BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019101
Article Type:	Research
Date Submitted by the Author:	11-Aug-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology, General practice / Family practice, Global health
Keywords:	medication errors, adverse drug events, error-related adverse drug events, prevalence, incidence, risk factor

Investigating the Epidemiology of Medication Errors and Error-related Adverse Drug Events in Adults in Primary Care, Ambulatory Care and Home Settings: a Systematic Review

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Keywords: medication errors, adverse drug events, error-related adverse drug events, drug related problems, prevalence, incidence, risk factor, primary care, ambulatory care, home setting, and adult.

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Strengths:

- It is the first review undertaken within community settings.
- A rigorous and transparent process has been employed, which included no language restrictions, an independent screening of titles and abstracts, independent data extraction and critical appraisal of included studies by two reviewers.
- The use of the International Classification for Patient Safety (ICPS) conceptual framework, which provides a comprehensive definition of each concept and type of error in the medicines' management process.

Limitations:

- This systematic review had different outcomes reported in a variety of ways using different tools and methodology that made combining results in one meta-analysis difficult.
- Despite the thorough process, no data were found regarding the dispensing and administration errors stage. This might be due to the lack of a 'dispensing error' and 'administration error' key-term in our search strategy, although 'medication therapy management' as a key-term was included.
- The studies addressed risk factors adjusted for different confounders, which makes it difficult to have one specific summary estimate.

Abstract

Objectives: To investigate the epidemiology of medication errors and error-related adverse events in adults in primary care, ambulatory care and patients' homes.

Design: Systematic review.

Data source: The Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Eastern Mediterranean Regional Office of the World Health Organization (WHO EMRO), MEDLINE, PsycINFO, and Web of Science were searched for publications between 1st January 2006 and 31st December 2015. A manual review of the bibliographies of all included studies was also conducted.

Data extraction and analysis: Two researchers independently extracted data from eligible studies including study setting, the number of patients included, incidence and/or prevalence of the outcomes and risk factors. The quality of the studies was independently assessed using the Critical Appraisal Skills Program (CASP) quality assessment tool for cohort and case-control studies and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Descriptive Studies for cross-sectional studies. Any disagreements were resolved by consensus or, if necessary, arbitration by a third reviewer. Synthesis of data was informed by an appreciation of the medicines' management process and the conceptual framework from the International Classification for Patient Safety (ICPS).

Results: 60 studies met the inclusion criteria, of which 53 studies focused on medication errors, three on error-related adverse events and four studies on risk factors only. The prevalence of prescribing errors was reported in 46 studies: prevalence estimates ranged widely from 2 - 94%. Inappropriate prescribing was the most common type of error reported. Only one study reported the prevalence of monitoring errors, finding that incomplete therapeutic/safety laboratory-test monitoring occurred in 73% of patients. The incidence of preventable adverse drug events (ADEs) was estimated as 15/1000 person-years, the prevalence of drug-drug interaction (DDI) -related adverse drug reactions (ADR) as 7% and the prevalence of preventable ADE as 0.4%. A number of patient, healthcare professional and medication-related risk factors were identified, including the number of medications used by the patient, increased patient age, the number of diseases or comorbidities, use of anticoagulants, cases where more than one

physician was involved in patients' care and care being provided by family physicians/general practitioners (GP).

Conclusion: A very wide variation in the medication-error and error-related adverse events rates is reported in the studies. This could be explained, at least in part, by clinical heterogeneity (i.e. differences in the populations studied), different methodologies employed for error detection and differences in the outcome measures (i.e. definitions of errors and adverse events). This review has identified important limitations and discrepancies in the methodologies used and gaps in the literature on the epidemiology and outcomes of medication errors in community settings.

Introduction

Patient safety is a public concern in healthcare systems across the world.(1) Medication errors (ME) and error-related adverse drug events (ADEs) are common and are responsible for considerable patient harm.(1) More specifically, ADEs can lead to morbidity, hospitalisation, increased healthcare costs and, in some cases, death.(1) It has been estimated that 5-6% of all hospitalisations are drug-related,(2, 3) with one estimate suggesting that ADEs causing hospital admission in the United Kingdom (UK) occur in around 10% of inpatients; approximately half of these ADEs are believed to be preventable.(4) The cost of drug-related morbidity and mortality was estimated in 2001 to be $177.4 billion annually in the United States of America (USA) alone.(5)

Since the release of *To Err is Human: Building a Safer Health System* by the Institute of Medicine (IOM)(6), which focused on acute care settings, most patient safety research has been conducted in hospital settings.(7, 8) Given that patients are increasingly managed in primary, ambulatory and home settings, there is an increased sense of urgency to further focus attention on community care contexts, particularly in relation to medication safety. With an aging population, particularly in economically-developed countries, as well as the use of polypharmacy, there is a need to empower patients, particularly those with chronic diseases, to self-care *safely*.

The aim of this systematic review is to investigate the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts (i.e. primary care, ambulatory and home settings). Box 1 provides definitions of the key terms employed in this review.

Methods

Protocol and reporting

The study protocol was developed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and was registered in PROSPERO.(9, 10) The detailed systematic review protocol has also been published.(11)

Eligibility criteria/ study selection:

Studies conducted in adults (≥18 years) who were looked after in the community and living in their own or family homes without home healthcare or nursing home were eligible for inclusion in this review. The studied patients could have been self-managing, receiving care in primary care or ambulatory care settings, or any combination of the above. Studies were included if they were population-based, cross-sectional or cohort studies, which were suitable to estimate the incidence and prevalence of medication errors or ADEs. These study designs and case-control studies were considered eligible to study risk factors for the development of error-related ADEs. Studies with prescribed and/or over-the-counter (OTC) medications as the exposure of interest were eligible.

Paediatric studies (<18 years) and studies on patients receiving care in hospital at home settings (i.e. continuous medical and/or nursing care provided to patients in their own homes), in nursing homes, as hospitalised in-patients or in emergency departments (ED) were excluded. Randomised controlled trials (RCT) were excluded since these could not be used to reliably assess the incidence and/or prevalence of the outcomes of interest. Existing reviews were also excluded since the focus was on the primary literature. Incompletely reported studies, e.g. in the form of abstracts, were not eligible for inclusion. Studies on illegal substance abuse, herbal products and those focusing on particular medications, were also excluded.

No restriction on the language of publication was employed.

Data sources and search strategy

Search terms were developed based on the systematic review protocol.(11) The search terms and detailed search strategies are presented in Appendix 1. Six biomedical databases were searched, including the Cumulative Index to Nursing and Allied Health

Literature (CINAHL), EMBASE, Eastern Mediterranean Regional Office of the World Health Organization (WHO EMRO), MEDLINE, PsycINFO, and Web of Science between 01 January 2006 and 31 December 2015. Google Scholar was searched for additional studies. An international panel of experts was also contacted to identify unpublished work and research in progress (Appendix 1). The reference list of all included studies was further reviewed for additional possible eligible studies.

The databases were searched by Ghadah Assiri (GA). The title and abstracts were then independently screened for eligible studies according to the above detailed selection criteria by GA and a second reviewer, Nada Shebl (NS). The corresponding authors of the eligible articles were contacted if additional information was needed. Disagreements were resolved by discussion between the reviewers or by arbitration by a third reviewer, Aziz Sheikh (AS), if a decision could not be reached. Full-text articles were retrieved from selected studies and reviewed according to the selection criteria. Each copy of the selected studies was retrieved and the reason for excluding other studies was clearly noted.

Data extraction and risk of bias assessment

Data were independently extracted and recorded onto a customised data extraction sheet by two reviewers [GA and NS, or GA and Mansour Mahmoud (MM)]. Discrepancies were resolved by discussion or by arbitration by an additional reviewer (AS), if necessary.

Key information such as study design, study type (retrospective, prospective), population of interest, exposure of interest, outcomes of interest and main findings were extracted.

The risk of bias assessment was independently carried out on each study by two reviewers [GA and NS, or GA and Nouf Aloudah (NA)] using the Critical Appraisal Skills Program (CASP) quality assessment tool for cohort and case-control studies,(12) and cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Descriptive Studies.(13) Any disagreements were resolved by consensus or by arbitration by a third reviewer (AS) if a decision could not be reached. Each study was given an overall grading as being at high, medium, or low risk of bias.

Data synthesis

Data were summarised in detailed data tables, which included information on the incidence, prevalence, relative risk and odds ratios (ORs), together with 95% confidence intervals, for each study (where available). A descriptive and narrative synthesis of the extracted data was undertaken.

The definition of incidence rate used in this review is: *"the number of patients with one or more [medication error or preventable ADE] (numerator) divided by the total number of patients at risk per time unit (denominator)."*(14) The definition of prevalence rate used in the data extraction is: *"the number of patients experiencing one or more [medication error or preventable ADE] (numerator) divided by the total number of patients in the study population (denominator)."*(15) The prevalence rate per population was either reported and extracted directly from the study or calculated from data provided in the included study.

We worked with the definitions of medication errors and error-related ADEs employed in individual studies. These errors may have occurred anywhere in the medicines' management process.(1) Medication errors were described according to: i). the stage in the medicines' management process when the error occurred i.e. prescribing, dispensing, administration and monitoring;(1) and ii). the type of error that occurred in each stage according to the conceptual framework for the International Classification for Patient Safety (ICPS) definitions (Box 2).(16)

Risk factors were categorised as patient, healthcare professional and medication-related risk factors.

Changes from the original protocol

The following changes were made from the plans described in the research protocol:(11) i). due to the large quantity of studies found during the initial search and because of medications and practice changes over the years, only studies published in the last 10 years were included: 01 January 2006 to 31 December 2015; ii). only studies with the incidence or prevalence rate per number of patients were included; and iii). meta-analysis was not possible due to the heterogeneity of outcomes, methods and definitions.

Results

A total of 13,033 potentially eligible studies were identified after removing duplicates, of which 59 studies met the inclusion criteria. One additional study was identified through hand-searching. Therefore, a total of 60 studies were included in the systematic review (Figure 1).

One study was available only in German, and one in Spanish. Those two papers were retrieved and translated into English by native speakers.(17, 18)

The key characteristics of all included studies are presented in Table 1. The quality assessments of these studies are summarised in Table 2.

Nine studies were conducted in Asia, four in Australia, 32 in Europe, eight in the North America, five in South America, and two were conducted across continents [one study covering two Australian countries, three European countries, one North American country and one South American country,(19) and one study across two Australian countries, four European countries, one North American country and one South American country].(20) Twenty-one studies were conducted in primary healthcare or general practice contexts, 19 studies in community settings, nine studies in ambulatory care or outpatient settings, five studies in community pharmacies, two studies in post-discharge settings and one study in a home setting, while three studies used secondary data analysis.

Eleven studies enrolled adults in all age groups (>18 years), three studies reported the mean age only,(21-23) one enrolled those of 55 years or older,(24) five enrolled those aged 60 years or older ,(25-29) and the majority of studies (n=40 studies, 67%) enrolled patients of 65 years or older. If the study included adult and paediatric data, only relevant adult data were extracted.

The quality of the cross-sectional or descriptive studies using the JBI Critical Appraisal Checklist was high for nine studies, moderate for 10 studies and low for one study. The quality of the cohort studies using the CASP quality assessment tool was high for 37 studies and moderate for three studies.

Different methods of medication errors and error-related adverse events identification were used in the studies, including data review (electronic/paper-based medical record review, lab review, prescription review), database analysis, patient survey (face-to-face or telephone interview and survey or questionnaire), patient self-report and home visits.

Medication errors

Incidence and/or prevalence

We found no study reporting data on the incidence of medication errors. Estimates of population-based medication error prevalence were available from 53 studies.(17-20, 22, 23, 25-27, 29-72)

Self-reported medication errors

The period prevalence of self-reported medication errors was measured in four cross-sectional studies by Adams R J (2009), Lu C Y (2011), Sears K (2012) and Mira J J (2013).(19, 20, 71, 72) In the first three studies, the period prevalence was reported as 2%, 6% and 6% respectively,(19, 20, 71) while in Mira's study, 75% of elderly patients with multiple comorbidities and polypharmacy (five or more drugs) reported having made at least one mistake with their medication (including errors related to dose, similar appearance of medications, and lack of understanding of the physician's instructions).(72) In this study, in 5% of cases, errors due to drug confusion had very severe consequences, requiring a visit to the emergency services or hospital admission.(72) That wide differences in prevalence were seen between the first three studies and the last may be due to population factors. Mira's study population comprised of older poly-medicated patients with multiple comorbidities. This elderly group had a greater risk of error, while the first three studies had populations including any patient over 18 years.

Medication error according to medicines' management process

1- Prescribing errors:

The point or period prevalence of prescribing errors was reported in 46 studies. In these studies, prescribing errors included errors in drug indications, drug-disease interactions, drug-drug interactions (DDI) and dosing error, as well as inappropriate prescribing, which was the most common error reported.

Indication

Koper D et al. (2013) found that, on average, 2.7 medications per patient were not indicated, with a total of 94% of patients having medications prescribed by the general practitioner, but not mentioned in the indication of the UpToDate®.(22)

Drug-disease interactions or contra-indications

Drug-disease interactions were measured in one study by Mand P (2014) with a prevalence of 10%.(30)

Drug-drug interactions

The prevalence of DDIs was measured in 11 studies and ranged from 2 - 58%.(22, 23, 25-27, 31-36) This could in part have been due to the fact that different DDI screening tools were used, namely: DDI compendia and (ePocrates RX), Thompson Micromedex program, database Pharmavista, program BotPlus of the General Council of Pharmacists' Official Colleges, British National Formulary 2010, Italian computerised interaction database, DrugDigest®, Drugs®, Micromedex® and Medscape®.

Inappropriate prescribing

A- The prevalence of potentially inappropriate medication (PIM) was measured in 37 studies in the elderly age group only (≥65 years) and ranged from 5 - 94%.(17, 18, 22, 25, 29, 34, 37-67) This extremely wide range of inappropriate prescribing prevalence estimates is likely to be, at least in part, due to the different detection tools used, namely: Beers 2003, the 2006 Health Plan Employer Data and Information Set (HEDIS), Improved Prescribing in the Elderly Tool (IPET), Medication Appropriate Index (MAI), PRISCUS and Screening Tool of Older Person's Prescriptions (STOPP) criteria. Johnell K (2008) and Haider S I (2009) mentioned two other specific criteria.(43, 45)

B- The prevalence of potential prescribing omission (PPO) was measured in five studies for the elderly age group only (≥65 years) ranging from (23 - 57%).(18, 48, 62, 63, 66) PPO was detected by Screening Tool to Alert doctors to Right Treatment

(START) and Assessing Care of Vulnerable Elders (ACOVE).

Dosing errors

Koper D (2013) found that over- and/or under-dosing was found in 44% of patients.(22)

2- **Monitoring errors:** Monitoring errors were measured in one study by Ramia E (2014), who found that 73% of patients had incomplete therapeutic/safety laboratory-test monitoring tests.(68)

3- **Other errors: discrepancy**

One study found that at least one discrepancy between the medication lists from the pharmacy, the general practitioner (GP), or the patient was present in 86.7% of patients.(69) In another study, almost half of the patients (47.6%; 95% CI 40.5-54.7) had one or more discrepancies in medication information at discharge.(70)

The reported point or period prevalence of medication errors in the community settings, including self-reported medication errors, prescribing errors (indication, drug-disease interaction, DDI, inappropriate prescribing, dosing error and inappropriate prescribing), monitoring error and discrepancies, had a very wide range from 2 - 94%.

Risk factors

Risk factors for medication errors were either related to patients, healthcare professionals and/or medications.

Patient-related risk factors

Patient-related risk factors for the development of medication errors were discussed in 33 studies.(17, 19, 26, 27, 29, 30, 34, 35, 37-40, 45, 46, 48-50, 52, 54, 55, 57, 59, 61-64, 66, 67, 69, 70, 72-74)

Seven risk factors related to patients were addressed in the included studies (in descending order of positive association): polypharmacy, increased age, number of diseases or comorbidities, female, low level of education, hospital admission and middle family income (Table 3).

Several definitions of polypharmacy existed, ranging from prescription of at least three to six medications concurrently. Twenty six studies showed a positive association between medication error and polypharmacy,(17, 26, 27, 29, 30, 34, 35, 37-39, 46, 48-50, 52, 54, 55, 61-64, 66, 67, 69, 70, 73) of which 18 mentioned the estimated OR ranging from 1.06 to 11.45.(17, 26, 27, 29, 30, 34, 35, 37, 39, 46, 49, 54, 61-64, 66, 70)

Older age (≥ 75 years) was associated with medication errors in 13 studies, (17, 27, 30, 35, 37, 45, 46, 48, 54, 62-64, 66) of which 10 mentioned the OR ranging from 1.02 to 4.03. (17, 27, 30, 35, 37, 46, 54, 63, 64, 66)

Healthcare professional-related risk factors

Nine risk factors related to healthcare professionals for the development of medication errors were identified (in descending order of positive association): more than one physician involved in their care, family medicine/GP speciality, age ≥ 51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits (see Table 4).(27, 39, 46, 49, 57, 64, 69, 72, 73)

Medication-related risk factors

Medication-related risk factors for the development of medication error were: multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication,(24), no medication administration routine, poor adherence and patients confused by generic and trade names.(75) In one study by Johnell K (2008), multi-dose drug dispensing users (i.e. medicines machine-packed into unit-dose bags for each time of administration) were more exposed to all indicators of potentially inappropriate drug.(43)

Receiving anticoagulant therapy (OR 2.38; 95% CI 2.15-2.64) was strongly associated in one study to potential drug-disease interactions.(30)

The use of OTC and/or prescribed drugs was a risk factor in two additional studies.(29, 40) The use of OTC medications was associated with PIM; the OR after adjusting for age, sex, education level, partnership, per capita income and occupation was (2.5; 95% CI 1.7-3.6) using Beers 2003 and (1.8; 95% CI 1.2-2.5) using Beers 2012.(29)

Error-related adverse events

Error-related adverse events or preventable ADEs were mentioned in six studies.(21, 28, 29, 69, 70, 76) The most frequently reported consequences were ED visits and hospitalisation.

Two methods for detecting ADE were applied: an ADE monitor (i.e. using computerised programs composed of rules that identified incidents suggesting that an ADE might be present),(21) and using trigger tools to detect ADEs.(76)

Incidence and/or prevalence

One study estimated preventable ADE incidence as 15/1000 person-years.(21) Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers were the most common medications associated with preventable ADE.(21) The estimate of the prevalence of preventable ADE was calculated from five studies as detailed below.(28, 29, 69, 70, 76)

All stages of medicines' management process

Field T S (2007) found the prevalence of patient error leading to an adverse event to be 0.38% i.e. less than 1% of the overall population experienced a medication related adverse event. He found that the majority of patient errors-related adverse events (n=129) occurred in modifying the medication regimen (42%), administering the medication (32%), or not following clinical advice about medication use (22%).(76) The medications associated with more than 10 preventable ADEs were anticoagulants/anti-platelets, cardiovascular drugs, diuretics, hypoglycaemics and non-opioid analgesics.(76)

Error-related adverse events according to medicines' management process

1- Prescribing errors

DDI: Obreli Neto P R (2012) found that DDI-related adverse drug reaction (ADR) occurred in 7% of patients.(28) Warfarin, digoxin, spironolactone and acetylsalicylic acid were the drugs most commonly associated with DDI-related ADRs.(28)

PIM: 46% of participants reported complaints related to ADEs by interview; 95% of these were caused by prescribed medications.(29)

Use of inappropriate drugs was associated with an increased risk of nursing home admission, hospitalisation, more outpatient visit days, ED visits, and having ADEs or ADRs.(41, 49, 60, 65)

2- Other errors

Adverse events (under-treatment due to deletions, ADR due to additions and DDI) related to discrepancy between the medication lists from the patient, the GP, or the pharmacy were identified in 24% of patients.(69) Two discrepancies were categorised as having the potential to cause severe patient harm.(70)

Risk factors

Risk factors for the error-related adverse events were discussed in three studies only.(28, 69, 76)

Patient- related risk factors

Field T S (2007) found that the number of regularly scheduled medications (seven or more medications (OR 3.3; 95% CI 1.5-7.0) and a Charlson Comorbidity Index (CCI) score of five or more (OR 15.0; 95% CI 6.5-34.5) were both associated with higher risk of patient error leading to preventable ADE.(76) Obreli Neto P R (2012) found that an age of 80 years or more (OR 4.4; 95 % CI 3.0–6.1, p<0.01), a CCI of four or more (OR 1.3; 95% CI 1.1-1.8, p<0.01) and consumption of five or more medications (OR 2.7; 95% CI 1.9-3.1, p<0.01), were associated with the occurrence of DDI-related ADRs.(28) In addition, Tulner L R (2009) found that the number of medications was significantly positively correlated with medication discrepancies and adverse patient events.(69)

Medication-related risk factors

The use of medication with narrow therapeutic indices such as warfarin were associated with an increased risk of DDI-related ADRs (OR 1.7; 95% CI 1.1-1.9, p<0.01).(28)

Discussion

Summary of main findings

The aim of this systematic review is to review previous studies conducted in the community of the incidence/prevalence of medication errors and associated adverse events and to identify the main risk factors. The researchers identified 60 studies carried

out in various countries providing a comprehensive assessment of the available evidence on the epidemiology of medication errors and error-related ADEs in community settings.

No relevant studies on the incidence of medication errors in these settings were found. The reported point or period prevalence of medication errors in community settings had a very wide range (i.e. 2 - 94%). This wide range appears, at least in part, to be due to the inconsistency in the definitions of the medication errors used in the studies, differences in populations studied, methodologies employed for error detection, and different outcome measures. More than half (37 studies) of the resulting studies were regarding the prescription of inappropriate drugs within the prescribing error stage in an elderly age group using different criteria. The comparison of those criteria is challenging due to the difference in medication use, consumption and availability of those medications to patients between countries. Further work is needed to review errors occurring at administration and dispensing stages of the medicines' management process.

As for preventable ADEs, which may in some cases occur as a result of medication errors, only one study reported error-related adverse events incidence, measured as 15/1000 person-years.(21) The prevalence of preventable ADE was further reported in five other studies and varied according to the medication error type that resulted in the adverse event.

The most common patient-related risk factors for both medication errors and preventable ADEs mentioned were the number of medications used by the patient and the increased age of patients.

Strengths and limitations

The main strengths of this systematic review are that a rigorous and transparent process has been employed, which included no language restrictions, an independent screening of titles and abstracts, independent data extraction and critical appraisal of included studies by two reviewers. It is the first review undertaken within community settings. The use of the ICPS conceptual framework,(16) which provides a comprehensive definition of each concept and type of error in the medicines' management process, is a further strength.

