patient, rather only general characteristics that were known to the hospital pharmacy were noted, e.g. older patient with dysphagia, older patient on polypharmacy.

2.1.4 | Usual care during hospital admission

In the Netherlands, the value of medication reconciliation and patient counselling in medication safety is well recognised by hospital pharmacists. Therefore, upon hospital discharge, the medication regimen is discussed with the patient and information is tailored to the patient's needs.[28] Subsequently, patients are given the possibility to collect their medication in the outpatient hospital pharmacy. Some medications as e.g. expensive oncolytic products can, however, only be obtained through the outpatient hospital pharmacy and not through the patient's community pharmacy.

2.1.5 | Statistics

Descriptive statistics were performed through Microsoft Excel.

2.2 | Database study

2.2.1 | Aims and data sources

To systematically evaluate MRPs as reported to PPS and shared for information with pharmacists. To explore which problems could have been mitigated by the drug product design.

2.2.2 | Data collection

All items in the PPS newsletters to pharmacists (2010–2016), the archive of practice stimuli (2017>) and the alerts to professional bodies (2005>) as published on the public PPS were independently identified by a US Board Certified Geriatric Pharmacist (F.K.C.) and a fifth-year pharmacy student (M.S.). For each item, a problem description was recorded, and it was evaluated if the item was duplicate or not. The outcomes were compared, and any differences were resolved.

TABLE 1 Definitions

Term	Description
Case	A description of a medication-related problem that was related to the pharmaceutical design of a drug product, which could enhance medication safety through intuitive design and that did not meet the exclusion criteria (see methods)
Category: formulation and dosage form	Cases where the problem related to the design of the unpacked drug product (i.e. preparation) or to any differences with products containing the same active substance or active moiety such as problems due to differences in the excipient composition between otherwise similar products, or problems due to swapping products with a different release mechanism such as a liposomal and conventional formulation.[25,26]
Category: packaging and administration device	Cases in which the inner or outer product packaging or (lack of) copacked administration device mainly contributed to the problem, e.g. a product where dose administration would involve 2 injections (one in each buttock), but where the packaging of some trademarks only included 1 injection rather than 2 injections for other trademarks.[25,26]
Category: user information	Cases where the problems were due to inadequate or confusing instructions in the authorised product information i.e. the summary of product characteristics (SmPC), package leaflet or the package label.[25,26]
Item	Any topic included for attention by pharmacists in the public Portal for Patient Safety
Medication-related problem	Events or circumstances involving medications that actually or potentially interfere with an optimum patient outcome. Medication-related problems include, but are not limited, to medication errors
Medication error	A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures[25]
Older person/people	Adults aged 65 years and beyond[6]
Pharmaceutical development	The process of turning an active pharmaceutical moiety into a medicine suitable for administration to the indicated patient group(s) by any of the relevant users e.g. healthcare professionals, patients, caregivers. This would include any related pharmaceutical aspects such as the control of raw materials, or the validation of analytical methods. Thus, the pharmaceutical development of a medicine relates to all aspects described in section 3.2.P of the marketing authorization dossier and to all the user instructions mentioned in the European SmPC section 6.0, in the patient information leaflet or on the package label[26,27]
Pharmaceutical design of a medicinal product	The composition, formulation, dosage form, route of administration, dosing frequency, packaging, measuring or administration device and the user instruction of a medicinal product[26,27]
Pharmaceutical design of a medicine	The variety in the pharmaceutical design of all the medicinal products of a certain medicine[26,27]
Product information	The information in the SmPC, in the package leaflet and on the inner or outer package label[26,27]

All items were independently evaluated with respect to the question if, from a hospital pharmacy perspective, any specific characteristics in the product design could have mitigated the risk for MRPs. If not, items were excluded from further evaluation. Background information was provided by a regulator (D.A.R.). Where appropriate, additional information was sought from a geriatrician (W.K.), expert in pharmacovigilance (F.H.) or hospital pharmacist (P.v.d.B.). All experts consented to the evaluation acknowledging a hospital pharmacy perspective. All remaining items were further referred to as a *case*.

