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High-risk medication in community care : a scoping review

**Reference:**

Dumitrescu Irina, Casteels Minne, De Vlieghe Kristel, Dilles Tinne.- High-risk medication in community care : a scoping review  
European journal of clinical pharmacology - ISSN 0031-6970 - Heidelberg, Springer heidelberg, 76(2020), p. 623-638  
Full text (Publisher's DOI): <https://doi.org/10.1007/S00228-020-02838-8>  
To cite this reference: <https://hdl.handle.net/10067/1662820151162165141>

# High-risk medication in community care: a scoping review

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## Disclaimer

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Funding

This study was not funded.

**Word count main document**

3902

**Contributors**

Conceiving the study: ID, MC and TD

Data extraction: ID and TD

Synthesis of findings: ID and TD

Drafting manuscript: ID

Critical review and revision of manuscript: ID, MC, KDV and TD

**Acknowledgement**

The authors would like to thank the biomedical information specialist from University of Antwerp, Barbara Lejeune, for helping with the development of the search strategy, dr Kristel Paque for the critical review and Anja Thys for copy editing the paper.

**Competing interests**

The authors declare that they have no conflict of interest.

## Abstract

**Purpose:** to review the international literature related to high-risk medication (HRM) in community care, in order to 1) propose a definition of HRM, and 2) list the medication that is considered HRM in community care.

**Methods:** scoping review. Five databases were systematically searched (MEDLINE, Scopus, CINAHL, Web Of Science and Cochrane) and extended with a hand search of cited references. Additional literature was searched as well. Two researchers reviewed the papers independently. All papers were subjected to a self-developed quality appraisal. Data were extracted, analysed and summarised in tables. Critical attributes were extracted in order to analyse the definitions.

**Results:** of the 109 papers retrieved, 36 met the inclusion criteria and were included in this review. Definitions for HRM in home care were used inconsistently among the papers and various recurrent attributes of the concept HRM were used. Taking the recurrent attributes and the quality score of the definitions into account, the following definition could be derived: “High risk medication are medications with an increased risk of significant harm to the patient. The consequences of this harm can be more serious than those with other medications.” A total of 66 specific medications or categories were extracted from the papers. Opioids, insulin, warfarin, heparin, hypnotics and sedatives, chemotherapeutic agents (excluding hormonal agents), methotrexate and hypoglycaemic agents were the most common reported HRM in community care.

**Conclusion:** the existing literature pertaining to HRM in community care was examined. The definitions and medicines reported as HRM in the literature are used inconsistently. We suggested a definition that can be used for future research and policy. Future research is needed to determine more precisely which medications are considered HRM in community care.

## Word count abstract

278

## Keywords

Community care, community health nurses, high-risk medication; home care nurse; medication care

## Contribution of the paper

What is already known about the topic?

- Home health agencies have followed the international accreditation trend, targeting the improvement of care delivery performance at the patients' home.
- In terms of accreditation, high-risk medication management is a Required Organisational Practice, meaning that organisations must have this essential practice in place.

What this paper adds

- In this article we propose a clear and uniformly interpreted definition of high-risk medication in community care to achieve a higher degree of consistency in future research.
- High risk medication in community care are medications with an increased risk of significant harm to the patient. The consequences of this harm can be more serious than with other medications.
- The inconsistent use of the term “high-risk medication in community care” has led to a catch-all concept and an unclear list of medications categorised as such. The list produced in this review can serve as a starting point for a practice guideline for healthcare providers in community care.

## Introduction

A documented and coordinated approach to safely manage high-risk medication (HRM) is an essential standard to be implied in order to obtain a label of accreditation and to improve patient safety [1].

Being pressured by a general accreditation trend and the need for standards of care, many community-based organisations aim for a higher quality of care as well [2]. One of the predetermined standards for organisations addresses all aspects of the medication management process, aiming at the prevention of patient incidents involving medication [3]. Improving the safety of medication management requires a multifaceted approach [4, 5]. It has been suggested that, while aiming to reduce the risk characteristic of medication and improving medication safety, systems should focus on drugs that pose an above average risk of harm [6].

Drug-related problems and adverse drug events are a serious burden to the healthcare system. Studies show that 12 to 25% of patients experience adverse drug events after hospital discharge or when receiving home care, with the majority of these events being preventable [7–11]. This harm, due to the lack of patient safety in this setting, represents 50% of the global healthcare harm burden [12, 13]. Faults in the medication management process should be addressed in order to improve the care and its safety and safely managing medication throughout the entire medication process is vital to ensure positive patient outcomes, reach patient safety goals and decrease healthcare costs.

HRM should be identified through medication error data, literature and organisational policies, instead of hastily drafting a list which doesn't rely on evidence [14]. In addition, each HRM or class should be evaluated, and procedures to improve safe use, such as the use of visible warning labels or providing training, should be identified, in order to set up an action plan [15].

When devising a HRM policy and working out specific guidelines for healthcare professionals in the community care, consensus is needed on what is considered HRM in this setting. A first literature search taught us that there is a variety of HRM lists and definitions for the concept and that clarity is needed in this matter. The terminology is complex as many terms are used interchangeably, and no precise definition of HRM for the community care has been given. This topic needs researching to create awareness and clarity for healthcare providers and the sake of patients' safety. As a first step in developing a HRM policy in community care, the primary objective of this study was to examine and map the existing literature related to HRM in community care and more specifically to:

- 1) Propose a definition of HRM in community care.
- 2) List the medication that is considered HRM in community care.