However, several limitations need to be considered. Firstly, despite the thorough process, no data were found regarding the dispensing error stage. This might be due to the lack of a 'dispensing error' key-term in our search strategy, although 'medication therapy management' as a key-term was included. However, 10 studies on dispensing errors were excluded because they failed to satisfy the inclusion criteria on one or more counts. Secondly, no data were found regarding the administration error stage. However, 14 studies on administration errors were also excluded for the same previous reason. Thirdly, this systematic review had different outcomes reported in a variety of ways using different tools and methodology that made combining results in one meta-analysis difficult. Lastly, the studies addressed risk factors adjusted for different confounders, which makes it difficult to have one specific summary estimate.

Comparison of the findings with previous studies

The definitional variation issue is supported by another two reviews.(77, 78) Other systematic reviews focusing on the safety of primary care contexts only have identified studies with vastly different prevalence estimates of the rates of medication errors. These reflect differences in definitions, sampling strategy and populations studied; none have investigated the risk factors for medication errors.(79, 80)

Implications for research, policy and practice

There is a need for: i). improvement in the quality of research in this area. It is important that all researchers provide a standardised set of outcome measures of medication errors or internationally accepted terminology and definitions of key concepts; ii). training and monitoring of healthcare professionals; iii). education of patients and the public to increase their knowledge of medication safety, particularly those with chronic diseases and polypharmacy with record of the currant medication list for each patient; and iv). involvement of medication safety pharmacists in the community. This would strengthen the quality of research, improve the development of strategies to detect and prevent these errors and provide a safer environment for the community to self-care *safely*.

Conclusions

A wide variation in the medication error and error-related adverse events rate between studies was found, and this may be due to the differences in their definitions,

methodologies employed for error detection or clinical heterogeneity i.e. differences in populations studied and different outcome measures. Most of the studies were conducted on elderly populations in economically-developed countries. Most studies focused only on inappropriate prescribing with relatively little attention to other stages such as administration and dispensing. The most common patient and medication-related risk factors for both medication errors and preventable ADEs were the number of medications used by the patient, increased age and receiving anticoagulant therapy. The most common healthcare professional-related risk factors for medication error was when more than one practitioner was involved in the care of patients and care provision by family medicine and GP specialities.

This study has identified important limitations and discrepancies in the methodology used to study medication errors and error-related adverse drug events in community settings. These findings should be considered when designing future research related to medication safety. More research is needed in the areas of incidence of medication errors, administration error and dispensing errors and researchers should use a more consistent set of definitions and outcomes in order to facilitate collation and synthesis of data.

Ethics and dissemination

The systematic review protocol was published in the British Medical Journal (BMJ) Open on 31 August 2016 and is registered with PROSPERO - an international prospective register of systematic reviews. It is reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). *Systematic Review Registration: (PROSPERO 2016: CRD42016048126).*

Contributorship

GA conceived the idea for this review, conducted the systematic literature search, study inclusion, data extraction and quality assessment. NS participated in the study inclusion, data extraction and quality assessment. MM participated in data extraction. NA participated in data extraction and quality assessment. GA led the writing and drafting of the manuscript, and this was commented on critically by AS, EG, HA and NS.

Funding

The systematic review protocol is a part of GA's Ph.D. study at the University of Edinburgh. King Saud University, College of Pharmacy funded the scholarship. AS is supported by the Farr Institute.

Conflicts of interest

None known.

Acknowledgments

We are grateful to Marshall Dozier for her help with formulating the search strategy; Kathrin Cresswell and Andrea Fuentes Pacheco for non-English studies translation; experts in the field for unpublished and in progress work and experts within the Farr Institute.

Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Boxes and figures

Adverse drug event (ADE): Bates et al. (1995) define ADE as, *"an injury resulting from medical intervention related to a drug."*(81) Some ADEs are caused by underlying medication errors and therefore they are preventable.
Medication error: The National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) defines a medication error as: *"any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health-care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use".*(82) Medication errors can result from any step of the medication-use process: selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration, or monitoring.(1)
Non-prescription drugs: Medicines that can be sold legally without a drug prescription.
Over-the-counter (OTC) drug: The FDA defines OTC dr*ugs as "drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription*".(83)
Prescription drug: Drugs that cannot be sold legally without a prescription.

Box 1: Key definitions

1- Administration error **"**Any discrepancy between how the medication is given to the patient and the administration directions from the physician or hospital guidelines"(1)
2- Prescribing error *"Medication error occurring during the prescription of a medicine that is about writing the drug order or taking the therapeutic decision, appreciated by any non intentional deviation from standard reference such as: the actual scientific knowledge, the appropriate practices usually recognized, the summary of the*

characteristics of the medicine product, or the mentions according to the regulations. A prescribing error notably can concern: the choice of the drug (according to the indications, the contraindications, the known allergies and patient characteristics, interactions whatever nature it is with the existing therapeutics, and the other factors), dose, concentration, drug regimen, pharmaceutical form, route of administration, duration of treatment, and instructions of use; but also the failure to prescribe a drug needed to treat an already diagnosed pathology, or to prevent the adverse effects of other drugs".(16)

Inappropriate prescribing

"*The use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition. Inappropriate prescribing also includes the use of medicines at a higher frequency and for longer than clinically indicated, the use of multiple medicines that have recognized drug–drug interactions and drug–disease interactions, and importantly, the under-use of beneficial medicines that are clinically indicated but not prescribed for ageist or irrational reasons*".(84)

3- Monitoring error

"*Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed theory*".(16)

4- Dispensing error

"*Deviation from the prescriber's order, made by staff in the pharmacy when distributing medications to nursing units or to patients in an ambulatory pharmacy setting*".(16)

5- Other: discrepancies

"*Any differences between the medication described by the patient and caregivers with the drugs listed by their general practitioners (GP) or between the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list*".(69, 70)

Box 2: Classification of definitions used in this systematic review

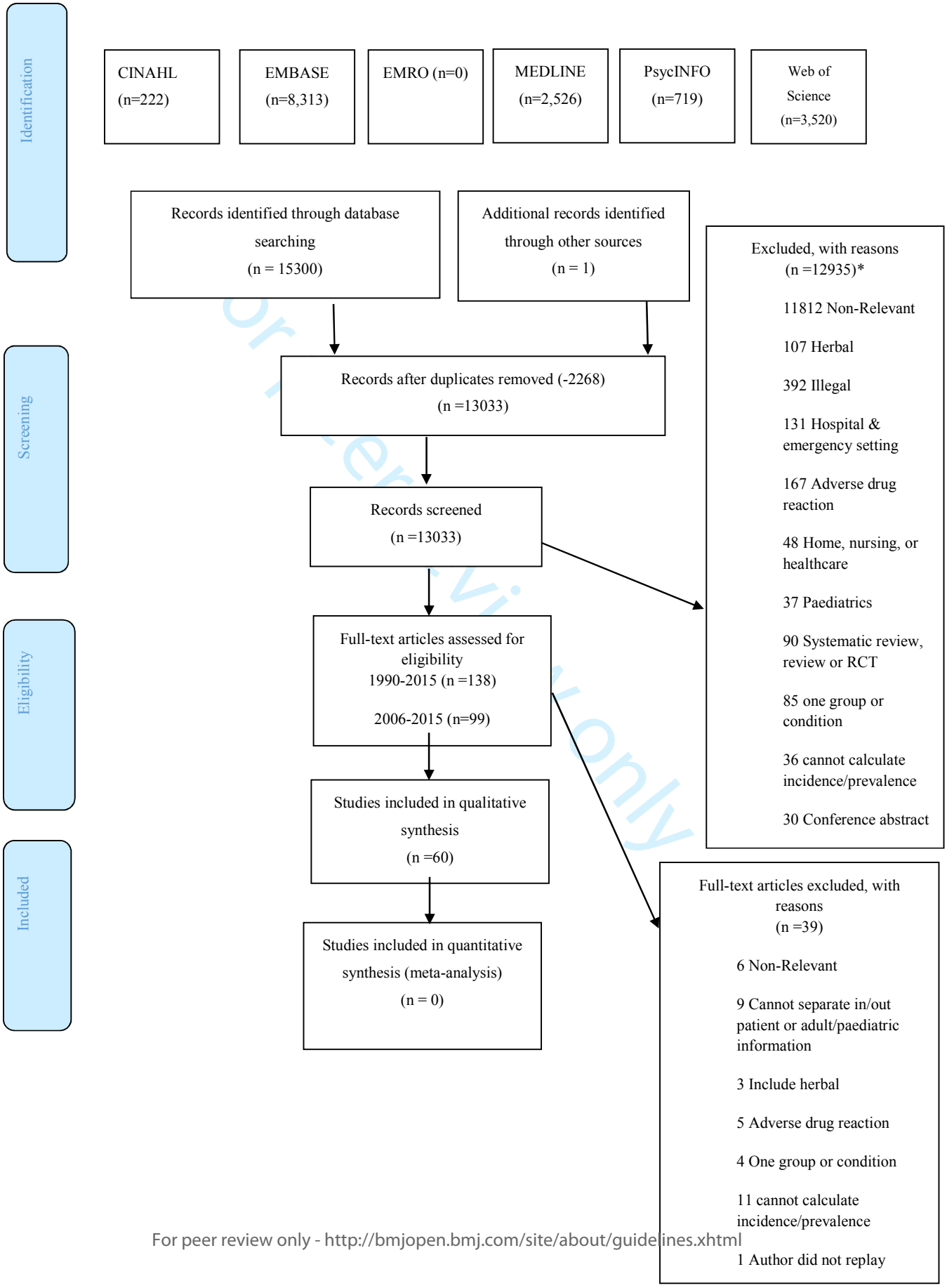

Figure 1: PRISMA flow diagram. (From: Moher D, Liberati A, Tetzlaff J. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement).

*Articles may be duplicated between the excluded groups

Table 1: Systematic review data extraction table

Key characteristics of included studies									
	Author Year	**Country/ city**	**Study Design/type**	**Population of interest**	**Exposure of interest**	**Outcome of interest**	**Main finding**	**Conclusion n/N (%)**	**Additional notes**
Self- reported medication errors									
1.	Adams R J, 2009(71)	Australia	Cross-sectional	Analysis of data from 3,522 adults participating in Stage 2 of the North West Adelaide Health Study aged ≥18 years	Unclear	Self-reported adverse event (medication, diagnosis and others). Using survey.	Of the total 3522 survey participants, 148 (4.2%) reported an adverse event causing harm in the previous 12 months, giving an annual incidence of 4.2% (95% CI, 3.4%–5.0%). Medication error: The main types of adverse events perceived as causing harm were **medication error** (reported by 46% of the 148 participants reporting adverse events).	Medication error prevalence 68/3,522= (1.9%)	Subjective data rather than objective
2.	Lu C Y, 2011(19)	Australia, Canada, New Zealand, the United Kingdom, the United States, Germany and the Netherlands	Cross-sectional (secondary analysis)	11,910 respondent adult aged ≥ 18 years. Data from the 2007 Commonwealth Fund International Health Policy Survey.	Prescribed drug	Self-reported medication error and compare factors associated with medication errors across the 7 countries. Using survey.	**Self-reported medication errors prevalence:** 752 respondents had medication error. [Australia=7.4%; Canada=5.7%; New Zealand=5.9%; UK=5.2%; U.S= 7%; Germany=5.2%; Netherland=8%]. Risk factors across countries included seeing multiple specialists, multiple chronic conditions, hospitalisation and multiple emergency room visits.	Medication error prevalence: 752/11,910= (6.3%)	Prevalence for medication error alone from table 1, while the risk factors for both medical and medication error.
3.	Sears K, 2012(20)	Australia, Canada, France, Germany, the Netherlands, New Zealand, the United Kingdom and the United	Descriptive (Secondary/retrospective analysis)	9,944 adults aged ≥ 18 years from the community setting	Taking medication regularly	Patient-related risk factors associated with self-reported medication errors. Using telephone survey.	**Medication error prevalence:** 570 respondents with medication errors occurring in the community setting. Approximately 4 out of every 5 self-reported medication errors occurred in the community setting.	Medication error prevalence: 570/9,944= (5.7%)	Risk factors for both hospital and community setting.

		States							
4.	Mira J J, 2013(72)	Alicante, Spain	Cross-sectional	382 elderly aged ≥65 years from primary care. Patients on polypharmacy (5 or more drugs) and with comorbidity: [cardiovascular (51.6%); diabetes (34.3%)]	Prescribed and self-medications .	Frequency of mistakes in communication between the physician and the patient and their medication error in the last year. Using semi-structured interviews.	**Medication error prevalence:** 75.1% of the patient reported having made at least one mistake with the medication in the last year. **Risk factors:** Multiple comorbidities ($P = 0.006$), frequent changes in prescription ($P = 0.02$), not considering the prescriptions of other physicians ($P = 0.01$), inconsistency in the messages ($P = 0.01$), being treated by various different physicians at the same time ($P = 0.03$), a feeling of not being listened to ($P < 0.001$) or loss of trust in the physician ($P < 0.001$). *The error due to drug confusion had very severe consequences, requiring a visit to the emergency service or hospital admission.	Medication error prevalence: 287/382= (75%)	*Consequence
Risk factor									
5.	Sorensen L, 2006(75)	4 states of Australia	Cross sectional, prospective	204 general practice patients living in their own home aged 37-99 years.	Prescribed drugs	Prevalence and interrelationships of medication-related risk factors for poor patient health outcomes identifiable through 'in-home' visit observations.	**Risk factors:** Prevalence of nominal medication-related risk factors and health outcomes among the sample of 204 patients 1-Multiple medication storage locations used = 17(8.3%), 2- Expired medication present = 40 (19.6%), 3- Discontinued medication repeats retained = 43(21%), 4- Hoarding of medications = 43 (21%), 5- Therapeutic duplication present= 50 (24.5%), Administration error: 6- No medication administration routine = 56 (27.5%), 7- Poor adherence = 107 (52.5%), 8- Confused by generic and trade names = 114 (55.9%).		
6.	Vuong T, 2006(24)	Melbourne, Australia	Descriptive	142 discharged adult aged ≥ 55 years who were returning to independent care at home Patient at risk of medication misadventure	Discharge prescribed drugs	Unnecessary medicine stored at home as a risk factor. Using home visit within 5 days of discharge.	Unnecessary medicine stored at home prevalence 85/142= (60%) 85 (60%) of 142 patients who received a home visit allowed removal of medicines that had expired or no longer required. **Prescribing error:** drug duplication prevalence: Thirty-two (27%) patients allowed removal of 82 duplicate packs of the same item that was no longer required.	Unnecessary medicine stored at home prevalence: 85/142= (60%)	No information on how many patients had unnecessary medicine. Information available is on the patient allowed to remove unnecessary medicine.

							A total of 390 medicines were removed with a mean of 4.6 medicines per patient (range 1–21).		
7.	Pit S W, 2008(73)	New South Wales, Australia.	Cross-sectional Study	849 elderly aged ≥ 65 years from general practice	Self-medications	Prevalence of self-reported risk factors for medication misadventures Tool used: Medication Risk Assessment Form (patient survey)	**Risk factors:** 1- Using at least one medication for more than 6 months (95%). 2-More than one doctor involved in their care (59%) 3- Had three or more health conditions (57%) 4- Used five or more medicines (54%). 5- Adverse drug reactions, in the last month 39% of participants experienced difficulties sleeping, felt drowsy or dizzy (34%), had a skin rash (28%), leaked urine (27%), had stomach problems (22%) or had been constipated (22%).		*ADR as a risk factor for medication misadventure may not be related to the use of medication in all cases
8.	Mosher H J, 2012(74)	Iowa, USA	Cohort prospective	310 elderly aged ≥65 years who were cognitively intact from a Veterans Administration primary care clinic	Taking 5 or more non-topical medications	Association of health literacy with medication knowledge, adherence, and ADEs. Using interview and chart review	Total 310 patients **Prevalence of ADEs** ADEs occurred in 51 patients (16.5%) of the patients within the first 3 months of the study, which increased, to 119 patients (38.4%) over the full 12-month follow-up period. **Risk factor:** Association of health literacy with ADEs: The incidence of ADEs at 3 and 12 months appeared higher among patients with low health literacy, but this was not statistically significant.	Low health literacy increase the risk of ADEs	
Medicines' management process:									
9.	Koper D, 2013(22)	Austria	Descriptive	169 patient form general practice taking 5 or more medicines. Mean age: 76.4 ± 8.5 SD years. Of the 169 patient, 158 were elderly aged ≥ 65 years	Prescribed and OTC drug	Medication errors including non-evidence based medications, dosing errors and potentially dangerous interactions in all patients. Potential interactions were identified using the Lexi-Interact® database. PIMs in subgroup of elderly patient according to the PRISCUS list. Using case report form filled by the general practitioners	**Prescribing error prevalence:** Indication: 158 of the 169 patients (93.5%) had at least one non-evidence-based medication. Dosing error: 74 of the 169 patients (43.8%) had at least one dosing error. Drug-drug interaction (DDI) prevalence: *Category D interactions*: 99 patients (58%) had at least one category D interaction. *Category X interactions*: 4 patients (2.4%) had at least one category X interaction. PIM prevalence 59 of seniors (37.3%) had at least one medication that was inappropriate.	Medication error prevalence: 1- non-evidence based medications: 158/169= (93.5%) 2-dosing error 74/169= (43.8%) 3-category D drug interaction 99/168= (58%). category X drug interaction 4/168= (2.4%) 4- PIMs 59/158=37.3%	A medication was classified as non-evidence based if the indication for use indicated by the *general practitioners (GP*) was not mentioned in any peer-reviewed chapter of UpToDate®
10.	Mand P, 2014(30)	Germany	Descriptive retrospective	24,619 elderly aged ≥65 years	Prescribed drug	Potential drug-disease interaction (PDDI)	**Prescribing error:** contraindication or drug-disease interaction prevalence:	PDDI prevalence (10.4%)	

				from family practice with at least one diagnosis named in the Beers list		frequency and whether there are gender- or age-related differences. Analysis from electronic patient records.	10.4% of elderly were exposed to at least one PDDI. **Risk factors:** 1-Patients over 75 years (OR 1.10; CI: 1.05 – 1.15) 2-Number of drugs prescribed (> 4 drugs: OR 1.91, CI: 1.83 – 2.00) 3-Blood clotting disorders/receiving anticoagulant therapy (OR 2.38, CI: 2.15 – 2.64) showed the strongest association with PDDI.		
11.	Gagne J J, 2008(33)	Regione Emilia-Romagna, Italy	Cohort Retrospective	4,222,165 Regional Emilia-Romagna residents. Outpatient aged from 0 to ≥85 years	Prescribed drug	Clinically important potential DDI. Risk factors. O outpatient prescription data from the Regional Emilia-Romagna. DDI screening tool: a list of clinically important potential DDIs included 12 drug pairs that could be captured using the Regional Emilia-Romagna database.	**Prescribing error:** DDI prevalence: Exposed to potential DDI adult (19 - ≥85 year) = 7,893. Unexposed adult= 7013. Total= 14,906.	DDI prevalence: 7,893/14,906= (53%)	Risk factors for all age group including paediatrics. All age group included so results should be considered cautiously.
12.	Dallenbach M F, 2007(23)	Geneva, Switzerland	Descriptive Retrospective file review	591 outpatients. Mean age 39 years.	Prescription drug and drug currently taking	Clinically significant adverse drug interactions (ADI). Prescription review. DDI screening tool: DDI compendia and (ePocrates RX) with clinical decision support	**Prescribing error:** DDI prevalence: In 135 of the consultations, a potentially clinically significant ADI was identified.	DDI prevalence: 135/591= (23%)	
13.	Obreli Neto P R, 2011(25)	Brazil	Cross-sectional	2,627 elderly aged (60-88 years) from the primary healthcare	Prescribed drug	Potential risks in drug prescriptions: DDI, Potentially Inappropriate Medicine (PIM). Using prescription review.	**Prescribing error:** DDI prevalence: Using (DrugDigest®) showed that 4.7% and 28.4% of elderly presented at least one potential DDI classified as major and moderate respectively. Using (Medscape®) showed that 3.4% and 19.3% of elderly presented at least one potential DDI classified as major and moderate	DDI prevalence: (3.1%)-(29.1%) PIM prevalence: (26.9%)	