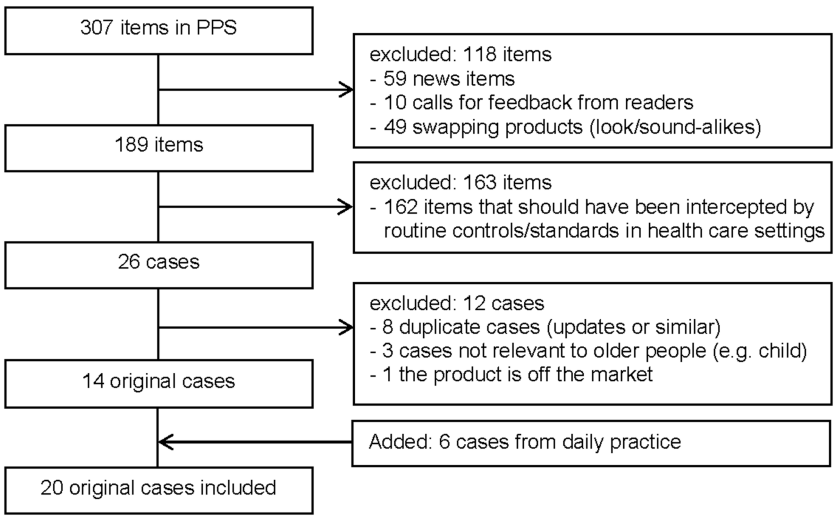

FIGURE 1 Flowchart of the selection of cases of the Portal for Patient Safety (PPS)

2.2.3 | Case categorization

Cases were independently classified by F.K.C. and M.S. into 3 categories: *formulation and dosage/strength*, *packaging and administration device* and *user information* according the definitions of Table 1. The outcome was discussed among all experts and additionally a professor in pharmaceutical technology (S.S.) until consensus was reached from a hospital pharmacy perspective.

2.3 | Observational study

2.3.1 | Aim

To investigate if cases were missed due to any reporting bias of well-known MRPs in PPS.

2.3.2 | Data source

Data were gathered from the hospital pharmacy of the regional teaching hospital OLVG, in Amsterdam, the Netherlands.

2.3.3 | Data collection

During the working activities of a US Board Certified Geriatric hospital pharmacist (F.K.C.) cases were listed over a 1-month period. Activities included: checking prescriptions; responding to questions from patients, nurses and medical doctors; attending multidisciplinary patient consultations; and evaluating medication-related hospitalization or re-hospitalization.

2.3.4 | Case selection and case categorization

The appropriateness of the selected cases was confirmed by 2 experts (M.S.; P.v.d.B.). Any selected cases were added to those retrieved from PPS and further handled likewise.

2.4 | Expert opinion

Two cases from each category (Table 1) were selected to discuss the (wider) implications of the problem for current clinical/hospital practice in the Netherlands.

3 | RESULTS

In total, 307 items were identified in PPS. After applying exclusion criteria, 26 cases remained (Figure 1). Following exclusion of 8 duplicates, 3 cases not related to older people and 1 case related to a product already withdrawn, a total of 14 cases remained to be included. Six additional cases were identified over the 1-month observation period in OLVG hospital, implying a relevant reporting bias in the public PPS. Evaluation of all 20 cases (Figure 1) indicated that many cases related to confusing product characteristics (including problems when interchanging drug products), packaging issues or incorrect or incomplete user instructions (Table 2). The following 6 example cases were selected.

3.1 | Category: formulation and dosage/strength

3.1.1 | Tramadol

Case description

According to Dutch professional standards, the recommended dose for older people is 10–25 mg once to 4 times daily. This dose can be gradually increased. The only authorised oral dosage form in the Netherlands to administer 10–25-mg dose is oral drops. Other dosage forms include a 100-, 150-, 200- or 300-mg retard tablet or a 50-mg capsule.[29]

Implications for clinical practice

The drops need to be diluted with water before intake. This handling is time-consuming and increases the risk of dosing errors due to miscounting or spilling liquid upon administration and/or swallowing. Moreover, the drops are packed in a container containing more doses than needed for 1 patient. All this implies that the use of tramadol drops in hospitals is impractical and prone to wastage. Therefore, in many hospitals older patients are treated with a 50-mg capsule already from start.