## Method

A scoping review methodology was used in this study [16–18]. This methodology aims to map key concepts underpinning a research area and is used in areas that have not been reviewed comprehensively before, perfectly fitting our research purpose. The methodological enhancement proposed by Daudt et al (2013) was used. The review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [19].

### Search methods and study selection

Relevant scientific literature was searched in 5 electronic databases: MEDLINE (PubMed), Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL: EBSCOhost), Web Of Science, and Cochrane between January 2018 and April 2018 (ID). A biomedical information specialist was consulted for developing the search strategy. The initial search strategy was developed for MEDLINE and adapted for the other databases. A mix of Medical Subject Headings (MeSH-terms) and free text terms of the following key concepts was used for the search strategy: “high-risk medication, home care services, primary health care, community health nurses” (see Supplement 1). No distinction was made between the use of “high-alert medication” or “high-risk medication”, as these terms are used interchangeably.

Papers were first screened for title and abstract, and by in-depth reading (ID and TD) of the full texts it was ensured that all papers focused on the primary objective of this review. Afterwards, the reference lists of the included papers were manually searched to identify additional relevant papers (ID). The entire study selection was checked by the last author (TD). The selection process and results are reported in a flow diagram according to the PRISMA reporting guidelines (see Figure 1) [19].

### Inclusion and exclusion criteria

We included papers from inception to end of April 2018. This scoping review considered all original studies that provided a clear description, definition and/or list of HRM specifically for the home care setting. To prevent loss of information, papers with multiple relevant settings as target population were also included. For example, studies about hospital discharges, but with HRM use and follow-up period at home, were included. Publications focusing exclusively on HRM use in intramural settings and studies about the increased risk of medication use in specific populations or settings were excluded, i.e. neonatal, obstetrics and gynaecology or paediatric populations, non-therapeutic or non-medical drug consumption or abuse, PWUD (“people who use drugs”) and genomically high risk drugs.

In accordance with the scoping review methodology, no limitation of papers was made based on study type, and the search was restricted to published and peer-reviewed papers with a qualitative or quantitative design [18]. Expert opinions, conference abstracts and reports and papers from organisations were excluded. No specific inclusion criteria were imposed for data collection method,

language or publication date. Papers in foreign languages were reviewed by international colleagues to ensure a correct interpretation of the papers.

## Data extraction

Data was extracted from each study (ID) using a unified self-developed matrix. General characteristics of all included studies were recorded in descriptive tables. For each paper, the HRM definition was extracted, as well as the list of HRM that was used by the author and a reference or source, if this was provided. Considering the aim of our review, study design and results were not used in the analysis of the papers. Unclarities and inconsistencies were discussed (ID and TD). Relevant characteristics of the papers are presented in Table 1.

## Quality appraisal

In line with the used methodology of scoping reviews, no methodological quality appraisal was performed [18]. The intention of this study was to identify and analyse the definitions of HRM used in literature and describe which medication was referred to as HRM. No primary study results of the included papers were used. When examining and assessing the papers, the quality of how authors defined HRM was considered. The research team therefore designed an appraisal tool. Authors either constructed a new definition of HRM, or referred to an existing definition. Quality indicators evaluated the extent to which a definition was constructed using scientifically sound methods, and the quality of the scientific source referred to. The criteria and the ratings are visualised in Box 1.

The “conceptual” quality appraisal based on this rating tool allowed us to thematically examine and assess the definitions used for HRM.

### Box 1: paper appraisal

Score 5: A definition of the concept HRM is developed in the paper. The authors conducted a study about HRM with the purpose to define the concept of HRM and additionally proposed a list of HRM. This paper is considered a key source paper.

Score 4: Both a definition and a list of HRM are reported in the paper, and a reference to a source has been made.

A. A reference to at least one key source (= source with rating 5) is made. Other sources may or may not have been used. (SCORE 4A)

B. A reference to any other source is made, and that source is not a key source. (SCORE 4B)

Score 3: Only a list of HRM is reported in the paper, and a reference to a source has been made. No definition of the concept HRM is reported in the paper.



- A. A reference to at least one key source (= source with rating 5) is made. Other sources may or may not have been used. (SCORE 3A)
- B. A reference to any other source is made, and that source is not a key source. (SCORE 3B)

Score 2: Both a definition and a list of HRM are reported in the paper, and no reference to a source is made. (SCORE 2)

Score 1: Only a list of HRM is reported in the paper, and no reference to a source has been made. No definition of the concept HRM is reported in the paper. (SCORE 1)

No score: The author referred to a paper in which another concept than HRM was defined.

## Data analysis

In order to analyse the evidence and come to the best overall definition, definitions of high quality (level 4 or higher) were selected and recurrent attributes were extracted. Based on the level of supporting evidence and recurrent attributes, we were able to draw up a definition. This is shown in Table 3.

All medications considered HRM by the authors from papers with a quality score of level 3 or higher, were listed. The frequency of inclusion in the list was calculated, creating a list of medications often to seldom considered as HRM in papers with a high quality definition. This is shown in Table 4.

## Results

The search yielded 109 citations and one additional paper was identified from reference lists. After removing duplicates, 79 potentially relevant references were screened for title and abstract. Of these, 22 were removed: 11 papers focused on HRM in another setting, 8 papers reported about persons who used drugs and 3 papers did not report about HRM. In total, 57 papers met criteria for full paper review. After reading the full text, another 21 papers were excluded: 4 papers focused on HRM in another setting, 2 were not available and 12 papers did not report about HRM. From the initial 110 papers, 36 were included in the study.