						DDI screening tool: (DrugDigest®, Medscape®, and Micromedex®) PIM using Beers criteria 2003.	respectively. Using (Micromedex®, showed that 3.1% and 29.1% of elderly presented at least one potential DDI classified as major and moderate respectively. **Prescribing error:** PIM prevalence 26.9% of the patients had prescriptions with at least one PIM.		
14.	Secoli S R, 2010(26)	Sao Paulo, Brazil	Cross-sectional	2,143 community-dwelling elderly aged ≥ 60 years. Data were obtained from the SABE (Health, Well-Being, and Aging) survey.	≥2 prescribed drug use	Potential DDIs and identify associated factors. Using home interview. DDI screening tool: Micromedex ® Healthcare Series.	**Prescribing error:** DDI prevalence: 568/2143= 26.5% **Risk factors:** The use of six or more medications (OR 3.37; 95% CI 2.08, 5.48) or having hypertension (OR 2.56; 95% CI 1.73, 3.79), diabetes (OR 1.73; 95% CI 1.22, 2.44) or heart problems (OR 3.36; 95% CI 2.11, 5.34) significantly increased the risk of Potential DDI.	DDI prevalence: 568/2,143= (26.5%)	
15.	Obreli Neto P R, 2012(27)	5 cities of Brazil	Cross-sectional	12,343 elderly aged ≥ 60 years from the primary public health system	Prescription for 2 or more drugs (Prescribed both within and across prescriptions)	Potential DDIs (presence of a minimum 5-days overlap in supply of an interacting drug pair) and predictor of DDI. Using medical prescriptions and patients' medical records review. DDI screening tool: DDI checker Programs (DrugDigest®, Drugs®, Micromedex® and Medscape®)	12,343 patients [(5,855 (exposed); 6,488(unexposed)] **Prescribing error:** DDI prevalence: 47.4% **Risk factors:** Female sex (OR = 2.49 [95% CI 2.29–2.75]), diagnosis of ≥ 3 diseases (OR = 6.43 [95% CI 3.25–12.44]), and diagnosis of hypertension (OR = 1.68 [95% CI 1.23–2.41]) were associated with potential DDIs. Age was associated with an increasing risk of DDIs. Number of prescribers, number of drugs consumed, ATC codes, and drugs that act on CYP450 presented positive associations with potential DDIs in univariate and multivariate analyses of drug therapy characteristics.	DDI prevalence: 5,855/12,343= (47.4%)	
16.	Indermitte J, 2007(31)	Switzerland	Descriptive	434 passer-by customers aged ≥18 years from community pharmacies	Prescription only medicines and OTC drug	Potential drug interactions. 1-Observation of customer contacts and interviews with passer-by customers purchasing selected OTC drugs, 2- Telephone interviews with regular customers treated with selected prescription only	**Prescribing error:** DDI prevalence: Observation of passer-by customers Of 1183 passer-by customers observed, 164 purchased at least one of the selected OTC drugs. One hundred and two (62.2%) of those subjects were interviewed. Forty-three (42.2%) mentioned taking prescribed drugs, and three of them were exposed to potential drug interactions of moderate severity.	DDI prevalence: 3/102= (3%) 69/434= (16%) 116/434= (26.7%)	

						medicines identified in community pharmacies' databases. DDI screening tool: database Pharmavista	Telephone interview with regular customers Out of 592 regular customers selected from the community pharmacy database, 434 (73.3%) could be interviewed. Prevalence of DDI in regular customers Sixty-nine (15.9%) of them were exposed to a potential drug interaction between purchased OTC drug for self-medication and their prescription only medicines. Furthermore, 116 (26.7%) regular customers were exposed to potential drug interactions within their prescribed drugs and in 28 (6.5%) multiple (>2) potential drug interactions were found.		
17.	Mahmood M, 2007(32)	USA	Cross-sectional retrospective	2,795,345 patients who filled prescriptions for medications involved potential DDI from 128 Veterans Affairs medical centres. Ambulatory care clinic	Prescribed drug	Clinically important DDI. Database analysis of pharmacy records. DDI screening tool: a list of 25 potential DDI.	**Prescribing error:** DDI prevalence: The overall rate of potential DDIs was 21.54 per 1000 veterans exposed to the object or precipitant medications of interest.	DDI prevalence: (2.15%)	Age not mentioned.
18.	Lapi F, 2009(34)	Dicomano, Italy	Cohort, a Two-Wave, Population-Based Survey	568 community-dwelling elderly aged ≥65 years	Prescription and nonprescription drugs used at least 1 week before enrolment.	Suboptimal prescribing: Inappropriate medication = 1991 Beers' criteria (13 items out of the original 39 (33.3%) Beers' list medications were considered) DDI screening tool: Micromedex_ Drug-Reax_ system. Using population based survey.	**Prescribing error**: Potential DDI Prevalence was significantly higher in 1999 compared to 1995 (30.5% vs. 20.1%; p < 0.001). Inappropriate prescriptions were significantly higher in 1995 compared to 1999 (9.1% vs. 5.1%; p 0.004). 1995 / 1999 / P-value Inappropriate medication: 47 (9.1%) / 26 (5.1%) / 0.004 DDI: 97 (20.1%) / 147 (30.5%) / <0.001 Major DDI: 20 (4.7%) / 24 (5.6%) / 0.585 **Risk factors:** Polypharmacy always predicted a substantial increase in the risk of the PIM and DDI.	Potential DDI prevalence: (30.5%) p < 0.001 Inappropriate medication prevalence: (5.1%), P=0.004	

19.	Nobili A, 2009(35)	Lecco, Italy	Cross-sectional Retrospective	58,800 community dwelling elderly aged ≥ 65 years registered under the Local Health Authority of Lecco.	Receiving at least two co-administered prescriptions	DDIs and associated risk factors (age, sex and number of prescriptions). DDI screening tool: Italian computerized interaction database. Analysed all prescriptions dispensed from 1 January 2003 to 31 December 2003.	**Prescribing error:** DDI prevalence: 9,427 elderly people (16%) were exposed to drug combinations with the potential for 13 932 severe DDIs. Mean number of DDI per patient was 0.2 (range 0–9). **Risk factors:** Age and number of chronic drugs were associated with an increasing risk of DDIs. The adjusted OR increased from 1.07 (95% CI 1.3–1.11) in patients aged 70–74 years to 1.52 (95% CI 1.46–1.60) in those aged 85 or older. Elderly taking more than five chronic drugs had a statistically significant higher risk of potentially severe DDIs (OR = 5.59; 95% CI 5.39–5.80) than those receiving less than 3 (reference category) or 3–5 chronic drugs (OR = 2.71; 95% CI 2.63–2.80).	Potentially severe DDI prevalence = 9,427/58,800 = (16%)	Only the interactions identified as severe were considered in these analyses.
20.	Guthrie B, 2015(36)	Scotland, UK	Cross-sectional	311,881 resident aged ≥ 20 years from the community-dispensed prescribing data. Living in own home 308,660.	Prescribed drugs	Potentially serious DDI. Patient characteristics associated with the presence of potentially serious DDI. DDI screening tool: Analysis community-dispensed prescribing data using British National Formulary 2010.	**Prescribing error**: DDI prevalence 40,689 adults (13%) had potentially serious DDI in 2010 [for both resident living in own home and care home]. Number of patient with potentially serous DDI for residence living in their own home in 2010= 13,615	DDI prevalence: 13,615 /308,660= (4.4%)	Resident living in both care home or own home. Risk factors for own home and care home
21.	Maio V, 2006(37)	Milia, Romagna. Italy	Cohort Retrospective	849,425 elderly outpatient aged ≥65 years from the Emilia Romagna outpatient prescription claims database	Prescribed drugs	PIM using the 2002 Beers' criteria and factors associated with PIM. Prescription review.	**Prescribing error:** PIM prevalence: A total of 152,641 (18%) elderly had one or more occurrences of PIM prescribing. **Risk factors:** 1-Older age (≥85 years) (odds ratio (OR) 1.18, 95% confidence interval (CI) 1.16-1.2, P value <0.05) 2- ≥ 10 drugs prescribed (OR 7.33, 95% CI 7.15-7.51, P value <0.05) 3- ≥ 4 chronic conditions (OR 1.76, 95% CI 1.72-1.81, P value <0.05)	PIM prevalence: 152,641/849,425= (18%)	
22.	Martins, S D O, 2006(38)	Lisbon, Portugal	Cross-sectional	213 elderly outpatient aged ≥65 years from 12 community pharmacies	Prescription and home medications	Inappropriate drug use (IDU) by 1997 Beers and 2003 Beers Explicit criteria.	**Prescribing error:** PIM prevalence: Using the 1997 Beers Explicit criteria, 75 occurrences of inappropriate medicines were detected in 59 patients (27.7%). Using the 2003 Beers Explicit criteria inappropriate medication	IDU prevalence: 59/213= (27.7%) using 1997 Beers. IDU prevalence: 82/213= (38.5%)	

						Using survey	was detected in 82 patients (38.5%). **Risk factors:** The occurrence of inappropriate medicines was significantly associated with the consumption of a high number of drugs	using 2003 Beers.	
23.	Pugh M J V, 2006(39)	Austin, Texas USA	Cross-sectional, retrospective	1,096,361outpatient elderly aged ≥ 65 years using national data from the Veterans Health Administration.	Prescribed drug only	Potentially inappropriate prescribing (IP) included in the 2006 Health Plan Employer Data and Information Set (HEDIS) criteria and to determine if patient risk factors are similar to those found using Beers criteria. Using database	**Prescribing error:** IP prevalence: Overall, 19.6% of older veterans were exposed to HEDIS 2006 drugs. **Risk factors:** 1- Patients receiving ≥10 medications were at greatest risk of exposure in men (OR 8.2, 95% CI 8-8.4) and women (OR 9.6, 95% CI 8.2-11.2). 2- Patient with more outpatient clinic visits (≥10) were at greater risk regardless of gender (OR 1.4, 95% CI 1.3-1.6) 3- Diagnosis with other mental illness (e.g., depression, anxiety) alone or in combination with serious mental illness was associated with higher risk of potentially IP for women (OR 1.3, 95% CI 1.1-1.5).	Potentially IP prevalence: 214,887/1,096,361= (19.6%)	
24.	Saab Y B, 2006(40)	Lebanon	Descriptive	277 elderly aged ≥65 years from 10 community pharmacies	Prescription and/or over the counter (OTC) medications	IDU (Beers criteria, Missing doses, inappropriate frequency of administration, poor memory, drug-disease interaction, DDI, inappropriate dose, duplicated therapy, discontinuation of therapy, adverse effect, and inappropriate indication). Factors that predict potentially inappropriate drug intake. Review patient profile using community pharmacy data and in-person interviews.	**Prescribing error:** PIM prevalence: The prevalence of elderly outpatient with at least one inappropriate medication: 165/277 (59.6%) [Include 5 patient had ADR] Inappropriate medication use was most frequently identified in terms of Beers' criteria (22.4%), missing doses (18.8), and incorrect frequency of administration (13%). Drug-disease interaction in 28 patient (10.1%) DDI 14 (5.1%) Duplicate therapy 12 (4.3%) **Risk factors:** Female sex (65.7% vs. 53.3% for males, p = 0.03). There were also significant associations between the likelihood of use of an inappropriate drug and (1) increased number of medical illnesses (p < 0.00002); (2) consumption of an OTC drug and/or prescription drug (p = 0.048 and p = 0.0035, respectively); and (3) consumption of both OTC and prescription drugs (p < 0.0002).	IDU prevalence: 62/277= (22.4%) using Beers' criteria	Just extracted the IDU by Beers criteria because the IDU include 5 cases of ADR and some patients had more than one IDU. Risk factors for all type of IDU.
25.	Zuckerman	USA	Cohort	487,383	Prescribed	Inappropriate medication	**Prescribing error**: PIM prevalence:	Inappropriate	

	I H, 2006(41)		retrospective	community dweller elderly aged ≥ 65 years. Data from MarketScan Medicare Supplemental and Coordination of Benefits database	drug	use using Beers criteria.	204,083 elderly used inappropriate medication. Use of inappropriate drugs was associated with a 31% increase in risk of nursing home admission, compared with no use of inappropriate drugs (adjusted relative risk 1.31, 99%CI 1.26–1.36).	medication use prevalence: 204,083/487,383= (41.9%)	
26.	Bregnhoj L, 2007(42)	Copenhage, Denmark	Cross-sectional	212 elderly aged ≥65 years with polypharmacy (≥ 5 drugs) patient from primary care	Subsidised and non-subsidised medications prescribed	IP measured by the Medication Appropriate Index (MAI: 10 criteria are indication, effectiveness, dosage, directions practicality, directions correctness, drug–drug interaction, drug–disease interaction, duplication, duration and expense). Patients exposed to polypharmacy were identified via the database recording the drug subsidy system of Danish pharmacies and questionnaire.	**Prescribing error**: IP prevalence: The main part of the patients namely 94.3% had one or more inappropriate ratings among their medications.	IP prevalence: 200/212= (94.3%)	
27.	Johnell K, 2008(43)	Sweden	Cross-sectional	731,105 People aged ≥75 years from the Swedish Prescribed Drug Register	Prescribed drug only and multi-dose drug dispensing	Whether the use of multi-dose drug dispensing is associated with potential IDU (IDU) (i.e. anticholinergic drugs, long acting benzodiazepines, concurrent use of ≥ 3 psychotropic drugs, and combinations of drugs that may lead to potentially serious DDIs). Information from the Swedish Prescribed Drug Register.	**Prescribing error:** PIM prevalence: Prevalence of potential IDU in Multi-dose dispensing users: 40.3% (women: 41%, men 38.5%) Prevalence of potential IDU In prescription users: 13.6% (women: 15%, men 11.5%) The multi-dose users had higher prevalence of all indicators of potential inappropriate drug than prescription users. 1-The younger elderly (aged 75-79 years) who used multi-dose drug dispensing had the highest frequency of all indicators of potential IDU. 2-Most indicators of IDU were more common in women than men. 3- Multi-dose drug dispensing among 75- to 79-year-olds was even more strongly associated with any IDU, anticholinergic drugs, three or more psychotropic drugs in both men and women, and long-acting benzodiazepines	PIM prevalence: multi-dose dispensing users: 292,737/731,105= (40%) Prescription users: 994, 30.3/731,105= (13.6%)	Multi-dose drug dispensing means that patients get their drugs machine dispensed into one unit for each dose occasion and packed in disposable bags.

							among men.		
28.	Berdot S, 2009(44)	Dijon, Bordeaux, Montpellier . France	Cohort Prospective	6,343 community dwelling elderly aged ≥ 65 years	Prescribed drug	PIM using 1997 and 2003 Beers criteria, Fick and Laroche. Face to face interview using standardised questionnaire.	**Prescribing error:** PIM prevalence: One-third (31.6%) of the study participants reported using at least one inappropriate medication at study entry.	PIM prevalence: 2,004 / 6,343= (31.6%) p <0.001	
29.	Haider S I, 2009(45)	Sweden	Cross-sectional register-based study	626,258 Older people aged 75-89 year from the Swedish Prescribed Drug Register	Prescribed drug only	If low education associated with potential IDU (i.e. anticholinergic drugs, long acting benzodiazepines, concurrent use of ≥ 3 psychotropic drugs, and clinically relevant potential drug–drug interaction (DDI)). Information from the Swedish Prescribed Drug Register.	**Prescribing error:** PIM prevalence: The proportion of participants reporting use of at least one potential IDU was 34.6%. **Risk factors:** Subjects with low education had a higher probability of potential IDU (OR 1.09, 95% CI 1.07–1.17). Older age, being a woman, and higher Charlson Comorbidity Index (CCI) were associated with the highest frequencies of potential IDU.	IDU prevalence: 216,685/626,258= (34.6%)	
30.	Lai H Y, 2009 (46)	Taiwan	Descriptive	2,133,864 patient aged ≥ 65 years between 2001-2004 from ambulatory care. National Health Insurance claim database	Prescribed drug	PIM prescribing using updated 2003 Beers criteria and the characteristics of and risk factors for such prescribing.	**Prescribing error:** PIM prevalence A mean of 63.8% of the older population received a PIM at least once a year in 2001–2004. Details: In 2001: 1,974,869 patients of which 1,297,425 had inappropriate prescription. (65.7) In 2002: 2,026,737 patients of which 1,312,147 had inappropriate prescription. (64.7) 2003: 2,077,677 patients of which 1,295,227 had inappropriate prescription. (62.3) 2004: 2,133,864 patients of which 1,333,792 had inappropriate prescribing (62.5)] **Risk factors:** The only patient characteristic associated with an increased likelihood of the prescribing of PIM was female sex (male sex: (OR 0.982 [95% CI, 0.980-0.983]), (p < 0.001) and when ≥4 drugs were prescribed (P < 0.001). Physician characteristics associated with a greater likelihood of the prescribing of PIM was: 1-Male sex (OR 1.206; 95% CI, 1.202–1.210, *P* < 0.001);	PIM prevalence: 2001: (65.7%) 2002: (64.7%) 2003: (62.3%) 2004: 1,333,792/2,133,864 = (62.5%)	

							2-Older age (43–50 years: OR 1.021; 95% CI, 1.018–1.025, $P < 0.001$; ≥51 years: OR 1.238; 95% CI, 1.235–1.242, $P < 0.001$); 3-Family medicine/ general practice (OR 1.267; 95% CI, 1.265–1.269, $P < 0.001$).		
31.	Ryan C, 2009(47)	Ireland	Cohort Prospective	500 patient aged ≥ 65 years from primary care	Prescribed drug	IP using 2003 Beers' criteria and improved prescribing in the elderly tool (IPET). Screening patients' medical records (electronic and paper).	**Prescribing error:** PIM prevalence 65 patients (13%) and 52 patients (10.4%) had at least one medicine prescribed inappropriately using 2003 Beers and IPET criteria respectively.	IP prevalence: Beers 2003: 65 /500= (13%) IPET: 52/500= (10.4%)	
32.	Ryan C, 2009(48)	Cork, Southern Ireland	Descriptive case record review	1,329 elderly aged ≥ 65 years from primary care	Prescribed drugs	A-1- PIM using 2003 Beers and Screening Tool of Older Person's Prescriptions (STOPP) criteria 2- Potential prescribing omissions (PPO) using Screening Tool to Alert doctors to Right Treatment (START) criteria B- Relationship between age and number of prescription drugs and IP. Case record through paper and electronic record review.	**Prescribing error:** PIM prevalence IP rate identified by Beers' criteria in 18.3% (243) of patients IP rate identified by STOPP was 21.4% (284). PPO was identified in 22.7% (302) of patients using the START tool. **Risk factors:** A significant correlation was found between the occurrence of PIM and 1-The number of medicines prescribed when calculated using Beers' criteria ($r_s = 0.270$, $P < 0.01$) and STOPP ($r_s = 0.356$, $P < 0.01$) using Spearman's ρ correlation test. 2-Age using Beers' criteria ($r_s = 0.068$, $P < 0.01$) and STOPP ($r_s = 0.071$, $P < 0.01$). 3-Increasing CCI score identified by STOPP ($r_s = 0.210$, $P < 0.01$).	PIM prevalence: Beers': 243/1329= (18.3%) STOPP: 284/1329= (21.4%) PPO prevalence: START: 302/1329= (22.7%)	Spearman's ρ correlation test.
33.	Akazawa M, 2010(49)	Tokyo, Japan	Cohort Retrospective	6,628 elderly patient aged ≥ 65 years from health insurance claim data	Prescribed drugs	PIM using modified Beers criteria in Japan. Drug utilization review using medical and pharmacy claim from database of (Japan Medical Data Center).	**Prescribing error:** PIM prevalence 43.6% (2,889/6,628) were prescribed at least one PIM. **Risk factors:** Factors positively associated with PIM prescriptions at a significance level of 5% included the following: Hospital admission (OR = 3.35, 95% CI 2.43-4.62); polypharmacy (OR = 5.69, 95% CI 5-6.48); prescriptions from a hospital (OR = 1.19), general medicine practitioner (OR = 1.46), or psychiatrist/neurologist (OR = 2.33); and comorbid conditions including peptic ulcer disease without bleeding (OR = 4.18 , 95% CI 3.52-4.97), depression (OR = 3.69), cardiac	PIM prevalence: 2,889/6,628= (43.6%)	*Consequence

							arrhythmias (OR = 1.93), other neurologic disorders (Parkinson's disease, multiple sclerosis, and epilepsy; OR = 1.88), and congestive heart failure (OR = 1.46). PIM users had significantly higher hospitalization risk (1.68-fold), more outpatient visit days (1.18-fold), and higher medical costs (33% increase) than did nonusers.		
34.	Zaveri H G, 2010(50)	Ahmedabad city, India	Descriptive Prospective	407 geriatric patients aged ≥ 65 years from medicine outpatient department	Prescribed drug	PIM using 2003 Beers criteria. Using prospective proforma data collection.	**Prescribing error:** PIM prevalence Out of 407 patients, 96 patients (23.6%) received at least one drug that was potentially inappropriate. **Risk factors:** There was highly significant association between the number of drugs prescribed and frequency of use of PIMs (P< 0. 0002).	PIM prevalence: 96/407= (23.6%)	
35.	Barnett K, 2011(51)	Tayside, Scotland, UK	Cohort	65,742 elderly aged 66-99 years living in home	Prescribed drug	PIM using 2003 Beers criteria and the association between exposure to PIM and mortality. Using dispensing and prescribing database and medical record.	**Prescribing error**: PIM prevalence PIM found in 20,304 (30.9%) patient living at home. **Risk factors:** After adjustment for age, sex and polypharmacy, 1-Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy 2-Reciveing at least one PIM were not associated with increased risk of mortality (adjusted OR 0.98, 95% CI 0.92 -1.05).	PIM prevalence: 20,304/65,742= (30.9%)	Risk factors for both care home and home
36.	Chang C B, 2011(52)	Taipei, Taiwan	Cohort	193elderly patient aged ≥ 65 years with polypharmacy (≥ 8 chronic medications) from Medication Safety Review Clinic in Taiwanese Elders (MSRC-Taiwan) study.	Prescribed drugs and dietary supplement excluding herbals	PIM using six different criteria and drug-related problem: the 2003 version of the Beers criteria (from the USA), the Rancourt (from Canada), the Laroche (from France), (STOPP; from Ireland), the Winit-Watjana (from Thailand) and the Norwegian General Practice (NORGEP) criteria (from Norway). Analyse baseline data	**Prescribing error**: PIM prevalence: The proportion of patients who had at least one PIM varied from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria). Approximately 31% (the STOPP criteria) to 42% (the NORGEP criteria) of PIMs identified were considered as drug related problems by the medication review team experts. **Risk factors:** In the bivariate analysis, the common characteristics associated with having at least one PIM in all criteria were a high number of chronic conditions and a high number of chronic medications.	PIM prevalence: (24% -73%)	

						from the MSRC-Taiwan study. Secondary data analysis.			
37.	Leikola S, 2011(53)	Finland	Cross-sectional	841,509 non-institutionalised elderly patient aged ≥ 65 years from Finland's Social Insurance Institution prescription register of all reimbursed drugs for outpatient	Prescribed and OTC medications that are reimbursed	PIM using 2003 Beers criteria.	**Prescribing error:** PIM prevalence 14.7% (n = 123,545) had received PIMs according to the Beers 2003 criteria.	PIM prevalence: 123,545/841,509= (14.7%)	
38.	Lin Y J, 2011(54)	Taiwan	Cross-sectional Retrospective analysis	327 elderly patient aged ≥ 65 years from outpatient clinic of a community health centre	Prescribed drugs	PIM using 2003 Beers criteria and risk factors of PIM use. Using data review.	**Prescribing error:** PIM prevalence The prevalence of patients having at least one PIM was 27.5% (90/327). **Risk factors:** Independent risk factors for PIMs are older age (OR = 1.05, 95% CI 1.00–1.09, p = 0.046), higher number of prescribed medications (OR = 1.06, 95% CI = 1.39–1.98, p < 0.001), and diagnosis of acute diseases (OR = 8.98, 95% CI 4.71–17.1, p < 0.001).	PIM prevalence: 90/327= (27.5%)	
39.	Woelfel J A, 2011(67)	California, USA	Cross-sectional	295 elderly aged ≥ 65 years from ambulatory population of Medicare beneficiaries	Prescribed drug	PIM using 2003 Beers criteria. Using medication review	**Prescribing error:** PIM prevalence 54 (18.3% beneficiaries were taking at least one PIM. **Risk Factors:** Number of medications was significantly greater in the PIM than the non-PIM group (p < 0.001)	PIM prevalence: 54/295= (18.3%)	
40.	Zhang Y J, 2011(55)	USA	Cohort Retrospective	3,570 Elderly community-based respondents aged ≥ 65 from 2007 Medical Expenditure Panel Survey (MEPS), a nationally representative survey of the US community-dwelling population	Prescribed drug	PIM using Zhan criteria and risk factors for PIM use. Information from MEPS database	**Prescribing error:** PIM prevalence PIM prevalence in 2007:13.84% (CI 12.52–15.17). PIM prevalence in 1996: 21.3% (CI 19.5–23.1). **Risk factors**: Older women, people taking ≥25 prescriptions, people with middle family income, people living in the South census region, and people who said they were in fair or poor health were more likely to have received an inappropriate medication during the year.	PIM prevalence: 13.84%-21.3%	
41.	Haasum Y,	Sweden	Cross-sectional	1,260,843 home-	Prescribed	Potentially IDU (use of	**Prescribing error**: PIM prevalence	Potentially IDU	Information on