Hospital pharmacy perspective

In general, oral liquid formulations should not be considered a suitable alternative dosage form for older people who can still swallow tablets or capsules intact. This is especially true for medications where under or overdosing pose a serious risk. Dosing issues as for tramadol, can be avoided by aligning the recommended doses with the respective subdoses in monodose forms (e.g. capsules or tablets) or easy to adapt monodose units e.g. mini-tablets.

3.1.2 | Buprenorphine

Case description

Buprenorphine patches are authorised in the Netherlands with different durations of use (Table 3). A patient using the innovator Butrans 20 μg/h/wk, had to increase the dose to 35 μg/h/wk. Butrans was not commercially available in this strength. The pharmacy therefore dispensed a *generic* patch. The patient was still in pain after using the *generic* patch for several months and increasing the dosage to 52.5 μg/h/wk. Ultimately, it turned out that the *generic* patch had to be administered every 3 days rather than once a week as with Butrans.

TABLE 2 Brief description of cases included from the Portal for Patient Safety (PPS) and daily practice (DP)

Case (origin)	Active substance (drug product)	Short case description
Formulation and dosage/strength (including drug product interchangeability)		
1 (DP)	Tramadol	Lack of a formulation in the necessary dose (dose advice according Dutch standard is 3 times 25 mg, while capsules contain 50 mg).
2 (PPS)	Buprenorphine (Butrans)	Different trademarks of patches have different release profiles. Patches were used longer than recommended (authorised durations: 3 days, 4 days, 1 week)
3 (PPS)	Dextran/hypromellose (Duratears)	Difference in preservation between the generic (benzalkonium chloride) and original drug product (polyquad). Benzalkonium cannot be used with contact lenses.
4 (PPS)	Amphotericin b (Ambisome, Abelcet and Fungizone)	The conventional formulation (Fungizone 1 mg/kg) is mistakenly used instead of the liposomal product (Abelcet and Ambisome 5 mg/kg). Two patients died.
5 (PPS)	Benzylpenicillin (Benzathine Benzylpenicillin)	The benzathine salt should be administered intramuscularly; however, the sodium salt can be administered intravenously/intramuscularly with a different dose. The drug product instructions were mixed up.
6 (DP)	Gliclazide (Diamicron)	Prescribers were unaware of the different pharmacokinetic profile of the 30- and 80-mg tablets. They considered that 80 mg equals 2.5 tablets of the 30 mg.
Packaging (inner and outer) and administration device		
7 (PPS)	Melphalan (Alkeran)	Unavailable in strips: due to the carcinogenic and mutagenic effects, the pharmacy dispensed an intact container containing more tablets than needed. The patient used the drug for too long without the rest week.
8 (PPS)	Chlorambucil (Leukeran)	See the melphalan case description above.
9 (PPS)	Capecitabin (Xeloda)	Lack of an explicit warning on the outer packaging that the drug product should not be used daily but in a scheme. The patient used the product for too long.
10 (PPS)	Colecalciferol	Lack of a warning that colecalciferol high dosed liquids should not be used daily. The patient took all the container contents at once.
11 (DP)	Omeprazole (Omecat) and pantoprazole (Pantoprazol Pensa)	The shelf life after opening the bottle (generic Omecat 100 capsules) and tablet container (generic Pantoprazol Pensa 90 tablets) is exactly the same as the amount of the containers (100 *vs* 90 days).
12 (PPS)	Nifedipine retard	Nifedipine has 4 oral formulations: capsule, film-coated tablet and sustained-release tablet (named OROS or MGA retard). The film-coated tablet and sustained-release tablet are both called *retard* by the manufacturer. However, the bioavailability of tablets differs. In

TABLE 2 (Continued)