## Study characteristics

Table 1 presents the characteristics of all 36 papers included in this review. Publication years ranged from 1999 to 2017. Data reported on international studies undertaken in the USA [20–37], Canada [38–41], Northern Ireland [42], Australia [43–46], Germany [47], Finland [48], the UK [49, 50], Scotland [51, 52] and Spain [53]. In two papers, no country was mentioned [54, 55].

The definitions and lists of HRM in the papers were presented from a focus on different healthcare professionals: pharmacists (n = 16), general practitioners (n = 9) and physicians, specialists (n = 7) and nurses (n = 5).

## Quality of papers

In 10 papers, authors referred to or relied on another concept than HRM, such as a definition of medication that should be avoided [33, 49] or drug-drug interactions [48]. As there was no clear definition of HRM, these papers were scored as level 0 and not further considered for analysis [28, 29, 31, 33, 38, 47–49, 52, 54]. Another 9 papers merely provided a list of HRM without a reference (level 1) [20, 21, 25, 26, 30, 34, 39, 46, 51], and 4 papers provided both a list and definition of HRM, again without a reference or supporting evidence (level 2) [27, 35, 45, 50].

The 13 remaining papers all provided or relied on a reference for the HRM list and/or definition. Of these, 3 provided a list of HRM but no definition (level 3) [24, 32, 40]. In the remaining 10 papers, both a list of HRM and a definition of HRM were provided (level 4) [22, 23, 36, 37, 41–44, 53, 55]. No paper in our review scored a level 5. The assessment for each study can be found in Table 2.

## Definitions of HRM

The lack of conceptual clarity necessitated an in-depth analysis of the definitions used in the papers. We aimed to identify and summarise attributes and characteristics related to the concept HRM in those papers with a quality score of level 4 or higher. In each of the 10 papers, we found a different definition for HRM. The source most commonly referred to when defining HRM in these 10 papers, was the Institute for Safe Medication Practice [56–61].

Although definitions for HRM were used inconsistently, several recurrent attributes emerged when defining HRM. These are shown in Table 3. The use of HRM in community care is mostly associated with a risk of certain events [22, 23, 36, 42, 43, 53]. These events can take the form of adverse (drug) events (A(D)Es) in general [37, 43], or more specifically patient harm [23], patient injury [36, 42, 55], falls [22, 44], frailty [44], hospitalisation [44], poor physical function [44] or even patient death [55]. Moreover, four authors described the consequences of HRM use as serious [36, 41, 53, 55], while the other authors did not make this distinction in severity.

When combining these attributes, HRM seem to imply a certain increased risk of ADE. Taking the recurrent attributes into consideration, we carefully propose the following definition for HRM in community care: “HRM are medications with an increased risk of significant harm to the patient. The consequences of this harm can be more serious than those with other medications.”

## Types of HRM

According to our exclusion criteria, papers about increased risks of medication use for children, pregnancy or obstetrics and gynaecology were discarded from the list [36, 37, 53]. When considering all 36 papers, a total of 209 specific medications or categories were cited. When exclusively focusing on those 13 papers that scored a level 3 or higher according to our assessment tool, 66 specific medications or categories were extracted from the articles with a median of 6 medications or categories reported per paper [range 1 – 43], confirming the inconsistent use of the concept of HRM.

In these 13 papers, HRM was reported in an inconsistent way. Only 8 of 66 HRM were mentioned in more than 4 papers, whereas the other 58 HRM were mentioned in 3 papers or less. The 8 most frequently reported medications or categories in community care were opioids (n = 8), insulin (n = 6), warfarin (n = 4), heparin (n = 4), hypnotics and sedatives (n = 4), chemotherapeutic agents (excluding hormonal agents) (n = 4), methotrexate (n = 4) and hypoglycaemic agents (n = 4). When dividing the list according to the class of medications reported, 13 different classes are reported. Drugs used for the cardiovascular or central nervous system, were most commonly listed as HRM. The list of medications in literature that are considered HRM in community care is shown in detail in Table 4. The medications in Table 4 were classified by the research team, based on the overall classification used in the papers.

Despite the clear inclusion criteria of the community care setting during our search, several types of hospital-administered medication, such as intravenous sedation agents and anaesthetic agents, proved to be included in the list during analysis of the HRM list. This indicates that some authors use pre-established lists of medication without adapting them to the reality of the community care setting, but use the list of medication as such [23, 36, 53].

## Discussion

In this review, we aimed to determine which definition can be used uniformly for HRM in community care and which medication can be considered HRM in community care. We analysed the existing literature accordingly. Our findings are that 1) no clear overall definition for this concept exists, although several recurrent attributes were found, and 2) no unique list of HRM for this setting was found. Authors predominantly draw on foreknowledge of medication that is known to involve certain risks, or fragmentary literature, considering only one or several medications as HRM.

The amplitude of different definitions and attributes specific to HRM analysed in this review demonstrate that “high-risk medication” is considered an attractive and superficial catch-all and that clarification is needed.