	2012(56)		Retrospective	dwelling elderly aged ≥ 65 year from the Swedish Prescribed Drug Register	drug only	anticholinergic drugs, long-acting benzodiazepines, concurrent use of ≥ 3 psychotropics, and potentially serious DDIs). Information from the Swedish Prescribed Drug Register	11.6% of the home-dwelling elderly were exposed to Potentially IDU.	prevalence: 145,749/1,260,843= (11.6%)	both institutionalised and home dwelling. Extracted home dwelling information only.
42.	Marroquin E C, 2012(18)	Cáceres, Spain	Descriptive	471 patient aged ≥ 65 years from health centers	Consumed medications	Potentially IP using STOPP/START criteria. Using patient interview and medical chart review.	**Prescribing error:** PIM prevalence 249 patients (52.8%, 95% CI 48.3-57.3) had potentially IP according to STOPP/START criteria. STOPP: 162 patients (34.3%, 95% CI 30.2-38.8%) START: 114 patients (24.2%, 95% CI 20.5-28.2%)	Potentially IP prevalence: 249/471= [(52.8%) (95% CI 48.3-57.3)]	
43.	Nyborg G, 2012(57)	Norway	Cross-sectional Retrospective	445,900 home dwelling elderly aged ≥ 70 years from the Norwegian Prescription Database	Prescribed drug	Prevalence of and predictors for PIM use by the Norwegian General Practice (NORGEP) criteria. Survey undertaken based on data from the Norwegian Prescription Database	**Prescribing error:** PIM prevalence 34.8% of the study population was exposed to at least one PIM. **Risk factors:** The odds of receiving potentially harmful prescriptions increased with the number of doctors involved in prescribing (OR 3.52, 99% CI 3.44–3.60 for those with ≥5 compared to those with 1 or 2 prescribers). Females were at higher risk for PIMs (OR 1.6, 99% CI 1.58–1.64).	PIM prevalence: 155,341 /445,900= [(34.8%) (99%CI 34.7-35)]	
44.	Yasein N A, 2012(58)	Jordan	Cross-sectional	400 elderly aged ≥65 years from family practice clinic	Prescribed drug	Polypharmacy (≥ 5drugs) and IP using 2003 Beers criteria. Using patient file and patient interview	**Prescribing error**: PIM prevalence Inappropriate medications as determined by Beers criteria independent of diagnosis accounted for 118 (29.5%) patients.	IP prevalence: 118/400= (29.5%)	
45.	Blozik E, 2013(59)	Helsana, Switzerland	Cohort	2008: 1,059,495 2009: 1,047,939 2010: 929,791 community dwelling adult aged > 18 years from claim data of Helsana.	Prescribed drug submitted for reimbursement	Prevalence of polypharmacy and PIM using 2003 Beers criteria or the PRISCUS list. Using analysis of data based on claim data from Switzerland health insurance	**Prescribing error:** PIM prevalence: According to 2003 Beers criteria: 10.3 % of the community-dwelling population aged > 65 years received at least one medication which is PIM, and according to the PRISCUS list1: 16.0 % of persons had a PIM. When using both Beers and PRISCUS criteria, 21.1 % of the population received at least one PIM. Of those persons older than 65 years asking for	PIM prevalence: 21.1%	There are huge discrepancies in estimating the prevalence of PIM depending on the definition used.

							reimbursement of medications, 12.9 % received at least one PIM according to 2003 Beers, 20.2 % according to PRISCUS, and 26.6 % of either definition. **Risk Factors:** Women were more likely to receive a PIM: 25.5 % of females as compared to 15.4 % of males when both Beers and PRISCUS definitions were used.		
46.	Cahir C, 2013(60)	Ireland	Cohort Retrospective	931 Community dwelling elderly aged ≥ 70 years from 15 general practices	Prescribed drug and OTC	The association between potentially IP using STOPP -and health related outcomes [ADEs, health related quality of life (HRQOL) and hospital accident and emergency department (ED)]. Using patient self-report and medical record.	**Prescribing error:** PIM prevalence Prevalence of potentially IP was 40.5% (n = 377). **ADE prevalence:** In total, 674 of 859 participants (78%) were classified as having at least one ADE during the study period. **Risk Factors:** Patients with ≥2 Potentially IP indicators were: 1-Twice as likely to have an ADE (adjusted OR 2.21; 95% CI 1.02, 4.83, P < 0.05), 2- Significantly lower mean HRQOL utility (adjusted coefficient −0.09, SE 0.02, P < 0.001), 3-A two-fold increased risk in the expected rate of ED visits (adjusted Incidence Rate Ratio 1.85; 95% CI 1.32, 2.58, P <0.001).	Potentially IP prevalence: 377/931= (40.5%) ADE prevalence: 674/931= (72%)	*Consequence. Type of ADE was not mentioned
47.	Weng M C, 2013(61)	Taiwan	Cross-sectional Retrospective	780 older patients aged ≥ 65 years from the outpatient geriatric clinic	Long-term Prescribed drugs (≥ 28 days) for chronic diseases. Not OTC	Impact of number of drugs prescribed on the risk of PIM using STOPP criteria. Patient medical chart review	**Prescribing error**: PIM prevalence 302 patients (39%) had at least one PIM. **Risk factors:** Multivariate analysis revealed that PIM risk was associated with the number of medications prescribed (P < 0.001) and the presence of cardiovascular (P < 0.001) or gastrointestinal disease (P = 0.003). Patients prescribed ≥ 5 drugs [adjusted (OR) = 5.4; had significantly higher PIM risk than those prescribed ≤ 2 drugs.	PIM prevalence: 302/780= (39%)	
48.	Zimmerman n T, 2013(17)	German	Cohort longitudinal analysis	follow-up3: N = 1,942 Baseline N =3,214 1,855 elderly aged ≥75 years from primary care. Data from the	Prescribed drug	PIM using Beers, PRISCUS list. By checking medications during visits to patients' homes.	**Prescribing error:** PIM prevalence At baseline, PIM prevalence is (848) 29 % according to the PRISCUS list, which decreased to (464) 25.0 % 4.5 years later (χ^2: 7.87, p = 0.004). The Beers list yielded a prevalence of (620) 21 % at baseline, decreasing after 4.5 years to	Prescribing error: PIM prevalence 17%-29%	

				prospective, multicenter, observational study "German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe),"			(317) 17.1 % (χ^2: 10.77, p = 0.000). **Risk factors:** By PRISCUS list: The risk for PIM increase with: 1-Increasing age of the patients (OR: 1.06, CI: 1.00 to 1.13; p = 0.037), 2-The presence of depression (OR: 2.42, CI: 1.65 to 3.57; p = 0.000), 3-Increasing number of prescription drugs (OR: 1.99; CI: 1.80 to 2.18; p = 0.000). By contrast, the risk of taking PIM decrease by using PRISCUS list with the number of present illness (OR: 0.88, CI: 0.80 to 0.97; p = 0.012). As the growing number of ingested prescription drugs increased the risk for the ingestion of PIM from the Beers list (OR: 1.66, CI: 1.50 to 1.84; p = 0.000).		
49.	Baldoni A D, 2014(29)	Ribeirao Preto, Brazil	Cross-sectional	1000 elderly aged ≥ 60 years from outpatient pharmacy	Prescribed drug, self-medication (309 user) and OTC (802 user)	Prevalence and factors associated with PIM using 2003 and 2012 Beers criteria. Using structured interview questionnaire	**Prescribing error:** PIM prevalence According to Beers criteria 2003, 480 (48.0 %) participants used at least one PIM, the mean being 1.38 (SD = 0.65) PIMs/person, ranging from one to five. According to Beers criteria 2012, 592 (59.2 %) participants used at least one PIM, the mean being 1.56 (SD = 0.81) PIMs/person, ranging from one to six. **Adverse drug event (ADE):** During the interview 45.5 % of participants reported complaints related to ADEs; 94.5 % of these were caused by prescribed medication. **Risk factors:** Factors that are associated with PIMs use were female gender, self-medication, use of OTC medications, complaints related to ADEs, psychotropic medication, more than five medications. *Ten medications with the highest prevalence of self-reported ADEs complaints are Clonidine, amitriptyline, metformin, fluoxetine, dexchlorpheniramine, diclofenac, captopril, acetyl salicylic acid, simvastatin, hydrochlorothiazide. Among them, five were	PIM prevalence by Beers criteria 2003, 480/1000= (48.0 %) PIM prevalence by Beers criteria 2012, 592/1000= (59.2 %)	*Error-related adverse event

							considered PIMs according to Beers criteria, of which clonidine, amitriptyline and dexchlorpheniramine are listed in both criteria, while fluoxetine is listed only in Beers criteria 2003 and diclofenac is listed only in Beers criteria 2012.		
50.	Castillo-Paramo A, 2014(62)	Spain	Cross-sectional	272 electronic record of elderly aged ≥65 years from primary healthcare	Prescribed drugs	PIM using STOPP/START criteria and version adapted to Spanish primary healthcare and factors may modulate PIM onset. Using electronic health record and paper clinical record	**Prescribing error:** PIM prevalence The prevalence of PIM (mis- and over-prescribing) using the STOPP original criteria was 37.5% (95% CI: 31.7 – 43.2), and 50.7% (95% CI: 44.7 – 56.6) using the STOPP Spanish AP2012 version. The prevalence of under-prescribing was 45.9% (95% CI: 40.0 – 51.8) with the START original criteria, and 43.0% (95% CI: 37.1 – 48.9) with the START AP2012 version. **Risk factors:** A significant correlation was found between the number of STOPP PIM and age or number of prescriptions, and between the number of START PIM with age, CCI and number of prescriptions.	PIM prevalence: 102/272 (STOPP) = [(37.5%) (95% CI: 31.7 – 43.2)] 138/272 (STOPP AP2012) = [(50.7%)(95% CI: 44.7 – 56.6)] 125/272 (START) = (45.9%) 117/272 (START AP2012) = (43%)	
51.	Vezmar Kovacevic S, 2014(63)	Serbia Belgrade	Cross-sectional Prospective	509 elderly aged ≥ 65 years from 5 community pharmacies	Prescribed drug	PIM and PPO using STOPP/START criteria. Using patient interview and medical, biomedical record	**Prescribing error**: PIM prevalence There were 164 PIM identified in 139 patients (27.3%) by STOPP and 439 PPO, identified in 257 patient, (50.5%) by START. **Risk factors:** Patients with more than four prescriptions had a higher risk for PIM (OR 2.85, 95% CI 1.97–4.14, p <0.001 and ≥ 9 medications OR 7.43, 95% CI 3.20–17.23, p<0.001). Patients older than 74 years were more likely to have a PPO (75–84 years OR 1.47, 95% CI 1.01–2.13, p= 0.041 and ≥85 years OR 1.79, 95% CI 1.19–2.83, p = 0.009).	PIM prevalence: 139/509= (27.3%) PPO prevalence: 257/509= (50.5%)	
52.	Amos T B, 2015(64)	Emilia-Romagna, Italy	Cohort Retrospective	865,354 elderly aged ≥ 65 years community dwelling From administrative care data	Prescribed drug only	PIM using updated Maio criteria and patient characteristic related to IP. Using Regional Emilia-Romagna administrative healthcare database.	**Prescribing error:** PIM prevalence A total of 240,310 (28%) older adults were exposed to at least one PIM. **Risk factors:** The oldest group (≥85) followed by patients aged 75–84 had 53% and 25% greater odds of receiving PIM than patients 65–75 years old, respectively [OR = 1.53,95% CI: 1.50–1.55; OR = 1.25, 95% CI: 1.23–1.26, respectively].	PIM prevalence: 240,310/ 865,354= (28%)	

							These odds of exposure to any PIM were slightly lower among males than females (OR = 0.98, 95% CI: 0.97–1.00). An increase in the number of medications prescribed to the patient corresponded with higher odds of PIM exposure. Older general practitioners (≥56), male GPs, and solo practice GPs were more likely to prescribe PIMs to their older patients.		
53.	Hedna K, 2015(65)	Sweden	Cohort retrospective	542 elderly aged ≥ 65 years from the Swedish Total Population Register (primary care)	Prescribed drug	Prevalence of Potentially IPs using STOPP criteria and to investigate the association between Potentially IPs and occurrence of ADRs. Using the Swedish Prescribed Drug Register, medical records and health administrative data	**Prescribing error:** PIM prevalence 226 patients using primary healthcare had Potentially IP. **Risk factors:** Persons prescribed Potentially IP had more than twofold-increased odds to experience ADRs (OR 2.47, 95 % CI (1.65–3.69); P <0.001), compared to that in persons without Potentially IP.	Potentially IP prevalence: 226/542= (42%)	* Error-related adverse event. The association between PIPs and occurrence of ADRs was for primary care, outpatient or inpatient and hospitalized patient.
54.	Moriarty F, 2015(66)	Ireland	Cohort Prospective	2,051 elderly aged ≥ 65 years from The Irish Longitudinal Study on ageing (TILDS). Community dwelling elderly.	Prescribed drug only	PIM and PPO using STOPP, Beers criteria, ACOVE (Assessing Care of Vulnerable Elders) indicators and START. Using face to face interview then follow up after 1 and 2 years	**Prescribing error: PIM prevalence** Baseline N%(95%CI) / Follow-up N%(95%CI) Any PIM using STOPP, Beers, ACOVE: 1,259 (61.4%) (CI 59.3-63.5) / 1,330 (64.8%) (CI 62.8-66.9) Any PPO using: 1,094 (53.3 %) (CI 51.2- / 1,161 (56.6%) (CI 54.5-58.8)	PIM: (36.7%-64.8%)	

							START, ACOVE: 55.5) Both PIM and PPO: 753 (36.7 %) / 843(41.1 %) **Risk factors:** Female sex, age and higher number of medicines were significantly associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be significantly associated with change in PPO prevalence.		
55.	Ramia E, 2014(68)	Lebanon	Cross sectional	284 outpatient aged ≥ 18 years visiting community pharmacy	Patient on ≥ one of the chronic medications mentioned in the study	The completion of therapeutic/safety monitoring tests. Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring.	**Monitoring error:** - 185 of the patients (65%) were found to complete some, but not all, of the recommended therapeutic/safety monitoring tests - 76 of the patients (27%) completed all recommended therapeutic/safety monitoring -23 of the patients (8%) did not complete any of the recommended monitoring tests	Incomplete therapeutic/safety laboratory-test monitoring tests prevalence: 208/284= (73%)	
Other: Discrepancies									
56.	Tulner L R, 2009(69)	Amsterdam , The Netherland	Descriptive prospective	120 elderly aged >65 years from Dutch geriatric outpatient	Using more than one prescribed or OTC medications	1-Frequency and relevancy of discrepancies in drug use 2-Frequency of medication discrepancy adverse patient events (MDAPEs) 3-Contributing factors- such as increasing age, cognitive status and depressive symptoms, the number of medications used, the number of physicians visited by the patient. By comparing the medication described by the patient and caregivers with the drugs listed by their general	**Other: Discrepancies prevalence:** At least one discrepancy (deletion, addition, or difference in dosage) between the medication lists from the patient, the GP, or the pharmacy was present in 104 patients (86.7%) involving 386 drugs. **Medication discrepancy adverse patient events:** Medication discrepancy adverse patient events were identified in 29 patients (24.2%). 7 patient had under-treatment due to deletions 9 patients had ADR due to additions 13 patient had DDI. **Risk factors:** Patients with ≥ 1 discrepancy reported using a higher mean number of drugs (5.9 vs. 4.0; $P <$ 0.05) and had more prescribing physicians in addition to their GP (1.1 vs. 0.43; $P <$ 0.05). Both the presence of discrepancies (Pearson' s 1", *0.293 ; P* s 0.05) and MDAPEs (Pearson's	Discrepancies prevalence: 104/120= (86.7%) *Error-related adverse event: MDAPEs: 29/120= (24.2%)	*Error-related adverse event

						practitioners.	1", 0.230; *P* = 0.012) were significantly correlated with the number of medications reported by the patient. *The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (82.9%), and formulations fix dermatologic or ophthalmologic diseases (81.3%).		
57.	Cornu P, 2012(70)	Brussels, Belgium	Cohort retrospective	189 elderly aged ≥65 years discharged from acute geriatric department of a Belgain university hospital	Prescribed drug	Incidence and type of discrepancies between the discharge letter for the primary care physician and the patient discharge medication and identify possible patient-related determinants for experiencing discrepancies. Discrepancies were categorized as omitted drug, unintended continuation (discontinued home medication documented as home medication), discrepant dose, missing dose, and discrepant brand, omission of a brand name, discrepant frequency, missing frequency, or an incorrect pharmaceutical form. By comparing the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list	**Other: Discrepancies prevalence:** Almost half of these patients (n=90, 47.6%) (95% CI 40.5-54.7) had 1 or more discrepancies in medication information at discharge. *Two discrepancies (1.2%) were categorized as having the potential to cause severe patient harm. These discrepancies consisted of a wrong dose (doubled the prescribed dose) of digoxin in the patient discharge medication list and the listing of a low-molecular-weight heparin in the patient discharge medication list that was intentionally omitted in the discharge letter because of the development of heparin-induced thrombocytopenia during hospitalization. **Risk factors:** The explorative multivariate model adjusted for age, sex, length of hospital stay, and residential situation showed that when the discharge letter contained more than 5 drugs, the likelihood of experiencing 1 or more drug discrepancies was 3.22 (95% CI 1.40 to 7.42; p = 0.006) times higher than when 5 or fewer drugs were mentioned. Increasing numbers of drugs in the discharge medication list (OR 1.19; 95% CI 1.07 to 1.32; p = 0.001) and discharge letter (OR 1.18; 95% CI 1.07 to 1.32; p = 0.001) were associated with a higher risk for discrepancies.	Discrepancies prevalence: 90/189= [(47.6%) (95% CI 40.5-54.7)]	*Error-related adverse event
Preventable ADEs									
58.	Field T S, 2007(76)	USA	Cohort	30,000 elderly ≥ 65 years from ambulatory care	Prescribed drug	ADE resulting from patients error and risk factors By electronic tracking of administrative data,	**Preventable ADE:** ADE resulting from patients error prevalence 113 individual experience ADE and potential ADE **Risk factor:**	ADE resulting from patients' error prevalence: 113/30,000 = (0.38%)	*ADE resulting from patients error

						review medical records, reports from clinicians, hospital discharge summaries and ED visit	In a multivariate analysis, there was a dose–response association between patient errors leading to ADEs and potential ADEs and regularly scheduled medications; compared with zero to two medications, the OR for three to four medications was (OR 2.0; 95% CI=0.9–4.2), for five to six medications was (OR 3.1; 95% CI=1.5– 7.0), and for seven or more medications was (OR 3.3; 95% CI=1.5–7.0). The strongest association was with the CCI; compared with a score of 0, the OR for a score of 1 to 2 was (OR 3.8; 95% CI=2.1–7.0), for a score of 3 to 4 was (OR 8.6; 95% CI=4.3–17.0), and for a score of 5 or more was (OR 15.0; 95% CI=6.5–34.5).		
59.	Gandhi T K, 2010(21)	Boston and Indianapolis ,USA	Cross-sectional	68,013 outpatient, mean age 48 and 47 years	Prescribed drug	ADE. Using electronic health record screening, chart review and ADE monitor	**Preventable ADE** incidence: The overall rate was 138 ADEs/1000 person-years across the two sites. Preventable ADEs rate 15 /1000 person-years across two sites. *Most commonly drugs associated with preventable ADE were the angiotensin-converting enzyme (ACE) inhibitors and beta blockers.	Preventable ADEs rate 15 /1000 person-years across two sites.	*Preventable ADE
60.	Obreli Neto P R, 2012(28)	Ourinhos microregion, Brazil	Cohort prospective	433 elderly aged ≥ 60 years from the primary public health system	Prescribed drugs both within and across prescriptions	DDI-related ADR incidence and factors. Using phone or face-to-face structured interview DDI screening tool: DDI checker Programs (DrugDigest®, Drugs®, Micromedex® and Medscape®)	**Preventable ADE:** DDI-related ADR incidence: Occurred in 30 patients (6.9 %). Gastrointestinal bleeding occurred in 37 % of the DDI-related ADR cases, followed by hyperkalemia (17 %) and myopathy (13 %). Seventeen DDI-related ADRs were classified as severity level 2, and hospital admission was necessary in 11 cases. *Warfarin was the most commonly involved drug (37%cases), followed by acetylsalicylic acid (17 %), digoxin (17 %), and spironolactone (17 %). **Risk Factors:** The multiple logistic regression showed that the following were associated with the occurrence of DDI-related ADRs: Age ≥80 years [OR 4.4; 95 % CI 3.0–6.1, p<0.01], CCI ≥4 (OR 1.3; 95 % CI 1.1–1.8, p<0.01), Consumption of five or more drugs (OR 2.7; 95 % CI 1.9– 3.1, p<0.01),	Incidence of DDI-related ADR 30/433= (6.9%)	*Error-related adverse event

							Use of warfarin (OR 1.7; 95 % CI 1.1–1.9, p<0.01)		

Abbreviations: ACE: Angiotensin-converting enzyme. ACOVE: Assessing Care of Vulnerable Elders. ADE: Adverse Drug Event. ADI: Adverse Drug Interaction. CI: Confidence Interval. DDI: Drug-Drug Interaction. ED: emergency department. GP: general practitioners. HEDIS: Health Plan Employer Data and Information Set. IPET: Improved Prescribing in the Elderly Tool. IDU: Inappropriate Drug Use. IP: Inappropriate Prescribing. MAI: Medication Appropriate Index. MDAPE: Medication Discrepancy Adverse Patient Event. OTC: Over-the-Counter. OR: Odds Ratio. PDDI: Potential drug-disease interaction. PIM: Potentially Inappropriate Medicine. PPO: Potential Prescribing Omissions. STOPP: Screening Tool of Older Person's Prescriptions. START: Screening Tool to Alert doctors to Right Treatment.