Case (origin)	Active substance (drug product)	Short case description
		addition, the sustained-release is dosed once a day, while the film-coated tablet is dosed twice a day. Many patients suffered from incorrect interchangeability.
13 (PPS)	Insulin (Lantus to Tresiba and NovoRapid to Humalog)	Patient was switched from Lantus to Tresiba and from NovoRapid to Humalog. The patient did not read the label and assumed that the blue pen with the green cap (Tresiba) was short-acting insulin, because it looked similar to the blue pen with the orange cap (NovoRapid). The patient used therefore a wrong dosage regime for almost a whole month.
14 (PPS)	Faslodex (fulvestrant)	The dosing is 2 injections, each 250 mg, 1 in each buttock. Underdosing has been reported because some packaging only contain 1250-mg injection (i.e. half of the recommended dose).
15 (PPS)	Methotrexate	A clear warning sign should be visible on the packaging where it states that methotrexate should only be used once a week. Many incidences with methotrexate involve a daily prescription or use with detrimental outcomes.
16 (PPS)	Depakine (300 mg/mL)	A nurse discovered that she could not read the dosage of the syringe of depakine liquid 300 mg/mL. The manufactured had changed the syringe: Only mg are found on the syringe, where previously mg and mL were mentioned. The maximum amount to be administered had also been adjusted from 450 to 400 mg.
User information		
17 (DP)	Posaconazol (Noxafil)	Lack of information that the tablets result in higher plasma concentrations than the suspension. It was unknown that the products cannot be interchanged.
18 (DP)	Multiple drug products	Lack of information whether drug product stability and/or bio-availability is altered by the joint intake of the products with food or drink, how to taper off or discontinue drug therapy, and whether tablets can be modified.
19 (DP)	Dabigatran (Pradaxa)	Lack of information that the product can be stored outside the immediate packaging for a maximum of 6 h at 25°C and 60% humidity only. Dabigatran is therefore not suitable for multiple drug dispensing systems.
20 (PPS)	Cabazitaxel (Jevtana)	Drug concentrate and diluent contained an overfill that was not clearly stated in the user information. This resulted in a 15.6% overdose in 8 patients. Although this problem was already reported in other European countries, Dutch pharmacists were not immediately informed by the company.

TABLE 3 Authorised patches in the Netherlands containing buprenorphine (2016)

Drug product name	Release rate	Duration of action	National licence number (RVG)	Marketing authorization holder
Butrans	5 μg/h	1 week	100975	Mundipharma pharmaceuticals BV
	10 μg/h	1 week	100978	
	20 μg/h	1 week	100979	
Butrans parallelimport	5 μg/h	1 week	114547/100975	Fisher Farma BV
	10 μg/h	1 week	114548/100978	
	20 μg/h	1 week	114549/100979	
Buprenorphine Sandoz	5 μg/h	1 week	114799	Sandoz
	10 μg/h	1 week	114800	
	20 μg/h	1 week	114802	
Buprenorphine Ranbaxy	35 μg/h	3 days	103490	Ranbaxy UK LTD
	52.5 μg/h	3 days	103491	
	70 μg/h	3 days	103492	
Transtec	35 μg/h	4 days	32909	Grunenthal BV
	52.5 μg/h	4 days	32910	
	70 μg/h	4 days	32911	
Buprenorphine Teva	35 μg/h	4 days	116173	Teva Netherlands BV
	52.5 μg/h	4 days	116174	
	70 μg/h	4 days	116175	

Implications for clinical practice

Currently, quality defects, drug shortages and national reimbursement rules have resulted in increased substitution rates in the Netherlands. These national rules imply that each insurance company has its own and different policy for a trademark of a specific medicine that is reimbursed for its clients only, and that, in turn, should thus be dispensed to a patient unless the patient is willing to pay for the medication itself. All this has contributed to a high workload in pharmacy practice and implies that pharmacies may need to have multiple trademarks in stock.

Hospital pharmacy perspective

It is necessary to reduce the risks associated with medication substitution. Realizing substitution rates in other countries have increased also,[30] hospital pharmacists consider that it is neither feasible to comply with the *regulatory* expectation that they will carefully consider the full product information (summary of product characteristics, package leaflet, package label) before a product is dispensed to a patient nor realistic to expect that they will themselves identify minor differences between the user instructions of otherwise similar products such as those in the duration of patch use. If (serious) risks due to differences in the design of products containing the same active substance (or moiety) in a similar dosage form and in the same dosage or strength is needed (e.g. to taper off), risk mitigation measures need to be present (Figure 2). Measures may e.g. include the use of a red warning box on the outer product packaging. For Butrans, the box should contain a statement on the duration of patch use.