The most common recurring attribute when defining HRM, is the occurrence of injury or harm (ADEs) as a consequence of HRM use. This harm can come from a medication error and be preventable, occurring in any stage of the medication process. On the other hand, the harm can be non-preventable and occur unintended without a medication error at normal doses and during normal use of the drug [62–64]. While analysing the definitions for HRM in community care in our scoping review, four authors mentioned that the risk of injury resulting from HRM would only exist if the medication is misused or used in error, hereby referring to preventable ADEs [41–43, 53]. It is estimated that between 12% and 25% of patients experience these ADEs when receiving home care or after hospital discharge. A part of these events, more often the more serious events, are indeed preventable [7–11]. However, earlier studies also estimated that in between 6% to 24% of hospitalised patients non-preventable events were present [65–67]. It is unclear whether HRM should be narrowed to medication with a risk of preventable ADEs or also include non-preventable ADEs.

HRM is mostly defined as medication with a heightened risk of events, without a clear cut-off on the level of risk from which medication is considered HRM. In none of the papers, a clear and objective description of what a heightened risk means, was found. On an individual level, it is impossible to predict the probability of harm as this depends on patient-specific criteria (e.g. comorbidity, polypharmacy) and is usually an individual estimate [68]. In general, data comparing the risk of harm between medication is limited, making it difficult to distinguish these higher and lower risks of medication and using a clear cut-off. We suggest the further use of the term ‘heightened risk’ when defining HRM in community care. When analysing the medication associated most with ADEs (both preventable and non-preventable), literature demonstrates that these are mostly cardiovascular drugs, anti-infectives, analgesics, CNS drugs, anticoagulants and opioids. This data is similar to the list of HRM in community care reported in our study [10, 62, 69, 70]. Additional research to define medication-specific risks of ADEs in community care is needed.

Some authors also mentioned the seriousness of the consequences following HRM use, but linked these severe consequences to misuse of HRM and made no measurable distinction between ‘normal’ and ‘severe’ consequences. As was already stated, the use of HRM can potentially cause harm, regardless of its correct or wrong use. With regards to the amount of harm, Sakuma et al demonstrated that several medication classes (more specifically antibiotics and antitumoral agents) are indeed associated with a higher rate of ADEs, but that medication with a higher risk of events doesn’t necessarily induce more severe ADEs [71]. It would therefore be reductive to claim that harm resulting from HRM use has more severe consequences.

The research team excluded reports and papers from organisations and conferences as a source of information. When analysing the sources and methods used by the authors in the papers to define HRM (with a quality level of 4 or higher), no less than 7 out of 10 authors referred to the Institute of Safe Medication Practice as their source [23, 36, 41–43, 53, 55]. Our proposed list and definition therefore coincide largely with their data, but also takes other literature into account.

Even though there is some linguistic uncertainty whether injuries due to HRM result from an error in the medication process (preventable ADE) or from the use of medication (ADR), one can expect that both types of harm can occur during the use of HRM, and a definition should encompass both. We propose using the term ‘harm’ to cover both the preventable and non-preventable ADEs in HRM use. Future research should however focus on the prevalence of ADR in home care patients to fill this gap. In addition, the heightened risk of the consequences is undeniable, but the severity of harm is unclear. Therefore, derived from the relevant papers in this review, we carefully propose the following definition for HRM in community care: “HRM in community care are medications with an increased risk of significant harm to the patient. The consequences of this harm can be more serious than those with other medications.”

Evidence should be offered in a summarised way to policymakers in order for it to be user-friendly [72]. In contrast to papers that focus on merely one or a few medications, we provide a complete list of medications that have been described in literature as HRM in community care. Even though this list of HRM can be considered vast and should be further refined to exclude medication that is not administered in a community setting, it can form the basis for researchers or community-based organisations to further develop their HRM-policy. After all, organisations are required to identify organisation-specific risks and incidents and thus determine which HRM will be addressed in their policy and clinical practice, thereby reducing this proposed list [15, 73]. A periodic evaluation of an organisation-specific list is also necessary to continuously identify new areas of improvement in medication management. Future research can also draw on this exhaustive list and refine it for a specific group of healthcare professionals, such as community care nurses or for specific patient settings, such as community-dwelling older adults.

## Strengths and limitations

Our study has many important strengths. Firstly, the scoping review methodology is based on earlier work of Arksey and O'Malley's six-stage framework. Later on, the method has been updated by Levac and colleagues and a methodological enhancement was proposed by Daudt et al. in 2013 [16, 17, 74]. Our scoping method has been enhanced in such a way that it can provide a rigorous and transparent method for examining evidence on a topic or question in specific research areas and thus allows the robust reporting of findings [16, 74, 75]. Secondly, very recently, the PRISMA guideline was also extended for Scoping Reviews, providing the possibility of a higher reporting quality. Our review gained methodological rigour through the use of a robust methodological approach according to previously cited guidelines and the guidance of the PRISMA protocol [16, 19, 74, 75]. Finally, our scoping review was enhanced through a quality appraisal of the included evidence, developed in the context of this study.

Certain limitations have to be acknowledged. It is possible that this review did not identify all available and relevant published or grey literature sources. A biomedical information specialist supported the work, addressing this potential limitation.

Many authors did not provide scientifically sound arguments in defining and listing HRM. Starting from these papers, we developed a definition, aiming for a more clear and consistent use of the concept in the future. However, some critical attributes of the definition are vague, such as 'a heightened risk' and 'significant harm', still allowing authors to freely interpret these concepts.