Table 2: Systematic review quality assessment

A. Joanna Briggs Institute critical appraisal checklist for descriptive/case series and cross-sectional

Was study based on a random or pseudo- random sample?
Were the criteria for inclusion in the sample clearly defined?
Were confounding factors identified and strategies to deal with them stated?
Were outcomes assessed using objective criteria?
If comparisons are being made, was there sufficient descriptions of the groups?
Was follow up carried out over a sufficient time period?
Were the outcomes of people who withdrew described and included in the analysis?
Were outcomes measured in a reliable way?
Was appropriate statistical analysis used?
Y = Yes, No = N, Unclear = U, Not applicable = NA

		1	2	3	4	5	6	7	8	9	Overall appraised	
1	Ramia E, 2014 (68) Adult	Y	Y	N	N	NA	NA	Y	Y	Y	High	Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring, may cause

												recall bias
2	Sorensen L, 2006 (75) Adult	Y	Y	N- Risk factors related to patient not studied	Y	NA	NA	Y	Y	Y	High	
3	Vuong T, 2006 (24) Adult	U	Y	N	Y	NA	NA	N	Y	Y, percentage was used but statistics was not described in the full text.	High	Unclear sampling strategy
4	Adams R J, 2009(71) Adult	Y	Y	Y (but for all type of adverse event)	N (self-reported adverse events)	NA	NA	N	Y	Y	High	Risk of recall bias and attribution with self-reported adverse events and
5	Gandhi T K, 2010 (21) Adult	U	Y	N	Y	Y	NA	NA	Y	Y	High	
6	Lu C Y, 2011(19)	Y	Y	Y	N (subjective patient-reported	Y	NA	NA (secondary analysi	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient-

	Adult				medication error)			s)				reported medication error pp
7	Sears K, 2012 (20) Adult	Y	Y	Y	N (subjective self-reported medication error)	Y	NA	NA (secondary analysis)	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient self-reported medication error
8	Koper D, 2013(22) Adult	N (convenience)	Y	N	Y	NA	NA	NA (100% participant)	Y	Y	High	Selection bias
9	Dallenbach, 2007 (23) Adult-DDI	N (consecutive)	N	N	Y	NA	NA	NA (retrospective)	Y	Y	Moderate	
10	Indermitte J, 2007 (31) Adult-DDI	Y (pharmacy choose). No (first 12 customer)	Y	N	Y	NA	NA	Y	Y	Y	High	
11	Mahmood, 2007 (32) Adult-DDI	Y	Y	N	Y	NA	NA	NA (retrospective)	Y	Y	High	Patients may actually be on other drugs so may not

												catch all the DDI.
12	Guthrie B, 2015 (36) Adult-DDI	Y	Y	Y (but for both own home and care home)	Y	Y	NA	NA (secondary analysis)	Y	Y	High	Risk factors for both own home and care home.
13	Martins S D O, 2006 (38) Elderly -PIM	N (1st came to pharmacy carrying prescription for 2 or more drugs)	Y	Y, but not all	Y	Y	NA	N	Y	Y	High	Self-reported data from elderly concerning drug use may lead to information bias.
14	Pugh M J V, 2006 (39) Elderly -PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	May underestimate the exposure because they do not account for OTC
15	Saab Y B, 2006(40) Elderly -PIM	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported data from elderly concerning drug use may decrease accuracy

16	Bregnhoj L, 2007 (42) Elderly -PIM	N (Each GP was asked to recruit 6 patients who were randomly selected)	Y	N	Y	NA	NA	Y	Y	Y	High	Selection bias
17	Johnell K, 2008 (43) Elderly -PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Did not look for comorbidity as a risk factor because data from Swedish Prescribing Drug Register
18	Haider S I, 2009 (45) Elderly -PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
19	Lai H Y, 2009 (46) Elderly – PIM	Y	Y	Y	Y	NA	NA	NA (secondary analysis)	Y	Y	High	Did not address comorbidity as a risk factor

20	Ryan C, 2009 (48) Elderly – PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	May underestimate the outcome because they do not account for OTC
21	Zaveri H G, 2010 (50) Elderly -PIM	U	Y	Y	Y	NA	NA	N	Y	Y	High	Not enough information in the article
22	Leikola S, 2011 (53) Elderly -PIM	Y	Y	N	Y	NA	NA	NA	Y	Y	High	May underestimate the outcome because database lacks diagnostic patient data, therefore used the Beers 2003 criteria independent of diagnoses and the data provide no information on the use

												of PIMs that are not reimbursable. Nine PIMs that were not reimbursable in Finland in 2007: triazolam, belladonna alkaloids, diphenhydramine, hydroxyzine, ferrous sulfate, bisacodyl, nitrofurantoin and clonidine.
23	Lin Y J, 2011 (54) Elderly -PIM	U	Y	Y	Y	NA	NA	NA	Y	Y	High	
24	Woelfel J A, 2011 (67) Elderly -PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
25	Haasum Y,	Y	Y	N	Y	Y	NA	NA (secon	Y	Y	High	

	2012 (56) Elderly -PIM							dary data analysis)				
26	Nyborg G, 2012 (57) Elderly -PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	
27	Yasein N A, 2012 (58) Elderly -PIM	N	Y	N	Y	Y	NA	N	Y	Y	Moderate	
28	Marroquin E C, 2012 (18) Elderly -PIM	N (convenience sample)	Y	N	Y	NA	NA	N	Y	Y	Moderate	Sampling strategy. Subjective information on socioeconomic and clinical variables may decrease accuracy
29	Weng M C, 2013 (61) Elderly -PIM	Y	Y	Y	Y	Y	NA	N	Y	Y	High	Sampling strategy

30	Baldoni A O, 2014 (29) Elderly -PIM	UC	Y	Y	Y	Y	NA	Y	Y	Y	High	
31	Castillo-paramo A, 2014 (62) Elderly -PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Electronic health record use limitations (incomplete record and quality of data)
32	Vezmar Kovacevic S, 2014 (63) Elderly -PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	
33	Nobili A, 2009 (35) Elderly- DDI	Y	Y	Y	Y	NA	NA	NA (administrative database)	Y	Y	High	The use of administrative database limit looking for comorbidity as a confounder.
34	Secoli S-R 2010 Elderly-DDI	U	Y	Y	Y	NA	NA	NA	Y	Y	High	May underestimate the true DDI prevalence

												because they do not account for OTC
35	Obreli Neto P R, 2012 (27) Elderly-DDI	Y	Y	Y	Y	NA	NA	NA (data from primary healthcare system)	Y	Y	High	May under estimate the DDI prevalence because 1- Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interactions involving combinations of three or more drugs so. 2- did not account for OTC
36	Pit S W, 2008 (73) Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	

37	Tulner L R, 2009 (69) Elderly	N (consecutive)	Y	Y	Y	NA	NA	Y	Y	Y	High	Information on medication described by the patient and caregivers may not always be accurate
38	Obreli Neto P R, 2011(25) Elderly DDI	Y	Y	N	Y	NA	NA	NA	Y	Y	High	
39	Mira J J, 2012 (72) Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported medication error from elderly concerning drug use may have recall bias
40	Mand P, 2014 (30) Elderly	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	

B. Critical Appraisal Skills Program (CASP) for cohort study

1 Did the study address a clearly focused issue?

2 Was the cohort recruited in an acceptable way?

3 Was the exposure accurately measured to minimise bias?

4 Was the outcome accurately measured to minimise bias?

5(a) Have the authors identified all important confounding factors?

List the ones you think might be important, that the author missed

5(b) Have they taken account of the confounding factors in the design and/or analysis?

6(a) Was the follow up of subjects complete enough?

6(b) Was the follow up of subjects long enough?

7 What are the results of this study?

8 How precise are the results?

9 Do you believe the results?

10 Can the results be applied to the local population?

11 Do the results of this study fit with other available evidence?

12 What are the implications of this study for practice?

Yes= Y, No=N, can't tell

	Study design: Cohort														
	Reference	**Quality domains**													
		1	**2**	**3**	**4**	**5 (a)**	**5 (b)**	**6(a)**	**6 (b)**	**7**	**8**	**9**	**10**	**11**	**12**	**Overall quality**
		Are the results of the study valid?								**What are the results?**			**Will the results help locally?**			
1	Maio V, 2006(37) PIM	Y	Y	Y	Y	Y- Age, gender, geographic location, number of medication, number of chronic condition and income None	N	Y	Y (1 year) retrospective	PIM prevalence 18%. Older age, polypharmacy, and greater number of chronic conditions were significant predictors of PIM use.	P value <0.05, 95 % CI	Y	Y	Y	-	Moderate

2	Zuckerman I H, 2006(41) PIM	Y	Y	Y	Y	Y-but used for irrelevant outcome -	Y	Y	Y (2 years)	Inappropriate medication use prevalence 41.9%	P= 0.01, 99% CI	Y	Can't tell (generalisability)	Y	Limited information from the database. Confounding factors were for the nursing home admission rather than for PIM.	Moderate
3	Field T S, 2007(76) Elderly	Y	Y	Y	Y	Y-Age, gender, comorbidity, number of medications None	Y	Y	Y (1 year)	ADE resulting from patients' error prevalence: 0.38%	P value <0.05	Y	Y	Y	Possible drug-related incidence for which necessary information was not documented in the medical record was not considered.	High

4	Gagne J J, 2008(33) DDI	Y	Y	Y	Y	Y- Age, gender, geographic location, comorbidity, number of medication prescribed. None	Y	Y	Y (1 year)	DDI: prevalence 53%	95% CI	Y	Y	Y	Applying the US list of clinically important DDI to Italy may underestimate the prevalence as it captured only 12 out of the 25 DDI original list. Unable to extract risk factors data as it for all age group.	High
5	Berdot S, 2009(44) Elderly PIM	Y	Y	Y	Y	Y-but for irrelevant outcome -	Y	Y	Y (4 years)	PMI prevalence 31.6%	95%CI, P value <0.05	Y	Y	Y	Self-report and data from healthcare insurance plan are not perfect for actual drug consumption. Recall bias. Confounding factors were for the risk of falls rather than for PIM.	High

6	Lapi F, 2009(34) Elderly PIM	Y	Y	Y	Y	Y- Comorbidity, polypharmacy, stroke, heart failure Age, gender	Y	Y	Y (1 year)	1999: IP prevalence: (5.1%) Potential DDI prevalence: (30.5%) Potential Major DDI: (5.6%) Polypharmacy, aws a predictors of PIM use.	P-value <0.05, 95% CI	Y	N	Y	Self-reported diagnosis and medication use may cause recall bias. Beers' list cannot be fully applied to Italy, it most reflect US drug market.	Moderate
7	Ryan C, 2009 (47) Elderly PIM	Y	Y	Y	Y	N -	Can't tell	Y	Y (6 month)	Medicine prescribed inappropriately Beers 2003: 13% IPET: 10.4%	Can't tell	Y	Y	Y	-	Low

8	Akazawa M, 2010(49) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, polypharmacy (>5 drugs), hospitalisation , comorbidities. None	Y	Y	Y (1 year)	Prevalence of PIM 43.6%. Inpatient service use, polypharmacy, and comorbidities were significant predictors of PIM use.	95%CI, P value <0.05	Y	Y	Y	Medical information cannot be taken from claim data, unobserved confounder. PIM not associated with age as several other studies.	High
9	Barnett K, 2011(51) Elderly PIM	Y	Y	Y	Y	Y- Age, sex, polypharmacy and place of residence. Comorbidity	Y	Y	Y(2yesrs)	PIM prevalence 30.9%. Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy	95%CI	Y	Y	Y	Comorbidity not accounted for. Risk factors for both care home and home	High
10	Chang C B, 2011(52) Elderly PIM	Y	Y	Y	Y	Y- Age, sex, education, number of chronic medication, number of chronic conditions, and number of ED visits.	Y	Y	Y (12,24 Week)	PIM: 24% - 73%. Number of chronic drugs and number of chronic conditions was a common risk factor in all criteria	P value < 0.05	Y	Y	Y	May underestimated the prevalence because several drugs in Taiwan was not available in the sex	High

						None									criteria	
11	Zhang Y J, 2011(55) Elderly PIM	Y	Y	Y	Y	Y- Race, gender, family income, educational level, census region, number of prescription, self-rated health status. None	Y	Y	Can't tell	Prevalence of PIM was from [(13.84%) (95% CI 12.52-15.17)] to [(21.3%) (95% CI 19.5-23.1)]	95%CI, P value <0.05	Y	Y	Y	Recall bias due to self-reported survey. Did not assess DDI, drug-disease interaction and under-use so may underestimate the prevalence	Moderate
12	Cornu P, 2012(70) Elderly	Y	Y	Y	Y	Y- Age, gender, residential situation before admission, residential situation after discharge, number of drugs in the discharge letter or list. Comorbidity	Y	Y	Y (from admission to discharge)	Almost half of these patients [(47.6%) (95% CI 40.5-54.7)] had 1 or more discrepancies in medication information at discharge.	95%CI, P value <0.05	Y	Can't tell	Y	Was done in one centre that may have different procedure of discharge	Moderate
13	Mosher H J, 2012(74)	Y	Y	Y	Y	Y- Health literacy	Y	Y	Y (3 and 12 months)	ADEs occurred in 51	P value <0.05	Y	Can't tell	Y	Results may be biased due	Moderate

	Elderly					Age, number of medications, comorbidity				patients (16.5%) of the patients within the first 3 months of the study, which increased, to 119 patients (38.4%) over the full 12-month follow-up period.					to sampling strategy	
14	Obreli Neto P R , 2012 (28) DDI	Y	Y	Y	Y	Y None	Y	Y	Y (4months)	Incidence of DDI-related ADR (6.9%)	95%CI, P value <0.05	Y	Y	N	Recall bias from weekly meeting with patient. Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interaction involving combinations of three or more drugs so the risk of DDI may be underestimated	Moderate

15	Blozic E, 2012 (59) Adult	Y	Y	Y	Y	Y- gender Age, number of medications, number of disease	Y	Y	Y (3 years)	Prevalence of PIM 21.1%	95% CI	Y	Y	Y	-	High
16	Cahir C, 2013(60) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, socioeconomic status, private health insurance, co-morbidity, number of repeat drug, social support and network, adherence. None	Y	Y	Y (6 months) retrospective study	Prevalence of potentially IP was 40.5%	95%CI	Y	N	Y	Recall bias due to self-reported ADE.	Moderate
17	Zimmermann T, 2013(17) Elderly PIM	Y	Y	Y	Y	Y- Gender age, number of medications, number of disease, depression, education None	Y	Y	Y (4.5 years)	At baseline PIM prevalence is (848) 29% according to the PRISCUS list, which decreased to (464) 25.0% 4.5 years later and 21% according to the Beers list decreasing	95%CI, P value <0.05, OR and CI for risk factors	Y	Y	Y	-	High

										after 4.5 years to (317) 17.1%						
18	Amos T B, 2015(64) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, geographic location, number of medication. Number of chronic conditions	Y	Y	Y (1 year) retrospective study	PIM prevalence 28 % and older age, female, number of medications increase risk of PIM	95%CI, P value <0.05	Y	Cant 'tell	Y	May underestimate the true PIM prevalence because they do not account for OTC	Moderate
19	Hedna K, 2015(65) Elderly PIM	Y	Y	Y	Y	N Age, gender, number of medication, number of chronic condition	Y	Y	Y (3 months) retrospective	Potentially IP Prevalence 42%. ADR caused by potentially IP.	95% CI, P value <0.05	Y	Cant 'tell	Y	Undetected confounders.	Moderate
20	Moriarty F, 2015(66) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, number of medication, number of chronic condition, level of education.	Y	Y	Y (1 year)	PIM prevalence (36.7%-64.8%). Female, age and higher number of medicines were	95% CI	Y	Y	Y	Lack of information on OTC from the pharmacy claim data.	High

						None				associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be associated with change in PPO prevalence.						

Table 3: Medication errors patient-related risk factors

Risk factor	Number of studies with positive association	Number of controlled studies	Controlled for	Specific information	OR or RR (95% or 99% CI) p-value
Age ≥ 75 years	13 (17, 27, 30, 35, 37, 45, 46, 48, 54, 62-64, 66)	10	NA	≥ 80 years	OR 1.021 (95% CI 1.018-1.023) p<0.001.(46)
			Adjusted for age, sex, number of regular medicine and diagnosed chronic condition	Older age	OR 1.03 (95% CI 1.02-1.04) p<0.05.(66)
			NA	Older age	OR 1.05 (95% CI 1-1.09) p=0.046.(54)
			NA	Older age	OR 1.06 (95% CI 1.0-1.13) p=0.037.(17)
			NA	≥ 75 years	OR 1.10 (95% CI 1.05-1.15) p<0.001.(30)
			NA	≥ 85 years	OR 1.18 (95% CI 1.16-1.20) p<0.05.(37)
			Adjusted for sex, age and number of chronic drugs	≥ 85 years	OR 1.52 (95% CI 1.46-1.6).(35)
			NA	≥ 85 years	OR 1.53 (95% CI 1.5-1.55) p< 0.01.(64)
			NA	≥ 85 years	OR 1.79 (95% CI 1.19-2.83) p=0.009.(63)

			Adjusted for sex, age	≥ 75 years	OR 4.03 (95% CI 3.79-4.28) p<0.001.(27)
Comorbidity or Number of disease or Chronic condition drug group (CCDG) score ≥ 4	10 (17, 19, 27, 37, 40, 49, 52, 66, 72, 73)	3	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of chronic conditions	PPO: OR 1.47 (95% CI 1.39-1.56) p<0.05.(66)
			NA	CCDG score ≥ 4	OR 1.76 (95% CI 1.72-1.81) P<0.05.(37)
			Adjusted for age, sex	Diagnosed disease ≥ 3	OR 6.43 (95% CI 3.25-12.44) p<0.001.(27)
Charlson Comorbidity Index (CCI)	3 (45, 48, 62)	1	NA	CCI < 2	RR 2.885 (95% CI 1.972-4.22) p=0.(62)
Female gender	10 (27, 29, 40, 45, 46, 55, 57, 59, 64, 66)	4	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition		PIM: OR 1.27 (95% CI 1.07-1.5) p<0.05.(66)
			Adjusted		OR 1.6 (99% CI 1.58-1.64).(57)
			Adjusted for age, sex, education level, partnership, per capita		Beers 2003: OR 2.5 (95% CI 1.9-3.5)

			income and occupation		Beers 2012: OR 1.8 (95% CI 1.3-2.5).(29)
			Adjusted for sex, age		OR 2.49 (95% CI 2.29-2.75) p<0.001.(27)
Health literacy or Low education	2 (45, 74)	1	Adjusted for age, sex, type of residential area and comorbidity		OR 1.09 (95% CI 1.07-1.17).(45)
Hospital admission	2 (19, 49)	1	NA		OR 3.35 (95% CI 2.43-4.62) p<0.05.(49)
Middle family income	1 (55)	NA	NA		
Polypharmacy	26 (17, 26, 27, 29, 30, 34, 35, 37-39, 46, 48-50, 52, 54, 55, 61-64, 66, 67, 69, 70, 73)	18	NA	Higher number of prescribed medications	OR 1.06 (95% CI 1.39-1.98) p<0.001.(54)
			Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of prescribed medications	PIM: OR 1.2 (95% CI1.17-1.24) p<0.05 PPO: OR 1.04 (95% CI 1.01-1.07) p<0.05.(66)
			NA	≥ 4 medications	OR 1.91 (95% CI 1.83-2.0) p<0.001.(30)
			NA	Higher number of prescribed medications	OR 1.99 (95% CI 1.80-2.18) p=0.000.(17)
			Adjusted for age, sex, education level, partnership, per capita income and occupation	≥ 5 medications	Beers 2003: OR 2.9 (95% CI 2.1-3.8) Beers 2012: OR 2.7 (95% CI 2-3.6).(29)
			Adjusted for disability, coronary artery disease, heart failure and other comorbidities	≥ 5 medications	IP: OR 2.9 (95% CI 1.5-5.8) Potential major DDI: 3.8 (95% CI 1.7-8.2).(34)

			Adjusted for age, sex, number of chronic conditions and number or drug consumed	≥ 3 medications	OR 3.21 (95% CI 2.78-3.59) p<0.001.(27)
			Adjusted for age, sex, length of hospital stay, and residential situation	≥ 5 medications	OR 3.22 (95% CI 1.40-7.42) p=0.006.(70)
			NA	≥ 6 medications	OR 3.37 (95% CI 2.08-5.48) p<0.001.(26)
			NA	≥ 7 medications	OR 4.528 (95% CI 4.52-4.54) p<0.001.(46)
			Adjusted for age, sex, CCI, history of cardiovascular disorder, history of digestive disorder	≥ 5 medications	OR 5.4 (95% CI 3-9.7) p<0.001.(61)
			Adjusted for sex, age and number of chronic drugs	≥ 6 medications	OR 5.59 (95% CI 5.39-5.80).(35)
			NA	≥ 5 medications	OR 5.69 (95% CI 5.0-6.48) p<0.05.(49)
			NA	≥ 6 medications	STOPP: RR 6.837 (95% CI 4.155-11.247) START: RR 2.051 (95% CI 1.25-3.367).(62)
			NA	≥ 10 medications	OR 7.33 (95% CI 7.15-7.51) p<0.05.(37)
			NA	≥ 9 medications	OR 7.43 (95% CI 3.20-17.23) p<0.001.(63)
			NA	≥ 10 medications	Male: OR 8.2 (95% CI 8-8.4) Female: OR 9.6 (95% CI 8.2-11.2).(39)
			NA	≥ 10 medications	OR 11.45 (95% CI 11.2 -11.7) p<0.01.(64)

Table 4: Medication errors healthcare professional-related risk factors

Risk factor	Number of studies with positive association	Number of controlled studies	Adjusted for	OR or RR or Beta (95% or 99% CI) p-value
Age ≥ 51 years	2 (46, 64)	2	NA	OR 1.03 (95% CI 1.01 -1.06) p<0.01.(64)
			NA	OR 1.238 (95% CI 1.235-1.242) p<0.001.(46)
More than one physician involved in their care	5 (27, 57, 69, 72, 73)	3	NA	Beta 0.7 (95% CI 0.5-1.0) p=0.034.(72)
			Adjusted for age, sex, number of chronic conditions and number or drug consumed	OR 1.39 (95% CI 1.17-1.67) p<0.001.(27)
			Adjusted for age and number of prescriber	OR 3.52 (99% CI 3.44-3.60).(57)
Male general practitioner	2 (46, 64)	2	NA	OR 1.07 (95% CI 1.05-1.10) p<0.01.(64)
			NA	OR 1.206 (95% CI 1.202-1.210) p<0.001.(46)
Frequent changes in prescription	1 (72)	1	NA	Beta 0.4 (95% CI 0.2-0.9) p=0.019.(72)
Not considering the prescription of other physicians	1 (72)	1	NA	Beta 1.9 (95% CI 1.1-3.2) p=0.013.(72)
Inconsistency in the information	1 (72)	1	NA	Beta 4.4 (95% CI 1.3-14.8) p=0.013.(72)
Outpatient clinic visit	1 (39)	1	NA	1.4 (Male 95% CI 1.3-1.4) (Female 95% CI 1.3-1.6).(39)

Family medicine/ general practice specialty	3 (46, 49, 64)	3	NA	OR 1.06 (95% CI 1.03-1.10) p<0.01.(64)
			NA	OR 1.267 (95% CI 1.265-1.269) p<0.001.(46)
			NA	OR 1.46 (95% CI 1.28-1.65) p<0.05.(49)

Table 4: Medication errors healthcare professional-related risk factors.