3.2 | Category: packaging and administration device

3.2.1 | Melphalan

Case description

A patient started treatment with melphalan tablets (Alkeran) during hospitalization. Upon hospital discharge, the patient still needed to use 7 tablets once daily for 4 days (i.e. 28 tablets in total). Melphalan is packed in a container counting 25 tablets. Due to melphalan's carcinogenic and mutagenic effects, the law on protection of workers in healthcare requires that tablets can only be taken from their container in a dust extraction hood. However, the dispensing pharmacy was not accommodated with such provision. Therefore, 2 intact containers were dispensed to the patient along with detailed oral instructions. Nevertheless, the tablets were used for 6 days before the patient realized that they should have stopped taking tablets. Unintentional prolonged use has also been described for other medications, such as chlorambucil (Leukeran), capecitabin (Xeloda) and colecalciferol.

Implications for clinical practice

Serious under- or overdosing may occur when the packaging and/or pack size are not tailored to the recommended product use. This case and other similar cases clearly indicate that counselling is not always sufficient to prevent human error.

Hospital pharmacy perspective

It is important that drug developers, marketing authorization holders and regulators realize that handling of products with carcinogenic and

FIGURE 2 Drug products with an explicit warning on the packaging (see the red box for methotrexate, fosavance stating that the medication should be used once weekly) and drugs without (oral oncolytics: Etoposid and capecitabin)

mutagenic effects can easily be avoided at an earlier layer in the provision of healthcare by selecting a single unit blister package for marketing. This would also avoid time-consuming handlings for repackaging by pharmacies. In view of this, the Dutch MEB has asked pharmaceutical companies for voluntary support to ensure that oncology products with a substance that is harmful upon handling are available in unit blister package on the Dutch market.

3.2.2 | Omeprazol and pantoprazol

Case description

Both proton pump inhibitors are packed in containers with an in-use shelf life equal to the number of tablets/capsules in the container.

Implications for clinical practice

This in-use shelf-life neither allows any intentional pause in use from the container (e.g. because of hospitalization) nor any unintentional pause (e.g. because the patient forgets to take their medicine). This is not considered realistic, meaning that patients who fail to identify that the in-use expiry date has ended while there are still some tablets/capsules left in the container may continue treatment with a product that may no longer be stable. A short in-use shelf-life also suggests that the medication is not stable after the container has been opened. This suggests that stability issues may occur when the product is stored in a multiple compliance aids (MCA; *pill boxes*) or multiple drug dispensing systems (MDD).[31]

Hospital pharmacy perspective

In-use-shelf-lives should be clear and practical. In the current situation this is not always the case, i.e. it is commonly not known if the lack of an in-use stability claim means that the in-use shelf-life is the same as the shelf-life of the unopened container, or that in-use stability has not been investigated. This situation should be improved. In addition, a badly selected packaging material should not be an excuse for a limited in-use shelf-life, whereas blister packaging may be more appropriate for medications that are sensitive to standard environmental conditions as they ensure stability on a unit dose basis. One should also consider that older patients might not close a vial correctly after opening due to re-opening issues.

3.3 | Category: user information

3.3.1 | Noxafil (Posaconazol)

Case description

The tablets and suspension are not interchangeable as the use of tablets results in higher plasma concentrations. Under- or overdosing has occurred in case of switches between tablets and suspension as the difference was unknown from the product information.