## Conclusion

In summary, we examined the existing literature pertaining to HRM in community care. Despite the inconsistencies in the definitions found in the relevant literature, the following definition can be proposed: "High risk medication in community care are medications with an increased risk of significant harm to the patient. The consequences of this harm can be more serious than those with other medications." A comprehensive list of 66 medications is extracted from the literature and forms the basis for the further development of healthcare organisations' medication management policies. Future research, focused on refining this list and possible interventions aimed at HRM in a community setting, could improve medication care and enhance the safety of patients in community care.

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## Tables

**Table 1: description of papers (in chronological order, then alphabetical for the author's name)<sup>1</sup>**

Nr. paper	First author	Year	Country	Setting	Healthcare professionals in the study	Definition of HRM, as used by the author	Source or method of definition
1	Homsted	2017	Maine, United States	Community Care	<ul style="list-style-type: none"> <li>• Care management social worker</li> <li>• Nurse Practitioner</li> <li>• Pain specialist</li> <li>• Pharmacists</li> <li>• Physician</li> <li>• Psychiatrist</li> </ul>	NP	NP
2	Hu	2017	Ontario, Canada	Academic Family Health Team	<ul style="list-style-type: none"> <li>• Family physician</li> </ul>	NP	<ul style="list-style-type: none"> <li>• Beers Criteria [76]</li> <li>• ARS [77]</li> </ul>
3	MacCallum	2017	Ontario, Canada	Community care	<ul style="list-style-type: none"> <li>• Community pharmacists</li> </ul>	NP	NP
4	Robb	2017	Northern Ireland	Community care	<ul style="list-style-type: none"> <li>• District nurses</li> </ul>	A medicine that has the highest risk of causing patient injury when misused.	<ul style="list-style-type: none"> <li>• Institute for Safe Medication Practices (ISMP) [56]</li> <li>• UK National Patient Safety Agency [78]</li> </ul>
5	Elliott	2016	Melbourne, Australia	Community care	<ul style="list-style-type: none"> <li>• Community nurses</li> </ul>	Medicines associated with heightened risk of an adverse medication event if taken or administered incorrectly.	ISMP [57]
6	Freyer	2016	Baden-Württemberg, Germany	Hospital (discharge)	<ul style="list-style-type: none"> <li>• Pharmacists</li> </ul>	Active substances or active ingredient groups with a particularly high potential for adverse drug effects.	Literature [54]

<sup>1</sup> NP = not provided; GP = General practitioner

Nr. paper	First author	Year	Country	Setting	Healthcare professionals in the study	Definition of HRM, as used by the author	Source or method of definition
7	Kouladjian	2016	Australia	Community care, general practitioners, hospital	<ul style="list-style-type: none"> <li>Pharmacists</li> <li>GP</li> <li>Specialists</li> </ul>	The use of the medications has been associated with adverse events (AEs) such as falls, frailty, hospitalization, and poor physical function in older adults.	<ul style="list-style-type: none"> <li>Literature [79]</li> <li>Drug Burden Index (DBI) [80]</li> </ul>
8	Phatak	2016	Illinois, United States	Hospital (discharge)	<ul style="list-style-type: none"> <li>Pharmacists</li> </ul>	NP	NP
9	Takahashi	2016	Minnesota, United States	Primary care	NP	NP	NP
10	Toivo	2016	Finland	Community care	<ul style="list-style-type: none"> <li>Community pharmacists</li> </ul>	Medication causing potential DDIs (drug-drug interactions), which have shown to be a significant cause for adverse drug events (ADEs).	Drug-drug interactions according to the FASS classification (class C & D cause clinically significant potential DDI) [81]
11	Ble	2015	UK	Primary care	<ul style="list-style-type: none"> <li>GP</li> </ul>	We defined HRM using the 2012 Beers' criteria, a list of 53 medications or medication classes potentially harmful in the older population. We focused on the 34 drugs or drug classes defined as 'drugs to avoid in older adults'.	Beers Criteria adapted for the UK [76]
12	Gilmore	2015	Baltimore, United States	Hospital, inpatient and outpatient (post-discharge follow-up)	<ul style="list-style-type: none"> <li>Inpatient and outpatient pharmacy teams</li> </ul>	NP	<ul style="list-style-type: none"> <li>Literature [82]</li> <li>Common knowledge</li> </ul>
13	McCarthy	2015	United States	Hospital (discharge)	NP	NP	Expert opinion (majority of prescriptions in own organisation)
14	Rushworth	2015	Scotland	Primary care	NP	NP	NP
15	Pugh	2014	United States	Hospital (readmission)	NP	The HEDIS HRME measure included some, but not all of the drugs included on the Beers criteria, retaining only those for which there was consensus that 1)	HEDIS High-Risk Medication in the Elderly (HRME) drugs [83]