Appendix 1: Search strategies

A. MEDLINE

1. Medication Errors/ae, cl, mt [Adverse Effects, Classification, Methods]
2. "Drug-Related Side Effects and Adverse Reactions"/
3. adverse drug event*.mp.
4. medication error*.mp.
5. Patient Safety/
6. drug safety.mp.
7. medication safety.mp.
8. prescribed medication*.mp.
9. prescribed drug*.mp.
10. Nonprescription Drugs/
11. over the counter medication*.mp.
12. patient error*.mp.
13. medication management.mp.
14. Medication Therapy Management/

15. drug related problem*.mp.

16. medication related problem*.mp.

17. preventable adverse drug event*.mp.

18. preventable adverse event*.mp.

19. potential adverse event*.mp.

20. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. household*.mp.

23. residence*.mp.

24. residential home.mp.

25. ambulatory care.mp.

26. Outpatients/

27. self care/ or self medication/ or self manage*.mp.

28. After-Hours Care/

29. out of hours medical care.mp.

30. Homebound Persons/

31. home visit.mp.

32. face to face home interview.mp.

33. face to face interview.mp.

34. Primary Health Care/

35. General Practice/

36. Family Practice/

37. Patient-Centered Care/

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. ((after or post) adj2 hospital discharge).mp.

40. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. Epidemiology/

42. Prevalence/

43. Incidence/

44. risk factor*.mp.

45. follow up.mp.

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. observational.mp.

50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51. 21 and 40 and 50

52. limit 51 to (humans and yr="1990 -2015")

B. EMBASE

1. adverse drug event*.mp.

2. medication error/

3. patient safety/

4. drug safety/

5. medication safety.mp.

6. prescription drug/

7. prescribed medication*.mp.

8. non prescription drug/

9. over the counter medication*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10. patient error*.mp.

11. medication therapy management/

12. medication management.mp.

13. drug related problem*.mp.

14. medication related problem*.mp.

15. preventable adverse drug event*.mp.

16. preventable adverse event*.mp.

17. potential adverse drug event*.mp.

18. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. household*.mp.

21. residence*.mp.

22. ambulatory care/

23. outpatient care/ or outpatient/

24. self care/

25. self medication/

26. self manage*.mp.

27. after hours care.mp.

28. out of hours medical care.mp.

29. home visit.mp.

30. interview/ or face to face interview.mp.

31. primary health care/

32. general practice/

33. patient centered care.mp. or patient care/

34. family practice.mp.

35. ((after or post) adj2 hospital discharge).mp.

36. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

37. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. epidemiology/

39. prevalence/

40. incidence/

41. risk factor*.mp.

42. follow up/

43. observational method/

44. cross-sectional study/ or cross sectional.mp.

45. cohort.mp.

46. case control study/ or case control.mp.

47. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. 19 and 37 and 47

49. limit 48 to (human and yr="1990 -2015")

C. PsycINFO

1. medication error*.mp.

2. adverse drug event*.mp.

3. drug related adverse event*.mp.

4. patient safety.mp.

5. drug safety.mp.

6. medication safety.mp.

7. exp Prescription Drugs/ or exp "Prescribing (Drugs)"/

8. prescribed medication*.mp.

9. exp Nonprescription Drugs/

10. over the counter medication*.mp.

11. patient error*.mp.

12. medication management.mp.

13. medication therapy management.mp.

14. drug related problem*.mp.

15. medication related problem*.mp.

16. preventable adverse event*.mp.

17. preventable adverse drug event*.mp.

18. potential adverse event*.mp.

19. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21. household*.mp.

22. residence*.mp.

23. residential home.mp.

24. ambulatory care.mp.

25. exp Outpatients/

26. self care.mp.

27. exp Self Medication/

28. exp Self Management/

29. after hours care.mp.

30. home visit.mp.

31. exp Home Visiting Programs/

32. exp Interviews/ or face to face interview.mp.

33. exp Primary Health Care/

34. exp General Practitioners/ or general practice.mp.

35. family practice.mp.

36. patient centered care.mp.

37. ((after or post) adj2 hospital discharge).mp.

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp Epidemiology/

41. incidence.mp.

42. prevalence.mp.

43. risk factor*.mp.

44. follow up.mp.

45. exp Observation Methods/

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. 20 and 39 and 49

51. limit 50 to (human and yr="1990 -2015")

D. Web of Science

#5	#4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#4	TS=(follow up) OR TS=(cross sectional) OR TS=(cohort) OR TS=(case control) OR TS=(observational study) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#3	TS=(epidemiology) OR TS=(incidence) OR TS=(prevalence) OR TS=(risk factor*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#2	**TOPIC:** (household) *OR* **TOPIC:** (residence) *OR* **TOPIC:** (ambulatory) *OR* **TOPIC:** (community) *OR* **TOPIC:** (outpatient) *OR* **TOPIC:** (general practice) *OR* **TOPIC:** (family practice) *OR* **TOPIC:** (primary health care) *OR* **TOPIC:** (patient centered care) *OR* **TOPIC:** (self care) *OR*

	TOPIC: (self manage*) *OR* **TOPIC:** (self medication*) *OR* **TOPIC:** (after hours care) *OR* **TOPIC:** (after hospital discharge) *OR* **TOPIC:** (post hospital discharge) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#1	**TOPIC:** (medication error*) *OR* **TOPIC:** (adverse drug event*) *OR* **TOPIC:** (drug related adverse event*) *OR* **TOPIC:** (medication related adverse event*) *OR* **TOPIC:** (patient safety) *OR* **TOPIC:** (drug safety) *OR* **TOPIC:** (patient error*) *OR* **TOPIC:** (drug related problem*) *OR* **TOPIC:** (preventable adverse drug event*) *OR* **TOPIC:** (potential adverse drug event*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015

E. CINAHL

S25	S21 AND S22 AND S23 Limiters – Published Date: 19900101-20151031

S24	S21 AND S22 AND S23
S23	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S22	S8 OR S9 OR S10 OR S11 OR S12 OR S13
S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S20	(MH "Case Control Studies")
S19	"cohort"
S18	(MH "Cross Sectional Studies")
S17	(MH "Prospective Studies")
S16	(MH "Risk Factors")
S15	(MH "Incidence")
S14	(MH "Prevalence")
S13	(MH "Family Practice") OR "general practice"
S12	(MH "Primary Health Care")
S11	(MH "Self Care")
S10	(MH "Ambulatory Care")
S9	(MH "Outpatients")

S8	"household*"
S7	"medication therapy management"
S6	"drug related problem*"
S5	"over the counter medication*"
S4	"prescribed medication*"
S3	"drug safety"
S2	(MH "Adverse Drug Event")
S1	(MH "Medication Errors")

F. Global Health Library (EMRO)

(Adverse drug event* OR medication error* OR patient error*) AND (outpatient OR ambulatory OR general practice OR family practice OR household OR community OR home visit OR after hospital discharge) AND (prevalence OR incidence OR risk factor* OR cross sectional OR cohort OR case control)

G. Google scholar

(Medication error* OR adverse drug event*) AND (home* OR ambulatory OR community OR outpatient OR general practice OR after discharge) AND (prevalence OR incidence OR risk factor* OR Cross sectional OR cohort OR case control)

2- Experts in the field was contacted by email:

	Date	Replay or not	Result
1- Tahir M khan from Malaysia	11/8/2015	Yes	(Medication error in the Southeast Asian countries) systematic review study
2- Azmi Hassali from Malaysia	11/8/2015	Yes	Referred to Tahir M khan
3- Izham M Ibrahim from Malaysia	11/8/2015	No	-
4- David Bates	11/8/2015	No	-

5- Tejal Gandhi	11/8/2015	No	-
6- Kathleen Walsh	11/8/2015	Yes	Published papers

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	51 (table2)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019101.R1
Article Type:	Research
Date Submitted by the Author:	12-Jan-2018
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology, General practice / Family practice, Global health
Keywords:	medication errors, adverse drug events, error-related adverse drug events, prevalence, incidence, risk factor

What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature

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Keywords: medication errors, adverse drug events, error-related adverse drug events, drug related problems, prevalence, incidence, risk factor, primary care, ambulatory care, home setting, and adult.

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Abstract

Objectives: To investigate the epidemiology of medication errors and error-related adverse events in adults in primary care, ambulatory care and patients' homes.

Design: Systematic review.

Data source: Six international databases were searched for publications between 1/1/2006-31/12/2015.

Data extraction and analysis: Two researchers independently extracted data from eligible studies and assessed the quality of these using established instruments. Synthesis of data was informed by an appreciation of the medicines' management process and the conceptual framework from the International Classification for Patient Safety (ICPS).

Results: 60 studies met the inclusion criteria, of which 53 studies focused on medication errors, three on error-related adverse events and four on risk factors only. The prevalence of prescribing errors was reported in 46 studies: prevalence estimates ranged widely from 2-94%. Inappropriate prescribing was the most common type of error reported. Only one study reported the prevalence of monitoring errors, finding that incomplete therapeutic/safety laboratory-test monitoring occurred in 73% of patients. The incidence of preventable adverse drug events (ADEs) was estimated as 15/1000 person-years, the prevalence of drug-drug interaction (DDI) -related adverse drug reactions (ADR) as 7% and the prevalence of preventable ADE as 0.4%. A number of patient, healthcare professional and medication-related risk factors were identified, including the number of medications used by the patient, increased patient age, the number of comorbidities, use of anticoagulants, cases where more than one physician was involved in patients' care and care being provided by family physicians/general practitioners (GP).

Conclusion: A very wide variation in the medication-error and error-related adverse events rates is reported in the studies, this reflecting heterogeneity in the populations studied, study designs employed and outcomes evaluated. This review has identified important limitations and discrepancies in the methodologies used and gaps in the literature on the epidemiology and outcomes of medication errors in community settings.

Strengths

- This is the first systematic review on the epidemiology of medication errors and medication associated harm in community settings. The use of the International Classification for Patient Safety (ICPS) conceptual framework helped with framing and organising the findings from this systematic review.
- A rigorous and transparent process has been employed, which included no language restrictions in undertaking searches, independent screening of titles, abstracts and full text papers, independent data extraction and critical appraisal of included studies by two reviewers.

Limitations

- Outcomes have been reported in a variety of ways using different tools and methodology which made it difficult to undertake any quantitative pooled summary of the results.
- Despite the comprehensiveness of the searches, we found no data regarding errors during medication dispensing and administration. This might be due to the lack of 'dispensing error' and 'administration error' terms in our search strategy, although 'medication therapy management' was included as a more over-arching search term.
- There is at present no agreed, consistently applied set of confounders that should be taken into account when trying to make causal inferences.

Introduction

Patient safety is a public concern in healthcare systems across the world.(1) Medication errors (ME) and error-related adverse drug events (ADEs) are common and are responsible for considerable patient harm.(1) More specifically, ADEs can lead to morbidity, hospitalisation, increased healthcare costs and, in some cases, death.(1) It has been estimated that 5-6% of all hospitalisations are drug-related,(2, 3) with one estimate suggesting that ADEs causing hospital admission in the United Kingdom (UK) occur in around 10% of inpatients; approximately half of these ADEs are believed to be preventable.(4) The cost of medication errors worldwide has been estimated as 4$2 billion/year.(5)

Since the release of *To Err is Human: Building a Safer Health System* by the Institute of Medicine (IOM; now the National Academy of Medicine)(6), which focused on acute care settings, most patient safety research has been conducted in hospital settings.(7, 8) Given that international and national policy drivers are for patients to be increasingly managed in primary, ambulatory and home settings in order to realise the goals of more accessible, patient-centred and efficient healthcare,(9) there is an increased sense of urgency to further focus attention on community care contexts, particularly in relation to medication safety. With an aging population, particularly in economically-developed countries, as well as the use of polypharmacy, there is a need to empower patients, particularly those with chronic diseases, to self-care safely.

The aim of this systematic review was to investigate the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts (i.e. primary care, ambulatory and home settings). Box 1 provides definitions of the key terms employed in this review.

Methods

Protocol and reporting

The study protocol was developed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and was registered in

PROSPERO.(10, 11) The detailed systematic review protocol has also been published.(12)

Eligibility criteria/ study selection:

Studies conducted in adults (≥18 years) who were looked after in the community and living in their own or family homes without home healthcare or nursing home were eligible for inclusion in this review. The studied patients could have been self-managing, receiving care in primary care or ambulatory care settings, or any combination of the above. Studies were included if they were population-based, cross-sectional or cohort studies, which were suitable to estimate the incidence and prevalence of medication errors or ADEs. These study designs and case-control studies were considered eligible to study risk factors for the development of error-related ADEs. Studies with prescribed and/or over-the-counter (OTC) medications as the exposure of interest were eligible.

Paediatric studies (<18 years) and studies on patients receiving care in hospital at home settings (i.e. continuous medical and/or nursing care provided to patients in their own homes), in nursing homes, as hospitalised in-patients or in emergency departments (ED) were excluded. Randomised controlled trials (RCT) were excluded since these could not be used to reliably assess the incidence and/or prevalence of the outcomes of interest. Existing reviews were also excluded since the focus was on the primary literature. Incompletely reported studies, e.g. in the form of abstracts, were not eligible for inclusion. Studies on illegal substance abuse, herbal products and those focusing on particular medications, were also excluded.

No restriction on the language of publication was employed.

Data sources and search strategy

Search terms were developed based on the systematic review protocol.(12) The search terms and detailed search strategies are presented in Appendix 1. In summary, these involved identifying search terms (and their synonyms) in relation to medication safety, community care settings and study design, and combining these concepts with the Boolean operator AND to identify studies that intersected all three search concepts of interest. Examples of the search terms used included: for the outcome: medication safety, medication error, preventable adverse drug event, patient error; for the setting: ambulatory care, outpatient, self-care, primary healthcare and general practice; and for the study design: cohort study, cross sectional study and observational study. Six

biomedical databases were searched, including the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Eastern Mediterranean Regional Office of the World Health Organization (WHO EMRO), MEDLINE, PsycINFO, and Web of Science between 01 January 2006 and 31 December 2015. Google Scholar was searched for additional studies. An international panel of experts was also contacted to identify unpublished work and research in progress (Appendix 1). The reference list of all included studies was further reviewed for additional possible eligible studies.

The databases were searched by Ghadah Assiri (GA). The title and abstracts were then independently screened for eligible studies according to the above detailed selection criteria by GA and a second reviewer, Nada Shebl (NS). The corresponding authors of the eligible articles were contacted if additional information was needed. Disagreements were resolved by discussion between the reviewers or by arbitration by a third reviewer, Aziz Sheikh (AS), if a decision could not be reached. Full-text articles were retrieved from selected studies and reviewed according to the selection criteria. Each copy of the selected studies was retrieved and the reason for excluding other studies was clearly noted.

Data extraction and risk of bias assessment

Data were independently extracted and recorded onto a customised data extraction sheet by two reviewers [GA and NS, or GA and Mansour Mahmoud (MM)]. Discrepancies were resolved by discussion or by arbitration by an additional reviewer (AS), if necessary.

Key information such as study design, study type (retrospective, prospective), population of interest, exposure of interest, outcomes of interest and main findings were extracted.

The risk of bias assessment was independently carried out on each study by two reviewers [GA and NS, or GA and Nouf Aloudah (NA)] using the Critical Appraisal Skills Program (CASP) quality assessment tool for cohort and case-control studies,(13) and cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Descriptive Studies.(14) Any disagreements were resolved by consensus or by arbitration by a third reviewer (AS) if a decision could not be reached. Each study was given an overall grading as being at high, medium, or low risk of bias.

Data synthesis

Data were summarised in detailed data tables, which included information on the incidence, prevalence, relative risk and odds ratios (ORs), together with 95% confidence intervals, for each study (where available). A descriptive and narrative synthesis of the extracted data was undertaken.

The definition of incidence rate used in this review is: *"the number of patients with one or more [medication error or preventable ADE] (numerator) divided by the total number of patients at risk per time unit (denominator)."*(15) The definition of prevalence rate used in the data extraction is: *"the number of patients experiencing one or more [medication error or preventable ADE] (numerator) divided by the total number of patients in the study population (denominator)."*(16) The prevalence rate per population was either reported and extracted directly from the included study or calculated from data provided in the study.

We worked with the definitions of medication errors and error-related ADEs employed in individual studies. These errors may have occurred anywhere in the medicines' management process.(1) Medication errors were described according to: i). the stage in the medicines' management process when the error occurred i.e. prescribing, dispensing, administration and monitoring;(1) and ii). the type of error that occurred in each stage according to the conceptual framework for the International Classification for Patient Safety (ICPS) definitions (Box 2).(17)

Risk factors were categorised as patient, healthcare professional and medication-related risk factors.

Changes from the original protocol

The following changes were made from the plans described in the research protocol:(12) i). due to the large quantity of studies found during the initial search and because of medications and practice changes over the years, only studies published in the last 10 years were included: 01 January 2006 to 31 December 2015; ii). only studies with the incidence or prevalence rate per number of patients were included; and iii). meta-analysis was not possible due to the heterogeneity of outcomes, methods and definitions.

Results

A total of 13,033 potentially eligible studies were identified after removing duplicates, of which 59 studies met the inclusion criteria. One additional study was identified through hand-searching. Therefore, a total of 60 studies were included in the systematic review (Figure 1).

One study was available only in German, and one in Spanish. Those two papers were retrieved and translated into English by native speakers.(18, 19)

The key characteristics of all included studies are presented in Table 1. The quality assessments of these studies are summarised in Table 2.

Nine studies were conducted in Asia, four in Australia, 32 in Europe, eight in the North America, five in South America, and two were conducted across continents [one study covering two Australian countries, three European countries, one North American country and one South American country,(20) and one study across two Australian countries, four European countries, one North American country and one South American country].(21) 19 studies were conducted in primary healthcare or general practice contexts, 15 studies in home or community settings, 16 studies in ambulatory care or outpatient settings, five studies in community pharmacies and two studies in post-discharge settings, while three studies used secondary data analysis.

Eleven studies enrolled adults in all age groups (>18 years), three studies reported the mean age only,(22-24) one enrolled those of 55 years or older,(25) five enrolled those aged 60 years or older ,(26-30) and the majority of studies (n=40 studies, 67%) enrolled patients of 65 years or older. If the study included adult and paediatric data, only relevant adult data were extracted.

The quality of the cross-sectional or descriptive studies using the JBI Critical Appraisal Checklist was high for nine studies, moderate for 10 studies and low for one study. The quality of the cohort studies using the CASP quality assessment tool was high for 37 studies and moderate for three studies.

Different methods of medication errors and error-related adverse events identification were used in the studies, including data review (electronic/paper-based medical record

review, lab review, prescription review), database analysis, patient survey (face-to-face or telephone interview and survey or questionnaire), patient self-report and home visits.

Medication errors

Incidence and/or prevalence

We found no study reporting data on the incidence of medication errors. Estimates of community setting medication error prevalence were available from 53 studies.(18-21, 23, 24, 26, 27, 29-73)

Self-reported medication errors

The period prevalence of self-reported medication errors was measured in four cross-sectional studies by Adams R J (2009), Lu C Y (2011), Sears K (2012) and Mira J J (2013).(20, 21, 72, 73) In the first three studies, the period prevalence was reported as 2%, 6% and 6% respectively,(20, 21, 72) while in Mira's study, 75% of elderly patients with multiple comorbidities and polypharmacy (five or more drugs) reported having made at least one mistake with their medication (including errors related to dose, similar appearance of medications, and lack of understanding of the physician's instructions).(73) In this study, in 5% of cases, errors due to drug confusion had very severe consequences, requiring a visit to the emergency services or hospital admission.(73) That wide differences in prevalence were seen between the first three studies and the last may be due to population factors. Mira's study population comprised of older poly-medicated patients with multiple comorbidities. This elderly group had a greater risk of error, while the first three studies had populations including any patient over 18 years.

Medication error according to medicines' management process

1- Prescribing errors:

The point or period prevalence of prescribing errors was reported in 46 studies. In these studies, prescribing errors included errors in drug indications, drug-disease interactions, drug-drug interactions (DDI) and dosing error, as well as inappropriate prescribing, which was the most common error reported.

Indication

Koper D et al. (2013) found that, on average, 2.7 medications per patient were not indicated, with a total of 94% of patients having medications prescribed by the general practitioner, but not mentioned in the indication of the UpToDate®.(23)

Drug-disease interactions or contra-indications

Drug-disease interactions were measured in one study by Mand P (2014) with a prevalence of 10%.(31)

Drug-drug interactions

The prevalence of DDIs was measured in 11 studies and ranged from 2 - 58%.(23, 24, 26, 27, 30, 32-37) This could in part have been due to the fact that different DDI screening tools were used, namely: DDI compendia and (ePocrates RX), Thompson Micromedex program, database Pharmavista, program BotPlus of the General Council of Pharmacists' Official Colleges, British National Formulary 2010, Italian computerised interaction database, DrugDigest®, Drugs®, Micromedex® and Medscape®.

Inappropriate prescribing

A- The prevalence of potentially inappropriate medication (PIM) was measured in 37 studies in the elderly age group only (≥65 years) and ranged from 5 - 94%.(18, 19, 23, 26, 29, 35, 38-68) This extremely wide range of inappropriate prescribing prevalence estimates is likely to be, at least in part, due to the different detection tools used, namely: Beers 2003, the 2006 Health Plan Employer Data and Information Set (HEDIS), Improved Prescribing in the Elderly Tool (IPET), Medication Appropriate Index (MAI), PRISCUS and Screening Tool of Older Person's Prescriptions (STOPP) criteria. Johnell K (2008) and Haider S I (2009) mentioned two other specific criteria.(44, 46)

B- The prevalence of potential prescribing omission (PPO) was measured in five studies for the elderly age group only (≥65 years) ranging from (23 - 57%).(19, 49, 63, 64, 67) PPO was detected by Screening Tool to Alert doctors to Right Treatment (START) and Assessing Care of Vulnerable Elders (ACOVE).