Implications for clinical practice

Healthcare professionals assume different oral dosage forms can be interchanged, unless clearly otherwise indicated. This understanding has been acknowledged by the regulatory authorities. Following multiple incidents, the company has sent out a Direct Healthcare Professional Communication explaining that the product information would be adjusted and that a warning would be added to the outer drug product packaging stating that both dosage forms cannot be interchanged 1:1.[32]

Hospital pharmacy perspective

The measures from the company are considered sufficient, yet the problem should have been considered by the company during drug product development and also by regulators during regulatory approval in the first place i.e. appropriate incentives should have been implemented from the moment both dosage forms were put on the market. Thus, it is important that the suitability of the product design at the time of marketing authorization is not only assessed by industry and regulators on its own merit, but also in the context of other products already on the market.

3.3.2 | Dabigatran (Pradaxa)

Case description

The capsule formulation decomposes due to moisture.

Implications for clinical practice

It should be acknowledged that older people may need to use an MCA or MDD to ease medication management. Where this will result in product decomposition, this should be clear to the users to avoid the risk for increased side effects or lack of efficacy.

Hospital pharmacy perspective

It is essential that tablets and capsules can be stored in MCAs and MDDs to ease medication management and ensure adequate patient adherence. It is expected that companies do their uttermost best to use (advanced) formulation technology to market tablets and capsules that can stand normal environmental conditions for a week to a month without relevant degradation. If this is not possible, information on other approaches is welcomed, e.g. indicating in which MCA and under which conditions the product can be stored otherwise.[33,34] In the Netherlands, hospital pharmacists were offered *dabigatran compliance aids* by the company. This branded aid could help patients to open the blister and to verify whether the product had been taken from the blister. It was however not, a suitable alternative for the smaller standard MCAs or MDDs that can also contain multiple medications in the same pocket.

4 | DISCUSSION

Medication safety requires attention in hospital pharmacy, especially in older people.[4] Realizing that to err is human and learning lessons from the Swiss cheese model, layered measures in risk mitigation in pharmaceutical services (e.g. product development, prescribing, procurement, storage, dispensing, counselling, reimbursement) are essential to reducing the overall patient risk.[35–37] This study identified 14 cases where the drug product design could be a layer to mitigate risk. A 1-month observation period in OLVG hospital revealed 6 additional cases, indicating relevant reporting bias in PPS. This suggests that well-known MRPs are either not reported by healthcare professionals to PPS or not disseminated by PPS to pharmacists. All 20 cases were discussed among experts. It was concluded that the cases had important implications for current clinical and hospital practice.

Currently, there are numerous publications discussing a specific MRP connected with the drug product design. Examples include studies that show that tablets may be difficult to swallow,[38,39] packages difficult to open[40,41] and/or user instructions not well understood.[12] However, general research on this subject matter is scarce and fragmented.[12,42,43] The case selection in this study was executed adopting a hospital pharmacy point of view.

To better acknowledge differences between real-world practice and regulatory principles/requirements, patient centricity has gained increased attention over the last decennia.[44,45] Our study showed how the drug product design including the (corresponding) user instruction(s) may influence clinical efficacy, side effects and user friendliness. This knowledge is useful for companies when developing new drug products, for healthcare professionals upon prescribing, procurement, dispensing and counselling, for insurance companies and experts in health technology assessment (HTA) when deciding on rules for reimbursement and for regulators to consider the need for any new guidance.[31]

In hospitals, seriously ill patients may be treated with expensive parenteral medications. However, it should be realized that short in-use shelf-live increase cost as products may need to be discarded when they have already been prepared in the pharmacy, but the appointment is cancelled or the doctor considers that the patient is too weak to receive the medication. Moreover, short in-use shelf-lives (e.g. shorter than 3 h) imply relevant challenges to hospital logistics. Acknowledging that hospital pharmacies can take adequate measures to prevent microbial contamination, it is important that the user instruction contains information on the product in-use shelf-life from a chemical–physical approach and that this in-use shelf-life is as long as reasonably possible and not based on lack of stability data. Recently, the European Medicines Agency (EMA) took measures to

avoid wastage by defining criteria for newly applied oral dosage forms i.e. the length of the in-use stability study should double the normal duration of use.[46] Measures for oral products already on the market and for other administration routes would also be appreciated.