Nr. paper	First author	Year	Country	Setting	Healthcare professionals in the study	Definition of HRM, as used by the author	Source or method of definition
						they should be avoided and 2) outcomes were considered high severity.	
16	Saedder	2014	NP	All (hospital, nursing home, home care)	NP	Drugs that actually cause serious MEs	<ul style="list-style-type: none"> <li>• Screening Tool of Older Person's Prescriptions (STOPP) [84]</li> <li>• Beers [85]</li> <li>• Inappropriate Prescribing in the Elderly Tool (IPET) [86]</li> </ul>
17	Taha	2014	United States	Hospital (readmission)	NP	NP	NP
18	Iniesta-Navalon	2013	Spain	Hospital (admission)	NP	HRM have a heightened risk due to the seriousness of the errors that these type of drugs entail, and where the implementation of procedures for its management during hospitalization is strongly recommended.	ISMP [58]
19	Martin	2013	United States	Hospital (discharge)	<ul style="list-style-type: none"> <li>• Pharmacists</li> </ul>	High-risk medications were defined as those whose unintentional omission from discharge documents could give rise to significant harm (and with little warning) during the interval between a patient's discharge and his or her first post-discharge physician visit.	NP
20	Broadhurst	2012	Canada	Home care	<ul style="list-style-type: none"> <li>• (Infusion) Nurses</li> </ul>	NP	ISMP [60]
21	Cohen	2012	United States	Community care	<ul style="list-style-type: none"> <li>• Pharmacists</li> </ul>	High-alert medications carry a major risk of causing serious injuries or death to patients if misused. Errors with these drugs are not necessarily more common, but the consequences are devastating.	<ul style="list-style-type: none"> <li>• ISMP National Medication Errors Reporting Program [59]</li> <li>• Pennsylvania Patient Safety Reporting System [87]</li> <li>• Food and Drug Administration MedWatch database [88]</li> </ul>



Nr. paper	First author	Year	Country	Setting	Healthcare professionals in the study	Definition of HRM, as used by the author	Source or method of definition
							<ul style="list-style-type: none"> <li>databases from participating pharmacies</li> <li>community pharmacy survey data [89]</li> <li>public litigation data [90]</li> <li>literature review</li> </ul>
22	Dreischulte	2012	UK	Primary care	<ul style="list-style-type: none"> <li>GP</li> <li>Pharmacists</li> </ul>	Drugs that have been shown to either commonly cause harm and/or cause severe harm in primary care.	NP
23	Foust	2012	United States	Hospital (discharge)	NP	Medications were identified as “high risk” if they fell within one of the six medication classifications associated with a majority (87%) of post-hospital ADEs	Literature [69]
24	Gaunt	2012	NP	Community Care	NP	High-alert medications carry a significant risk of causing serious injury or death to patients when they are used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients.	ISMP [57]
25	Stafford	2012	Australia	Hospital (discharge), primary care	<ul style="list-style-type: none"> <li>GP</li> <li>GP practice managers</li> <li>Haematologists</li> <li>Nurses</li> <li>Stroke physician</li> <li>Community and hospital pharmacists</li> <li>Patients</li> </ul>	Warfarin is recognized as a high-risk medication for adverse events, and the risks are particularly heightened in the period immediately following a patient’s discharge from hospital.	NP
26	Guthrie	2011	Scotland	Primary care	<ul style="list-style-type: none"> <li>GP</li> </ul>	We defined a new set of indicators of hazardous prescribing for drugs prescribed in situations identified as clearly high risk in national safety alerts	Literature [91]

Nr. paper	First author	Year	Country	Setting	Healthcare professionals in the study	Definition of HRM, as used by the author	Source or method of definition
						and commonly implicated in serious harm, as measured by emergency hospital admission due to an adverse drug event.	
27	Stafford	2011	Australia	Hospital (discharge)	• Community pharmacists	NP	NP
28	Blalock	2010	North Carolina, United States	Community care	NP	Medications that have been associated with an increased risk of falling	Literature [92]
29	Unroe	2010	North Carolina, United States	Hospital (discharge)	• Pharmacists	The medications have a higher risk of patient harm, a higher risk of subtherapeutic and suprathreshold drug concentrations, or both.	<ul style="list-style-type: none"> <li>• ISMP [61]</li> <li>• North Carolina Narrow Therapeutic Index (NTI) list [93]</li> </ul>
30	Jones	2009	Alberta, Canada	Hospital - community	• Pharmacists	Warfarin has been identified in hospitals as a high-alert medication, as errors in dosage or administration can have severe consequences.	ISMP [60]
31	Ferreri	2008	Carolina, United States	Community care	• Pharmacists	NP	Literature [94–97]
32	Leonard	2008	United States	Hospital (discharge)	• Pharmacists	NP	NP
33	Fenton	2006	Washington, United States	Primary care	• GP	NP	NP
34	Metlay	2005	Pennsylvania, United States	Community care	• Pharmacists	Narrow therapeutic windows resulting in above-average risk of serious adverse events	NP
35	Counsell	2000	Ohio, United States	Community care	NP	NP	Beers Criteria [98]

Nr. paper	First author	Year	Country	Setting	Healthcare professionals in the study	Definition of HRM, as used by the author	Source or method of definition
36	Coleman	1999	Seattle, United States	Primary care	<ul style="list-style-type: none"> <li>Primary care physician</li> </ul>	<p>Those medications for which there is empirical evidence regarding the potential to threaten functional status in older adults. The main adverse effects targeted were confusion, sedation, mental status changes, and predisposition to inducing orthostatic hypotension. By referring to these medications as high-risk we did not mean to imply that there would be no acceptable indication for these medications. Rather, we attempted to account for the cumulative effect of risk incurred by repeated prescribing of medications that are associated with a significant risk for adverse outcomes in older adults.</p>	<ul style="list-style-type: none"> <li>Literature [99, 100]</li> <li>Discussions with national experts</li> <li>Knowledge of the pharmacologic effects in older patients (e.g., longer half-life)</li> </ul>