Dosing errors

Koper D (2013) found that over- and/or under-dosing was found in 44% of patients.(23)

2- **Monitoring errors:** Monitoring errors were measured in one study by Ramia E (2014), who found that 73% of patients had incomplete therapeutic/safety laboratory-test monitoring tests.(69)

3- **Other errors: discrepancy**

One study found that at least one discrepancy between the medication lists from the pharmacy, the general practitioner (GP), or the patient was present in 86.7% of patients.(70) In another study, almost half of the patients (47.6%; 95% CI 40.5-54.7) had one or more discrepancies in medication information at discharge.(71)

The reported point or period prevalence of medication errors in the community settings, including self-reported medication errors, prescribing errors (indication, drug-disease interaction, DDI, inappropriate prescribing, dosing error and inappropriate prescribing), monitoring error and discrepancies, had a very wide range from 2 - 94%. Figure 2 shows the medication errors prevalence estimates stratified according to the settings. The highest prevalence was in primary healthcare or general practice (94%).

Risk factors

Risk factors for medication errors were either related to patients, healthcare professionals and/or medications.

Patient-related risk factors

Patient-related risk factors for the development of medication errors were discussed in 33 studies.(18, 20, 27, 29-31, 35, 36, 38-41, 46, 47, 49-51, 53, 55, 56, 58, 60, 62-65, 67, 68, 70, 71, 73-75)

Seven risk factors related to patients were addressed in the included studies: polypharmacy, increased age, number of diseases or comorbidities, female, low level of education, hospital admission and middle family income (Table 3).

Several definitions of polypharmacy existed, ranging from prescription of at least three to six medications concurrently. Twenty-six studies showed a positive association between

medication error and polypharmacy,(18, 27, 29-31, 35, 36, 38-40, 47, 49-51, 53, 55, 56, 62-65, 67, 68, 70, 71, 74) of which 18 mentioned the estimated OR ranging from 1.06 to 11.45.(18, 27, 29-31, 35, 36, 38, 40, 47, 50, 55, 62-65, 67, 71)

Older age (≥ 75 years) was associated with medication errors in 13 studies, (18, 27, 31, 36, 38, 46, 47, 49, 55, 63-65, 67) of which 10 mentioned the OR ranging from 1.02 to 4.03. (18, 27, 31, 36, 38, 47, 55, 64, 65, 67)

Healthcare professional-related risk factors

Nine risk factors related to healthcare professionals for the development of medication errors were identified: more than one physician involved in their care, family medicine/GP speciality, age ≥ 51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits (see Table 4).(27, 40, 47, 50, 58, 65, 70, 73, 74)

Medication-related risk factors

Medication-related risk factors for the development of medication error were: multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication,(25), no medication administration routine, poor adherence and patients confused by generic and trade names.(76) In one study by Johnell K (2008), multi-dose drug dispensing users (i.e. medicines machine-packed into unit-dose bags for each time of administration) were more exposed to all indicators of potentially inappropriate drug.(44)

Receiving anticoagulant therapy (OR 2.38; 95% CI 2.15-2.64) was strongly associated in one study to potential drug-disease interactions.(31)

The use of OTC and/or prescribed drugs was a risk factor in two additional studies.(29, 41) The use of OTC medications was associated with PIM; the OR after adjusting for age, sex, education level, partnership, per capita income and occupation was (2.5; 95% CI 1.7-3.6) using Beers 2003 and (1.8; 95% CI 1.2-2.5) using Beers 2012.(29)

Error-related adverse events

Error-related adverse events or preventable ADEs were mentioned in six studies.(22, 28, 29, 70, 71, 77) The most frequently reported consequences were ED visits and hospitalisation.

Two methods for detecting ADE were applied: an ADE monitor (i.e. using computerised programs composed of rules that identified incidents suggesting that an ADE might be present),(22) and using trigger tools to detect ADEs.(77)

Incidence and/or prevalence

One study estimated preventable ADE incidence as 15/1000 person-years.(22) Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers were the most common medications associated with preventable ADE.(22) The estimate of the prevalence of preventable ADE was calculated from five studies as detailed below.(28, 29, 70, 71, 77)

All stages of medicines' management process

Field T S (2007) found the prevalence of error caused by patients leading to an adverse event to be 0.38% i.e. less than 1% of the overall population experienced a medication related adverse event. He found that the majority of patient errors-related adverse events (n=129) occurred in modifying the medication regimen (42%), administering the medication (32%), or not following clinical advice about medication use (22%).(77) The medications associated with more than 10 preventable ADEs were anticoagulants/anti-platelets, cardiovascular drugs, diuretics, hypoglycaemics and non-opioid analgesics.(77)

Error-related adverse events according to medicines' management process

1- Prescribing errors

DDI: Obreli Neto P R (2012) found that DDI-related adverse drug reaction (ADR) occurred in 7% of patients.(28) Warfarin, digoxin, spironolactone and acetylsalicylic acid were the drugs most commonly associated with DDI-related ADRs.(28)

PIM: 46% of participants reported complaints related to ADEs by interview; 95% of these were caused by prescribed medications.(29)

Use of inappropriate drugs was associated with an increased risk of nursing home admission, hospitalisation, more outpatient visit days, ED visits, and having ADEs or ADRs.(42, 50, 61, 66)

2- Other errors

Adverse events (under-treatment due to deletions, ADR due to additions and DDI) related to discrepancy between the medication lists from the patient, the GP, or the pharmacy were identified in 24% of patients.(70) Two discrepancies were categorised as having the potential to cause severe patient harm.(71)

Risk factors

Risk factors for the error-related adverse events were discussed in three studies only.(28, 70, 77)

Patient- related risk factors

Field T S (2007) found that the number of regularly scheduled medications (seven or more medications (OR 3.3; 95% CI 1.5-7.0) and a Charlson Comorbidity Index (CCI) score of five or more (OR 15.0; 95% CI 6.5-34.5) were both associated with higher risk of patient error leading to preventable ADE.(77) Obreli Neto P R (2012) found that an age of 80 years or more (OR 4.4; 95 % CI 3.0–6.1, p<0.01), a CCI of four or more (OR 1.3; 95% CI 1.1-1.8, p<0.01) and consumption of five or more medications (OR 2.7; 95% CI 1.9-3.1, p<0.01), were associated with the occurrence of DDI-related ADRs.(28) In addition, Tulner L R (2009) found that the number of medications was significantly positively correlated with medication discrepancies and adverse patient events.(70)

Medication-related risk factors

The use of medication with narrow therapeutic indices such as warfarin were associated with an increased risk of DDI-related ADRs (OR 1.7; 95% CI 1.1-1.9, p<0.01).(28)

Discussion

Summary of main findings

We sought to critically review previous studies conducted in the community of the incidence/prevalence of medication errors and associated adverse events and to identify the main risk factors. We identified 60 studies carried out in various countries providing a comprehensive assessment of the available evidence on the epidemiology of medication errors and error-related ADEs in community settings.

No relevant studies on the incidence of medication errors in these settings were found. The reported point or period prevalence of medication errors in community settings had a very wide range (i.e. 2-94%). This wide range appears, at least in part, to be due to the inconsistency in the definitions of the medication errors used in the studies, differences in populations studied, methodologies employed for error detection, and different outcome measures. More than half (37 studies) of the resulting studies were regarding the prescription of inappropriate drugs within the prescribing error stage in an elderly age group using different criteria. The comparison of those criteria is challenging due to the difference in medication use, consumption and availability of those medications to patients between countries. Further work is needed to review errors occurring at administration and dispensing stages of the medicines' management process.

As for preventable ADEs, which may in some cases occur as a result of medication errors, only one study reported error-related adverse events incidence, measured as 15/1000 person-years.(22) The prevalence of preventable ADE was further reported in five other studies and varied according to the medication error type that resulted in the adverse event.

The most common patient-related risk factors for both medication errors and preventable ADEs mentioned were the number of medications used by the patient and the increased age of patients.

Strengths and limitations

The main strengths of this systematic review are that a rigorous and transparent process has been employed, which included no language restrictions, an independent screening of

titles and abstracts, independent data extraction and critical appraisal of included studies by two reviewers. It is the first review undertaken within community settings. The use of the ICPS conceptual framework,(17) which provides a comprehensive definition of each concept and type of error in the medicines' management process, is a further strength.

However, several limitations need to be considered. Firstly, despite the thorough process, no data were found regarding the dispensing error stage. This might be due to the lack of a 'dispensing error' key-term in our search strategy, although 'medication therapy management' as a key-term was included. However, 10 studies on dispensing errors were excluded because they failed to satisfy the inclusion criteria on one or more counts. Secondly, no data were found regarding the administration error stage. However, 14 studies on administration errors were also excluded for the same previous reason. Thirdly, this systematic review had different outcomes reported in a variety of ways using different tools and methodology that made combining results in one meta-analysis difficult. Lastly, the studies addressed risk factors adjusted for different confounders, which makes it difficult to generate comparable estimates and/or make causal inferences about whether the harm resulted from the medication error.

Comparison of the findings with previous studies

The definitional variation issue is supported by another two reviews.(78, 79) Other systematic reviews focusing on the safety of primary care contexts only have identified studies with vastly different prevalence estimates of the rates of medication errors. These reflect differences in definitions, sampling strategy and populations studied; none have investigated the risk factors for medication errors.(80, 81)

Implications for research, policy and practice

There is a need for: i). improvement in the quality of research in this area. It is important that all researchers provide a standardised set of outcome measures of medication errors or internationally accepted terminology and definitions of key concepts; ii). training and monitoring of healthcare professionals with the involvement of medication safety pharmacists in the community; iii). empowering and educating the patients and the public, particularly those with chronic diseases and polypharmacy to increase their knowledge of medication safety with a record of the current medication list for each patient; iv). patient use of tools and technology particularly for monitoring and follow-up; and v). encourage

the reporting of medication errors, administration errors and dispensing errors.(82) This would strengthen the quality of research, improve the development of strategies to detect and prevent these errors and provide a safer environment for the community to self-care safely.

Conclusions

We found a very wide variation in the medication error and error-related adverse events rate between studies, which, at least in part, reflects differences in their definitions, methodologies employed for error detection or clinical heterogeneity i.e. differences in populations studied and different outcome measures. Most of the studies were conducted on elderly populations in economically-developed countries. There is therefore clearly a need to extend this work to low- and middle-income countries, particularly give the WHO's recent launch of a Global Medication Safety Challenge.(82, 83) Furthermore, most studies focused only on inappropriate prescribing with relatively little attention to other stages such as administration and dispensing. The most common patient and medication-related risk factors for both medication errors and preventable ADEs were the number of medications used by the patient, increased age and receiving anticoagulant therapy. The most common healthcare professional-related risk factors for medication error was when more than one practitioner was involved in the care of patients and care provision by family medicine and GP specialities.

This study has identified important limitations and discrepancies in the methodology used to study medication errors and error-related adverse drug events in community settings. These findings need to be considered in the context of designing future research related to medication safety. More research is needed in the areas of incidence of medication errors, administration error and dispensing errors and reporting. Researchers should use a more consistent set of definitions and outcomes in order to facilitate collation and synthesis of data.

Ethics and dissemination

The systematic review protocol was published in the British Medical Journal (BMJ) Open on 31 August 2016 and is registered with PROSPERO - an international prospective register of systematic reviews.(11, 12) It is reported using Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA). *Systematic Review Registration: (PROSPERO 2016: CRD42016048126).*

Contributorship

GA conceived the idea for this review, conducted the systematic literature search, study inclusion, data extraction and quality assessment. NS participated in the study inclusion, data extraction and quality assessment. MM participated in data extraction. NA participated in data extraction and quality assessment. GA led the writing and drafting of the manuscript, and this was commented on critically by AS, EG, HA and NS.

Funding

The systematic review protocol is a part of GA's Ph.D. study at the University of Edinburgh. King Saud University, College of Pharmacy funded the scholarship. AS is supported by the Farr Institute.

Conflicts of interest

None known.

Acknowledgments

We are grateful to Marshall Dozier for her help with formulating the search strategy; Kathrin Cresswell and Andrea Fuentes Pacheco for non-English studies translation; experts in the field for unpublished and in progress work and experts within the Farr Institute. The project was financially supported through Prince Abdullah bin Khalid Celiac Disease Research Chair, vice dean ship of research chairs, King Saud University and the University of Edinburgh.

Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Boxes

Adverse drug event (ADE): Bates et al. (1995) define ADE as, *"an injury resulting from medical intervention related to a drug."*(84) Some ADEs are caused by underlying medication errors and therefore they are preventable.
Medication error: The National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) defines a medication error as: *"any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health-care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use".*(85) Medication errors can result from any step of the medication-use process: selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration, or monitoring.(1)
Non-prescription drugs: Medicines that can be sold legally without a drug prescription.
Over-the-counter (OTC) drug: The FDA defines OTC dr*ugs as "drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription*".(86)
Prescription drug: Drugs that cannot be sold legally without a prescription.

Box 1: Key definitions.

1- Administration error
"Any discrepancy between how the medication is given to the patient and the administration directions from the physician or hospital guidelines"(1)
2- Prescribing error
"Medication error occurring during the prescription of a medicine that is about writing the drug order or taking the therapeutic decision, appreciated by any non intentional deviation from standard reference such as: the actual scientific knowledge, the appropriate practices usually recognized, the summary of the

characteristics of the medicine product, or the mentions according to the regulations. A prescribing error notably can concern: the choice of the drug (according to the indications, the contraindications, the known allergies and patient characteristics, interactions whatever nature it is with the existing therapeutics, and the other factors), dose, concentration, drug regimen, pharmaceutical form, route of administration, duration of treatment, and instructions of use; but also the failure to prescribe a drug needed to treat an already diagnosed pathology, or to prevent the adverse effects of other drugs".(17)

Inappropriate prescribing

"*The use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition. Inappropriate prescribing also includes the use of medicines at a higher frequency and for longer than clinically indicated, the use of multiple medicines that have recognized drug–drug interactions and drug–disease interactions, and importantly, the under-use of beneficial medicines that are clinically indicated but not prescribed for ageist or irrational reasons*".(87)

3- Monitoring error

"*Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed theory*".(17)

4- Dispensing error

"*Deviation from the prescriber's order, made by staff in the pharmacy when distributing medications to nursing units or to patients in an ambulatory pharmacy setting*".(17)

5- Other: discrepancies

"*Any differences between the medication described by the patient and caregivers with the drugs listed by their general practitioners (GP) or between the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list*".(70, 71)

Box 2: Classification of definitions used in this systematic review.

Figures

Figure 1: PRISMA flow diagram. (From: Moher D, Liberati A, Tetzlaff J. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement).

*Articles may be duplicated between the excluded groups.

Figure 2: Medication errors prevalence estimates according to settings.

Table 1: Systematic review data extraction table

Key characteristics of included studies									
	Author Year	**Country/ city**	**Study Design/type**	**Population of interest**	**Exposure of interest**	**Outcome of interest**	**Main finding**	**Conclusion n/N (%)**	**Additional notes**
Self- reported medication errors									
1.	Adams R J, 2009(72)	Australia	Cross-sectional	Analysis of data from 3,522 adults participating in Stage 2 of the North West Adelaide Health Study aged ≥18 years	Unclear	Self-reported adverse event (medication, diagnosis and others). Using survey.	Of the total 3522 survey participants, 148 (4.2%) reported an adverse event causing harm in the previous 12 months, giving an annual incidence of 4.2% (95% CI, 3.4%–5.0%). Medication error: The main types of adverse events perceived as causing harm were **medication error** (reported by 46% of the 148 participants reporting adverse events).	Medication error prevalence 68/3,522= (1.9%)	Subjective data rather than objective
2.	Lu C Y, 2011(20)	Australia, Canada, New Zealand, the United Kingdom, the United States, Germany and the Netherlands	Cross-sectional (secondary analysis)	11,910 respondent adult aged ≥ 18 years. Data from the 2007 Commonwealth Fund International Health Policy Survey.	Prescribed drug	Self-reported medication error and compare factors associated with medication errors across the 7 countries. Using survey.	**Self-reported medication errors prevalence:** 752 respondents had medication error. [Australia=7.4%; Canada=5.7%; New Zealand=5.9%; UK=5.2%; U.S= 7%; Germany=5.2%; Netherland=8%]. Risk factors across countries included seeing multiple specialists, multiple chronic conditions, hospitalisation and multiple emergency room visits.	Medication error prevalence: 752/11,910= (6.3%)	Prevalence for medication error alone from table 1, while the risk factors for both medical and medication error.
3.	Sears K, 2012(21)	Australia, Canada, France, Germany, the Netherlands, New Zealand, the United Kingdom and the United	Descriptive (Secondary/retrospective analysis)	9,944 adults aged ≥ 18 years from the community setting	Taking medication regularly	Patient-related risk factors associated with self-reported medication errors. Using telephone survey.	**Medication error prevalence:** 570 respondents with medication errors occurring in the community setting. Approximately 4 out of every 5 self-reported medication errors occurred in the community setting.	Medication error prevalence: 570/9,944= (5.7%)	Risk factors for both hospital and community setting.

		States							
4.	Mira J J, 2013(73)	Alicante, Spain	Cross-sectional	382 elderly aged ≥65 years from primary care. Patients on polypharmacy (5 or more drugs) and with comorbidity: [cardiovascular (51.6%); diabetes (34.3%)]	Prescribed and self-medications .	Frequency of mistakes in communication between the physician and the patient and their medication error in the last year. Using semi-structured interviews.	**Medication error prevalence:** 75.1% of the patient reported having made at least one mistake with the medication in the last year. **Risk factors:** Multiple comorbidities ($P = 0.006$), frequent changes in prescription ($P = 0.02$), not considering the prescriptions of other physicians ($P = 0.01$), inconsistency in the messages ($P = 0.01$), being treated by various different physicians at the same time ($P = 0.03$), a feeling of not being listened to ($P < 0.001$) or loss of trust in the physician ($P < 0.001$). *The error due to drug confusion had very severe consequences, requiring a visit to the emergency service or hospital admission.	Medication error prevalence: 287/382= (75%)	*Consequence
Risk factor									
5.	Sorensen L, 2006(76)	4 states of Australia	Cross sectional, prospective	204 general practice patients living in their own home aged 37-99 years.	Prescribed drugs	Prevalence and interrelationships of medication-related risk factors for poor patient health outcomes identifiable through 'in-home' visit observations.	**Risk factors:** Prevalence of nominal medication-related risk factors and health outcomes among the sample of 204 patients 1-Multiple medication storage locations used = 17(8.3%), 2- Expired medication present = 40 (19.6%), 3- Discontinued medication repeats retained = 43(21%), 4- Hoarding of medications = 43 (21%), 5- Therapeutic duplication present= 50 (24.5%), Administration error: 6- No medication administration routine = 56 (27.5%), 7- Poor adherence = 107 (52.5%), 8- Confused by generic and trade names = 114 (55.9%).		
6.	Vuong T, 2006(25)	Melbourne, Australia	Descriptive	142 discharged adult aged ≥ 55 years who were returning to independent care at home Patient at risk of medication misadventure	Discharge prescribed drugs	Unnecessary medicine stored at home as a risk factor. Using home visit within 5 days of discharge.	Unnecessary medicine stored at home prevalence 85/142= (60%) 85 (60%) of 142 patients who received a home visit allowed removal of medicines that had expired or no longer required. **Prescribing error:** drug duplication prevalence: Thirty-two (27%) patients allowed removal of 82 duplicate packs of the same item that was no longer required.	Unnecessary medicine stored at home prevalence: 85/142= (60%)	No information on how many patients had unnecessary medicine. Information available is on the patient allowed to remove unnecessary medicine.