The importance of user instructions is emphasized by serious and sometimes fatal cases as e.g. accidental swapping of conventional and liposomal amphotericin formulations[47–49] or swapping daily and weekly dosing regimens of methotrexate.[50,51] This indicates that users may not have adequate understanding of some drug delivery approaches and that this would require specific risk mitigation measures in the drug product design such as the package label.

Currently, postmarketing surveillance is well accepted, but commonly focusing on monitoring the drug product safety to detect (rare) adverse drug reactions. We consider that more emphasize should be given to postmarketing surveillance on MRPs and any patient and/or caregiver's burden associated with the product use as required by the EMA Good Vigilance Practice Guideline Module VI.[52] The fact that patients or caregivers can now report adverse drug reactions directly to pharmacovigilance systems in Europe, may help to increase the reporting and subsequently knowledge on these issues.[53] However, the limited number of included cases compared to the number of cases by a small observational study suggest that more awareness and vigilance for MRPs by especially doctors and pharmacists is required.

More multi- and interdisciplinary work is needed to understand real-world hospital pharmacy practice. Human factor studies can be useful to assess which problems can be expected in a specific setting and population.[54] Whereas human factor studies are common in other domains, they are not (yet) in medicines. However, these studies may help assessing the use of medications in patients suffering from e.g. low health literacy, frailty, cognitive or visual decline, and/or limited dexterity. For example, it appeared that older patients do not seem to like liquid dosage forms because it makes them feel being treated as a child.[55] In conformity of the case description for tramadol, all this indicates that liquid and oral solid medications may not be interchangeable from a user acceptability perspective.

From a hospital pharmacy point of view, drug developers in industry and academia, regulators, HTA experts need to think ahead of possible MRPs. Accepting real-world experience by involving healthcare professionals and patients in drug development and exploring the added value of knowledge from other domains such as human factors should become reality for every medication. Medication incident registries provide important opportunities to evaluate the use of medications in real world practice,[19] yet potential underreporting should be considered. International conferences by scientific organizations such as the German APV, the Drug Information Association, the European Geriatric Medicine Society or the European Association of Hospital Pharmacists may provide valuable opportunities to disseminate existing knowledge among different disciplines.

The strength of this study is that the work was conducted by a multidisciplinary team of experts who identified the drug product design as a potential risk mitigation strategy to foster medication safety in older people. However, the study has some limitations also. Firstly, a strict demarcation exists neither among disciplines on definitions nor on what can reasonably be expected by hospital professionals in intercepting a problem. In addition, such demarcations may be country specific as healthcare standards may vary. Rather than debating the demarcation line, we propose that for any item in the *grey zone* stakeholders combine forces and explore what they can do to improve the situation. Secondly, the selected cases from OLVG hospital cannot be fully representative for all hospitals, due to differences in the trademarks purchased. Thirdly, cases were selected by a small expert panel. This methodology was considered sufficiently robust in the context of the aim of this study. A more thorough evaluation according a Delphi procedure is left for future research.

5 | CONCLUSION

Hospital pharmacists face many challenges in ensuring medication safety in older people. As to err is human, it is important to adopt a layered risk prevention strategy. Close collaboration and concerted actions among healthcare professionals, the pharmaceutical industry, academia, regulatory authorities and HTA bodies are important to mitigate the risk of MRPs. Two lessons from this study are that: (i) it is important to pay increased attention to the importance of the product design with regards to its formulation, dose strength and packaging and also to the specific administration requirements of medicines that are not adapted to the real world context of users; (ii) it is important to ensure that the summary of product characteristics/package leaflets of all marketed products are complete and up to date.

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COMPETING INTERESTS

At the start of this study, Birgit van Soest, Florence van Hunsel, Wilma Knol and Diana van Riet-Nales were all members of the Committee on Clinical Practice of the MEB in the Netherlands. At present, Fatma Karapinar is a member of the European Association for Hospital Pharmacists. She holds a certificate in geriatric pharmacy. Diana van Riet-Nales is an expert of the EMA. No other conflicts apply.

CONTRIBUTORS

The contribution of all coauthors is described in the methods section. The following additional information applies. Birgit van Soest provided background information on PPS to all co-authors. All coauthors critically reviewed the paper prior to submission.

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