**Table 2: quality assessment (in descending order of the final score) for all papers**

First author	Year	List and definition	Only a list	Reference provided?	Does the reference relate the definition to <u>HRM</u> ?			Final score
					Yes, and a key source is used (level score A)	Yes, and no key source is used (level score B)	No, the definition is related to <u>another concept</u> (level 0)	
Jones	2009	X		Yes	Yes			4A
Unroe	2010	X		Yes	Yes			4A
Gaunt	2012	X		Yes	Yes			4A
Cohen	2012	X		Yes	Yes			4A
Iniesta-Navalon	2013	X		Yes	Yes			4A
Elliott	2016	X		Yes	Yes			4A
Robb	2017	X		Yes	Yes			4A
Blalock	2010	X		Yes		Yes		4B
Foust	2012	X		Yes		Yes		4B
Kouladjian	2016	X		Yes		Yes		4B
Broadhurst	2012		X	Yes	Yes			3A
Ferreri	2008		X	Yes		Yes		3B
McCarthy	2015		X	Yes		Yes		3B
Metlay	2005	X		No				2
Stafford	2012	X		No				2
Dreischulte	2012	X		No				2
Martin	2013	X		No				2
Fenton	2006		X	No				1
Leonard	2008		X	No				1
Stafford	2011		X	No				1
Taha	2014		X	No				1
Rushworth	2015		X	No				1
Phatak	2016		X	No				1
Takahashi	2016		X	No				1
MacCallum	2017		X	No				1
Homsted	2017		X	No				1
Coleman	1999	X		Yes		Yes		0
Counsell	2000		X	Yes		Yes		0
Guthrie	2011	X		Yes		Yes		0

First author	Year	List and definition	Only a list	Reference provided?	Does the reference relate the definition to <u>HRM</u> ?			Final score
					Yes, and a key source is used (level score A)	Yes, and no key source is used (level score B)	No, the definition is related to <u>another concept</u> (level 0)	
Saedder	2014	X		Yes			Yes	0
Pugh	2014	X		Yes			Yes	0
Gilmore	2015		X	Yes			Yes	0
Ble	2015	X		Yes			Yes	0
Toivo	2016	X		Yes			Yes	0
Freyer	2016	X		Yes			Yes	0
Hu	2017		X	Yes			Yes	0

**Table 3: analysis of HRM definitions and recurrent attributes (in chronological order, then alphabetical for the author’s name) for papers with score 4 or higher**

Author	Year	Definition used	Recurrent attributes							
			Risk	ADE	Harm	Injury, falls	Death	Serious	Error/misuse	Procedure
Robb	2017	A medicine that has the highest risk of causing patient injury when misused	X			X			X	
Elliott	2016	Medicines associated with heightened risk of an adverse medication event if taken or administered incorrectly	X	X					X	
Kouladjian	2016	The use of the medications has been associated with adverse events (AEs) such as falls, frailty, hospitalization, and poor physical function in older adults.		X		X				
Iniesta-Navalon	2013	HRM have a heightened risk due to the seriousness of the errors that these type of drugs enfold, and where the implementation of procedures for its management during hospitalization is strongly recommended	X						X	X
Cohen	2012	High-alert medications carry a major risk of causing serious injuries or death to patients if misused. Errors with these drugs are not necessarily more common, but the consequences are devastating.	X			X	X	X	X	
Foust	2012	Medications were identified as “high risk” if they fell within one of the six medication classifications associated with a majority (87%) of post-hospital ADEs		X						
Gaunt	2012	High-alert medications carry a significant risk of causing serious injury or death to patients when they are used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients.	X			X	X	X	X	

Blalock	2010	Medications that have been associated with an increased risk of falling	X			X				
Unroe	2010	The medications have a higher risk of patient harm, a higher risk of subtherapeutic and supratherapeutic drug concentrations, or both.	X		X					
Jones	2009	Warfarin has been identified in hospitals as a high-alert medication, as errors in dosage or administration can have severe consequences.			X			X	X	

**Table 4: HRM in home care (in chronological order, then alphabetical for the author's name) for papers with score 3 or higher<sup>2</sup>**

Category	Robb 2017	Elliott 2016	Koula- djian 2016	Mc Carthy 2015	Iniesta- Navalo n 2013	Broad- hurst 2012	Cohen 2012	Foust 2012	Gaunt 2012	Blalock 2010	Unroe 2010	Jones 2009	Ferreri 2008	n (%) <sup>3</sup>
Cardiovascular drugs														
· <i>cardiovascular drugs</i>							X							1 (8%)
· nesiritide											X			1 (8%)
· nitroprusside sodium for injection					X						X			2 (15%)
· digoxin											X			1 (8%)
· <i>adrenergic agonists, iv</i>					X						X			2 (15%)
· <i>adrenergic antagonists, iv</i>					X						X			2 (15%)
· <i>antiarrhythmics, IV</i>					X									1 (8%)
· amiodarone											X			1 (8%)
· procainamide hydrochloride											X			1 (8%)
· <i>antiplatelets (mono or dual)</i>					X									1 (8%)
· glycoprotein iib/iiia inhibitors											X			1 (8%)
· <i>cardioplegic solutions</i>					X						X			2 (15%)

<sup>2</sup> Corrected for medication for children, pregnancy or obstetrics and gynaecology

<sup>3</sup> Number of papers reporting the medication as HRM (absolute and relative), from a total of 13 papers

General categories of medications are indicated in italics



Category	Robb 2017	Elliott 2016	Koula- djian 2016	Mc Carthy 2015	Iniesta- Navalo n 2013	Broad- hurst 2012	Cohen 2012	Foust 2012	Gaunt 2012	Blalock 2010	Unroe 2010	Jones 2009	Ferreri 2008	n (%) <sup>3</sup>
· <i>inotropic medications, iv</i>					X						X			2 (15%)
Blood and coagulants														
· <i>thrombolytics</i>					X						X			2 (15%)
· <i>(oral) anticoagulants</i>		X			X			X						3 (23%)
· warfarin							X		X		X	X		4 (31%)
· epoprostenol, IV					X									1 (8%)
· heparin					X		X		X		X			4 (31%)
Pain medication														
· colchicine injection											X			1 (8%)
· <i>analgesics</i>								X						1 (8%)
· <i>narcotics</i>											X			1 (8%)
· <i>opioids</i>		X		X	X		X		X	X	X		X	8 (62%)
Central nervous system drugs														
· lithium		X									X			2 (15%)
· <i>hypnotics &amp; sedatives</i>			X							X	X		X	4 (31%)
· <i>moderate sedation agents, IV</i>					X									1 (8%)
· <i>antidepressants</i>										X			X	2 (15%)

Category	Robb 2017	Elliott 2016	Koula- djian 2016	Mc Carthy 2015	Iniesta- Navalo n 2013	Broad- hurst 2012	Cohen 2012	Foust 2012	Gaunt 2012	Blalock 2010	Unroe 2010	Jones 2009	Ferreri 2008	n (%) <sup>3</sup>
· <i>anticonvulsants - antiepileptics</i>								X		X			X	3 (23%)
· carbamazepine							X		X		X			3 (23%)
· ethosuximide											X			1 (8%)
· phenytoin											X			1 (8%)
· <i>antipsychotics</i>										X			X	2 (15%)
· <i>benzodiazepines</i>										X			X	2 (15%)
· <i>anticholinergic - anti parkinsonian drugs</i>			X											1 (8%)
· <i>skeletal muscle relaxants</i>										X			X	2 (15%)
Gastrointestinal medication														
· <i>intestinal antispasmodics</i>													X	1 (8%)
Anaesthesia														
· <i>anaesthetic agents, general, inhaled and iv</i>											X			1 (8%)
· <i>neuromuscular blocking agents</i>					X						X			2 (15%)
· lidocaine, iv											X			1 (8%)
Antitumoral drugs														

Category	Robb 2017	Elliott 2016	Koula- djian 2016	Mc Carthy 2015	Iniesta- Navalo n 2013	Broad- hurst 2012	Cohen 2012	Foust 2012	Gaunt 2012	Blalock 2010	Unroe 2010	Jones 2009	Ferreri 2008	n (%) <sup>3</sup>
· <i>chemotherapeutic agents excluding hormonal agents</i>		X												1 (8%)
· <i>chemotherapeutic agents, oral excluding hormonal agents</i>					X		X		X		X			4 (31%)
· <i>chemotherapeutic agents, parenteral</i>					X						X			2 (15%)
· methotrexate					X	X	X		X		X			5 (38%)
Hormonal drugs														
· levothyroxine											X			1 (8%)
· propylthiouracil							X		X					2 (15%)
· corticosteroids								X						1 (8%)
Diabetes														
· <i>hypoglycaemic agents</i>					X		X		X		X			4 (31%)
· metformin							X		X					2 (15%)
· insulin	X	X			X		X		X		X			6 (46%)
Infections														
· <i>antibiotics</i>								X						1 (8%)
· <i>antiretroviral agents</i>							X		X					2 (15%)

Category	Robb 2017	Elliott 2016	Koula- djian 2016	Mc Carthy 2015	Iniesta- Navalo n 2013	Broad- hurst 2012	Cohen 2012	Foust 2012	Gaunt 2012	Blalock 2010	Unroe 2010	Jones 2009	Ferreri 2008	n (%) <sup>3</sup>
Immunity														
· immunosuppressants		X					X		X					3 (23%)
· cyclosporine											X			1 (8%)
· promethazine					X									1 (8%)
Respiratory drugs														
· theophyllin											X			1 (8%)
Minerals, vitamins, etc														
· potassium phosphates injection					X						X			2 (15%)
· potassium chloride for injection concentrate							X				X			2 (15%)
· magnesium sulfate injection					X						X			2 (15%)
· sodium chloride injection, hypertonic					X						X			2 (15%)
· hypertonic glucose solutions ( $\geq 20\%$ )					X						X			2 (15%)
· sterile water for injection, inhalation and irrigation (excluding pour bottles) in containers of 100 mL or more							X							1 (8%)

Category	Robb 2017	Elliott 2016	Koula- djian 2016	Mc Carthy 2015	Iniesta- Navalo n 2013	Broad- hurst 2012	Cohen 2012	Foust 2012	Gaunt 2012	Blalock 2010	Unroe 2010	Jones 2009	Ferreri 2008	n (%) <sup>3</sup>
Other														
· epidural or intrathecal medications					X						X			2 (15%)
· liposomal forms of drugs					X						X			2 (15%)
· NTI (narrow therapeutic index) medications											X			1 (8%)
· dialysis solutions, peritoneal and haemodialysis							X				X			2 (15%)
· total parenteral nutrition solutions					X						X			2 (15%)
· radiocontrast agents, iv					X						X			2 (15%)
<b>Total number of medications reported per paper</b>	<b>1</b>	<b>6</b>	<b>2</b>	<b>1</b>	<b>31</b>	<b>1</b>	<b>12</b>	<b>6</b>	<b>12</b>	<b>7</b>	<b>43</b>	<b>1</b>	<b>8</b>	