							A total of 390 medicines were removed with a mean of 4.6 medicines per patient (range 1–21).		
7.	Pit S W, 2008(74)	New South Wales, Australia.	Cross-sectional Study	849 elderly aged ≥ 65 years from general practice	Self-medications	Prevalence of self-reported risk factors for medication misadventures Tool used: Medication Risk Assessment Form (patient survey)	**Risk factors:** 1- Using at least one medication for more than 6 months (95%). 2-More than one doctor involved in their care (59%) 3- Had three or more health conditions (57%) 4- Used five or more medicines (54%). 5- Adverse drug reactions, in the last month 39% of participants experienced difficulties sleeping, felt drowsy or dizzy (34%), had a skin rash (28%), leaked urine (27%), had stomach problems (22%) or had been constipated (22%).		*ADR as a risk factor for medication misadventure may not be related to the use of medication in all cases
8.	Mosher H J, 2012(75)	Iowa, USA	Cohort prospective	310 elderly aged ≥65 years who were cognitively intact from a Veterans Administration primary care clinic	Taking 5 or more non-topical medications	Association of health literacy with medication knowledge, adherence, and ADEs. Using interview and chart review	Total 310 patients **Prevalence of ADEs** ADEs occurred in 51 patients (16.5%) of the patients within the first 3 months of the study, which increased, to 119 patients (38.4%) over the full 12-month follow-up period. **Risk factor:** Association of health literacy with ADEs: The incidence of ADEs at 3 and 12 months appeared higher among patients with low health literacy, but this was not statistically significant.	Low health literacy increase the risk of ADEs	
Medicines' management process:									
9.	Koper D, 2013(23)	Austria	Descriptive	169 patient form general practice taking 5 or more medicines. Mean age: 76.4 ± 8.5 SD years. Of the 169 patient, 158 were elderly aged ≥ 65 years	Prescribed and OTC drug	Medication errors including non-evidence based medications, dosing errors and potentially dangerous interactions in all patients. Potential interactions were identified using the Lexi-Interact® database. PIMs in subgroup of elderly patient according to the PRISCUS list. Using case report form filled by the general practitioners	**Prescribing error prevalence:** Indication: 158 of the 169 patients (93.5%) had at least one non-evidence-based medication. Dosing error: 74 of the 169 patients (43.8%) had at least one dosing error. Drug-drug interaction (DDI) prevalence: *Category D interactions*: 99 patients (58%) had at least one category D interaction. *Category X interactions*: 4 patients (2.4%) had at least one category X interaction. PIM prevalence 59 of seniors (37.3%) had at least one medication that was inappropriate.	Medication error prevalence: 1- non-evidence based medications: 158/169= (93.5%) 2-dosing error 74/169= (43.8%) 3-category D drug interaction 99/168= (58%). category X drug interaction 4/168= (2.4%) 4- PIMs 59/158=37.3%	A medication was classified as non-evidence based if the indication for use indicated by the *general practitioners (GP*) was not mentioned in any peer-reviewed chapter of UpToDate®
10.	Mand P, 2014(31)	Germany	Descriptive retrospective	24,619 elderly aged ≥65 years	Prescribed drug	Potential drug-disease interaction (PDDI)	**Prescribing error:** contraindication or drug-disease interaction prevalence:	PDDI prevalence 2,560/24,619=	

				from family practice with at least one diagnosis named in the Beers list		frequency and whether there are gender- or age-related differences. Analysis from electronic patient records.	10.4% of elderly were exposed to at least one PDDI. **Risk factors:** 1-Patients over 75 years (OR 1.10; CI: 1.05 – 1.15) 2-Number of drugs prescribed (> 4 drugs: OR 1.91, CI: 1.83 – 2.00) 3-Blood clotting disorders/receiving anticoagulant therapy (OR 2.38, CI: 2.15 – 2.64) showed the strongest association with PDDI.	(10.4%)	
11.	Gagne J J, 2008(34)	Regione Emilia-Romagna, Italy	Cohort Retrospective	4,222,165 Regional Emilia-Romagna residents. Outpatient aged from 0 to ≥85 years	Prescribed drug	Clinically important potential DDI. Risk factors. Outpatient prescription data from the Regional Emilia-Romagna. DDI screening tool: a list of clinically important potential DDIs included 12 drug pairs that could be captured using the Regional Emilia-Romagna database.	**Prescribing error:** DDI prevalence: Exposed to potential DDI adult (19 - ≥85 year) = 7,893. Unexposed adult= 7013. Total= 14,906.	DDI prevalence: 7,893/14,906= (53%)	Risk factors for all age group including paediatrics. All age group included so results should be considered cautiously.
12.	Dallenbach M F, 2007(24)	Geneva, Switzerland	Descriptive Retrospective file review	591 outpatients. Mean age 39 years.	Prescription drug and drug currently taking	Clinically significant adverse drug interactions (ADI). Prescription review. DDI screening tool: DDI compendia and (ePocrates RX) with clinical decision support	**Prescribing error:** DDI prevalence: In 135 of the consultations, a potentially clinically significant ADI was identified.	DDI prevalence: 135/591= (23%)	
13.	Obreli Neto P R, 2011(26)	Brazil	Cross-sectional	2,627 elderly aged (60-88 years) from the primary healthcare	Prescribed drug	Potential risks in drug prescriptions: DDI, Potentially Inappropriate Medicine (PIM). Using prescription review. DDI screening tool:	**Prescribing error:** DDI prevalence: Using (DrugDigest®) showed that 4.7% and 28.4% of elderly presented at least one potential DDI classified as major and moderate respectively. Using (Medscape®) showed that 3.4% and 19.3% of elderly presented at least one potential DDI classified as major and moderate respectively.	DDI prevalence: (3.1%)-(29.1%) PIM prevalence: (26.9%)	

						(DrugDigest®, Medscape®, and Micromedex®) PIM using Beers criteria 2003.	Using (Micromedex®, showed that 3.1% and 29.1% of elderly presented at least one potential DDI classified as major and moderate respectively. **Prescribing error:** PIM prevalence 26.9% of the patients had prescriptions with at least one PIM.		
14.	Secoli S R, 2010(30)	Sao Paulo, Brazil	Cross-sectional	2,143 community-dwelling elderly aged ≥ 60 years. Data were obtained from the SABE (Health, Well-Being, and Aging) survey.	≥2 prescribed drug use	Potential DDIs and identify associated factors. Using home interview. DDI screening tool: Micromedex ® Healthcare Series.	**Prescribing error:** DDI prevalence: 568/2143= 26.5% **Risk factors:** The use of six or more medications (OR 3.37; 95% CI 2.08, 5.48) or having hypertension (OR 2.56; 95% CI 1.73, 3.79), diabetes (OR 1.73; 95% CI 1.22, 2.44) or heart problems (OR 3.36; 95% CI 2.11, 5.34) significantly increased the risk of Potential DDI.	DDI prevalence: 568/2,143= (26.5%)	
15.	Obreli Neto P R, 2012(27)	5 cities of Brazil	Cross-sectional	12,343 elderly aged ≥ 60 years from the primary public health system	Prescription for 2 or more drugs (Prescribed both within and across prescriptions)	Potential DDIs (presence of a minimum 5-days overlap in supply of an interacting drug pair) and predictor of DDI. Using medical prescriptions and patients' medical records review. DDI screening tool: DDI checker Programs (DrugDigest®, Drugs®, Micromedex® and Medscape®)	12,343 patients [(5,855 (exposed); 6,488(unexposed)] **Prescribing error:** DDI prevalence: 47.4% **Risk factors:** Female sex (OR = 2.49 [95% CI 2.29–2.75]), diagnosis of ≥ 3 diseases (OR = 6.43 [95% CI 3.25–12.44]), and diagnosis of hypertension (OR = 1.68 [95% CI 1.23–2.41]) were associated with potential DDIs. Age was associated with an increasing risk of DDIs. Number of prescribers, number of drugs consumed, ATC codes, and drugs that act on CYP450 presented positive associations with potential DDIs in univariate and multivariate analyses of drug therapy characteristics.	DDI prevalence: 5,855/12,343= (47.4%)	
16.	Indermitte J, 2007(32)	Switzerland	Descriptive	434 passer-by customers aged ≥18 years from community pharmacies	Prescription only medicines and OTC drug	Potential drug interactions. 1-Observation of customer contacts and interviews with passer-by customers purchasing selected OTC drugs, 2- Telephone interviews with regular customers treated with selected prescription only medicines identified in	**Prescribing error:** DDI prevalence: Observation of passer-by customers Of 1183 passer-by customers observed, 164 purchased at least one of the selected OTC drugs. One hundred and two (62.2%) of those subjects were interviewed. Forty-three (42.2%) mentioned taking prescribed drugs, and three of them were exposed to potential drug interactions of moderate severity. Telephone interview with regular customers	DDI prevalence: 3/102= (3%) 69/434= (16%) 116/434= (26.7%)	

						community pharmacies' databases. DDI screening tool: database Pharmavista	Out of 592 regular customers selected from the community pharmacy database, 434 (73.3%) could be interviewed. Prevalence of DDI in regular customers Sixty-nine (15.9%) of them were exposed to a potential drug interaction between purchased OTC drug for self-medication and their prescription only medicines. Furthermore, 116 (26.7%) regular customers were exposed to potential drug interactions within their prescribed drugs and in 28 (6.5%) multiple (>2) potential drug interactions were found.		
17.	Mahmood M, 2007(33)	USA	Cross-sectional retrospective	2,795,345 patients who filled prescriptions for medications involved potential DDI from 128 Veterans Affairs medical centres. Ambulatory care clinic	Prescribed drug	Clinically important DDI. Database analysis of pharmacy records. DDI screening tool: a list of 25 potential DDI.	**Prescribing error:** DDI prevalence: The overall rate of potential DDIs was 21.54 per 1000 veterans exposed to the object or precipitant medications of interest.	DDI prevalence: (2.15%)	Age not mentioned.
18.	Lapi F, 2009(35)	Dicomano, Italy	Cohort, a Two-Wave, Population-Based Survey	568 community-dwelling elderly aged ≥65 years	Prescription and nonprescription drugs used at least 1 week before enrolment.	Suboptimal prescribing: Inappropriate medication = 1991 Beers' criteria (13 items out of the original 39 (33.3%) Beers' list medications were considered) DDI screening tool: Micromedex_ Drug-Reax_ system. Using population based survey.	**Prescribing error**: Potential DDI Prevalence was significantly higher in 1999 compared to 1995 (30.5% vs. 20.1%; p < 0.001). Inappropriate prescriptions were significantly higher in 1995 compared to 1999 (9.1% vs. 5.1%; p 0.004). 1995 / 1999 / P-value Inappropriate medication: 47 (9.1%) / 26 (5.1%) / 0.004 DDI: 97 (20.1%) / 147 (30.5%) / <0.001 Major DDI: 20 (4.7%) / 24 (5.6%) / 0.585 **Risk factors:** Polypharmacy always predicted a substantial increase in the risk of the PIM and DDI.	Potential DDI prevalence: (30.5%) p < 0.001 Inappropriate medication prevalence: (5.1%), P=0.004	
19.	Nobili A,	Lecco, Italy	Cross-sectional	58,800 community	Receiving	DDIs and associated risk	**Prescribing error:** DDI prevalence:	Potentially severe	Only the

	2009(36)		Retrospective	dwelling elderly aged ≥ 65 years registered under the Local Health Authority of Lecco.	at least two co-administered prescriptions	factors (age, sex and number of prescriptions). DDI screening tool: Italian computerized interaction database. Analysed all prescriptions dispensed from 1 January 2003 to 31 December 2003.	9,427 elderly people (16%) were exposed to drug combinations with the potential for 13 932 severe DDIs. Mean number of DDI per patient was 0.2 (range 0–9). **Risk factors:** Age and number of chronic drugs were associated with an increasing risk of DDIs. The adjusted OR increased from 1.07 (95% CI 1.3–1.11) in patients aged 70–74 years to 1.52 (95% CI 1.46–1.60) in those aged 85 or older. Elderly taking more than five chronic drugs had a statistically significant higher risk of potentially severe DDIs (OR = 5.59; 95% CI 5.39–5.80) than those receiving less than 3 (reference category) or 3–5 chronic drugs (OR = 2.71; 95% CI 2.63–2.80).	DDI prevalence = 9,427/58,800 = (16%)	interactions identified as severe were considered in these analyses.
20.	Guthrie B, 2015(37)	Scotland, UK	Cross-sectional	311,881 resident aged ≥ 20 years from the community-dispensed prescribing data. (General Practice) Living in own home 308,660.	Prescribed drugs	Potentially serious DDI. Patient characteristics associated with the presence of potentially serious DDI. DDI screening tool: Analysis community-dispensed prescribing data using British National Formulary 2010.	**Prescribing error**: DDI prevalence 40,689 adults (13%) had potentially serious DDI in 2010 [for both resident living in own home and care home]. Number of patient with potentially serous DDI for residence living in their own home in 2010= 13,615	DDI prevalence: 13,615 /308,660= (4.4%)	Resident living in both care home or own home. Risk factors for own home and care home
21.	Maio V, 2006(38)	Milia, Romagna. Italy	Cohort Retrospective	849,425 elderly outpatient aged ≥65 years from the Emilia Romagna outpatient prescription claims database	Prescribed drugs	PIM using the 2002 Beers' criteria and factors associated with PIM. Prescription review.	**Prescribing error:** PIM prevalence: A total of 152,641 (18%) elderly had one or more occurrences of PIM prescribing. **Risk factors:** 1-Older age (≥85 years) (odds ratio (OR) 1.18, 95% confidence interval (CI) 1.16-1.2, P value <0.05) 2- ≥ 10 drugs prescribed (OR 7.33, 95% CI 7.15-7.51, P value <0.05) 3- ≥ 4 chronic conditions (OR 1.76, 95% CI 1.72-1.81, P value <0.05)	PIM prevalence: 152,641/849,425= (18%)	
22.	Martins, S D O, 2006(39)	Lisbon, Portugal	Cross-sectional	213 elderly aged ≥65 years from 12 community pharmacies	Prescription and home medications	Inappropriate drug use (IDU) by 1997 Beers and 2003 Beers Explicit criteria. Using survey	**Prescribing error:** PIM prevalence: Using the 1997 Beers Explicit criteria, 75 occurrences of inappropriate medicines were detected in 59 patients (27.7%). Using the 2003 Beers Explicit criteria inappropriate medication was detected in 82 patients (38.5%).	IDU prevalence: 59/213= (27.7%) using 1997 Beers. IDU prevalence: 82/213= (38.5%) using 2003 Beers.	

							Risk factors: The occurrence of inappropriate medicines was significantly associated with the consumption of a high number of drugs		
23.	Pugh M J V, 2006(40)	Austin, Texas USA	Cross-sectional, retrospective	1,096,361outpatient elderly aged ≥ 65 years using national data from the Veterans Health Administration.	Prescribed drug only	Potentially inappropriate prescribing (IP) included in the 2006 Health Plan Employer Data and Information Set (HEDIS) criteria and to determine if patient risk factors are similar to those found using Beers criteria. Using database	**Prescribing error:** IP prevalence: Overall, 19.6% of older veterans were exposed to HEDIS 2006 drugs. **Risk factors:** 1- Patients receiving ≥10 medications were at greatest risk of exposure in men (OR 8.2, 95% CI 8-8.4) and women (OR 9.6, 95% CI 8.2-11.2). 2- Patient with more outpatient clinic visits (≥10) were at greater risk regardless of gender (OR 1.4, 95% CI 1.3-1.6) 3- Diagnosis with other mental illness (e.g., depression, anxiety) alone or in combination with serious mental illness was associated with higher risk of potentially IP for women (OR 1.3, 95% CI 1.1-1.5).	Potentially IP prevalence: 214,887/1,096,361= (19.6%)	
24.	Saab Y B, 2006(41)	Lebanon	Descriptive	277 elderly aged ≥65 years from 10 community pharmacies	Prescription and/or over the counter (OTC) medications	IDU (Beers criteria, Missing doses, inappropriate frequency of administration, poor memory, drug-disease interaction, DDI, inappropriate dose, duplicated therapy, discontinuation of therapy, adverse effect, and inappropriate indication). Factors that predict potentially inappropriate drug intake. Review patient profile using community pharmacy data and in-person interviews.	**Prescribing error:** PIM prevalence: The prevalence of elderly outpatient with at least one inappropriate medication: 165/277 (59.6%) [Include 5 patient had ADR] Inappropriate medication use was most frequently identified in terms of Beers' criteria (22.4%), missing doses (18.8), and incorrect frequency of administration (13%). Drug-disease interaction in 28 patients (10.1%) DDI 14 (5.1%) Duplicate therapy 12 (4.3%) **Risk factors:** Female sex (65.7% vs. 53.3% for males, p = 0.03). There were also significant associations between the likelihood of use of an inappropriate drug and (1) increased number of medical illnesses (p < 0.00002); (2) consumption of an OTC drug and/or prescription drug (p = 0.048 and p = 0.0035, respectively); and (3) consumption of both OTC and prescription drugs (p < 0.0002).	IDU prevalence: 62/277= (22.4%) using Beers' criteria	Just extracted the IDU by Beers criteria because the IDU include 5 cases of ADR and some patients had more than one IDU. Risk factors for all type of IDU.
25.	Zuckerman I H,	USA	Cohort retrospective	487,383 community	Prescribed drug	Inappropriate medication use using Beers criteria.	**Prescribing error**: PIM prevalence: 204,083 elderly used inappropriate medication.	Inappropriate medication use	

	2006(42)			dweller elderly aged ≥ 65 years. Data from MarketScan Medicare Supplemental and Coordination of Benefits database			Use of inappropriate drugs was associated with a 31% increase in risk of nursing home admission, compared with no use of inappropriate drugs (adjusted relative risk 1.31, 99%CI 1.26–1.36).	prevalence: 204,083/487,383= (41.9%)	
26.	Bregnhoj L, 2007(43)	Copenhage, Denmark	Cross-sectional	212 elderly aged ≥65 years with polypharmacy (≥ 5 drugs) patient from primary care	Subsidised and non-subsidised medications prescribed	IP measured by the Medication Appropriate Index (MAI: 10 criteria are indication, effectiveness, dosage, directions practicality, directions correctness, drug–drug interaction, drug–disease interaction, duplication, duration and expense). Patients exposed to polypharmacy were identified via the database recording the drug subsidy system of Danish pharmacies and questionnaire.	**Prescribing error**: IP prevalence: The main part of the patients namely 94.3% had one or more inappropriate ratings among their medications.	IP prevalence: 200/212= (94.3%)	
27.	Johnell K, 2008(44)	Sweden	Cross-sectional	731,105 People aged ≥75 years from the Swedish Prescribed Drug Register (secondary data analysis)	Prescribed drug only and multi-dose drug dispensing	Whether the use of multi-dose drug dispensing is associated with potential IDU (IDU) (i.e. anticholinergic drugs, long acting benzodiazepines, concurrent use of ≥ 3 psychotropic drugs, and combinations of drugs that may lead to potentially serious DDIs). Information from the Swedish Prescribed Drug Register.	**Prescribing error:** PIM prevalence: Prevalence of potential IDU in Multi-dose dispensing users: 40.3% (women: 41%, men 38.5%) Prevalence of potential IDU In prescription users: 13.6% (women: 15%, men 11.5%) The multi-dose users had higher prevalence of all indicators of potential inappropriate drug than prescription users. 1-The younger elderly (aged 75-79 years) who used multi-dose drug dispensing had the highest frequency of all indicators of potential IDU. 2-Most indicators of IDU were more common in women than men. 3- Multi-dose drug dispensing among 75- to 79-year-olds was even more strongly associated with any IDU, anticholinergic drugs, three or more psychotropic drugs in both men and women, and long-acting benzodiazepines among men.	PIM prevalence: multi-dose dispensing users: 292,737/731,105= (40%) Prescription users: 994, 30.3/731,105= (13.6%)	Multi-dose drug dispensing means that patients get their drugs machine dispensed into one unit for each dose occasion and packed in disposable bags.

28.	Berdot S, 2009(45)	Dijon, Bordeaux, Montpellier . France	Cohort Prospective	6,343 community dwelling elderly aged ≥ 65 years	Prescribed drug	PIM using 1997 and 2003 Beers criteria, Fick and Laroche. Face to face interview using standardised questionnaire.	**Prescribing error:** PIM prevalence: One-third (31.6%) of the study participants reported using at least one inappropriate medication at study entry.	PIM prevalence: 2,004 / 6,343= (31.6%) p <0.001	
29.	Haider S I, 2009(46)	Sweden	Cross-sectional register-based study	626,258 Older people aged 75-89 year from the Swedish Prescribed Drug Register (secondary data analysis)	Prescribed drug only	If low education associated with potential IDU (i.e. anticholinergic drugs, long acting benzodiazepines, concurrent use of ≥ 3 psychotropic drugs, and clinically relevant potential drug–drug interaction (DDI)). Information from the Swedish Prescribed Drug Register.	**Prescribing error:** PIM prevalence: The proportion of participants reporting use of at least one potential IDU was 34.6%. **Risk factors:** Subjects with low education had a higher probability of potential IDU (OR 1.09, 95% CI 1.07–1.17). Older age, being a woman, and higher Charlson Comorbidity Index (CCI) were associated with the highest frequencies of potential IDU.	IDU prevalence: 216,685/626,258= (34.6%)	
30.	Lai H Y, 2009 (47)	Taiwan	Descriptive	2,133,864 patient aged ≥ 65 years between 2001-2004 from ambulatory care. National Health Insurance claim database	Prescribed drug	PIM prescribing using updated 2003 Beers criteria and the characteristics of and risk factors for such prescribing.	**Prescribing error:** PIM prevalence A mean of 63.8% of the older population received a PIM at least once a year in 2001–2004. Details: In 2001: 1,974,869 patients of which 1,297,425 had inappropriate prescription. (65.7) In 2002: 2,026,737 patients of which 1,312,147 had inappropriate prescription. (64.7) 2003: 2,077,677 patients of which 1,295,227 had inappropriate prescription. (62.3) 2004: 2,133,864 patients of which 1,333,792 had inappropriate prescribing (62.5)] **Risk factors:** The only patient characteristic associated with an increased likelihood of the prescribing of PIM was female sex (male sex: (OR 0.982 [95% CI, 0.980-0.983]), (p < 0.001) and when ≥4 drugs were prescribed (P < 0.001). Physician characteristics associated with a greater likelihood of the prescribing of PIM was: 1-Male sex (OR 1.206; 95% CI, 1.202–1.210, *P* < 0.001); 2-Older age (43–50 years: OR 1.021; 95% CI,	PIM prevalence: 2001: (65.7%) 2002: (64.7%) 2003: (62.3%) 2004: 1,333,792/2,133,864 = (62.5%)	

							1.018–1.025, $P < 0.001$; ≥51 years: OR 1.238; 95% CI, 1.235–1.242, $P < 0.001$); 3-Family medicine/ general practice (OR 1.267; 95% CI, 1.265–1.269, $P < 0.001$).		
31.	Ryan C, 2009(48)	Ireland	Cohort Prospective	500 patient aged ≥ 65 years from primary care	Prescribed drug	IP using 2003 Beers' criteria and improved prescribing in the elderly tool (IPET). Screening patients' medical records (electronic and paper).	**Prescribing error:** PIM prevalence 65 patients (13%) and 52 patients (10.4%) had at least one medicine prescribed inappropriately using 2003 Beers and IPET criteria respectively.	IP prevalence: Beers 2003: 65 /500= (13%) IPET: 52/500= (10.4%)	
32.	Ryan C, 2009(49)	Cork, Southern Ireland	Descriptive case record review	1,329 elderly aged ≥ 65 years from primary care	Prescribed drugs	A-1- PIM using 2003 Beers and Screening Tool of Older Person's Prescriptions (STOPP) criteria 2- Potential prescribing omissions (PPO) using Screening Tool to Alert doctors to Right Treatment (START) criteria B- Relationship between age and number of prescription drugs and IP. Case record through paper and electronic record review.	**Prescribing error:** PIM prevalence IP rate identified by Beers' criteria in 18.3% (243) of patients IP rate identified by STOPP was 21.4% (284). PPO was identified in 22.7% (302) of patients using the START tool. **Risk factors:** A significant correlation was found between the occurrence of PIM and 1-The number of medicines prescribed when calculated using Beers' criteria ($r_s = 0.270$, $P < 0.01$) and STOPP ($r_s = 0.356$, $P < 0.01$) using Spearman's ρ correlation test. 2-Age using Beers' criteria ($r_s = 0.068$, $P < 0.01$) and STOPP ($r_s = 0.071$, $P < 0.01$). 3-Increasing CCI score identified by STOPP ($r_s = 0.210$, $P < 0.01$).	PIM prevalence: Beers': 243/1329= (18.3%) STOPP: 284/1329= (21.4%) PPO prevalence: START: 302/1329= (22.7%)	Spearman's ρ correlation test.
33.	Akazawa M, 2010(50)	Tokyo, Japan	Cohort Retrospective	6,628 elderly patient aged ≥ 65 years from health insurance claim data (secondary data analysis)	Prescribed drugs	PIM using modified Beers criteria in Japan. Drug utilization review using medical and pharmacy claim from database of (Japan Medical Data Center).	**Prescribing error:** PIM prevalence 43.6% (2,889/6,628) were prescribed at least one PIM. **Risk factors:** Factors positively associated with PIM prescriptions at a significance level of 5% included the following: Hospital admission (OR = 3.35, 95% CI 2.43-4.62); polypharmacy (OR = 5.69, 95% CI 5-6.48); prescriptions from a hospital (OR = 1.19), general medicine practitioner (OR = 1.46), or psychiatrist/neurologist (OR = 2.33); and comorbid conditions including peptic ulcer disease without bleeding (OR = 4.18 , 95% CI 3.52-4.97), depression (OR = 3.69), cardiac arrhythmias (OR = 1.93), other neurologic	PIM prevalence: 2,889/6,628= (43.6%)	*Consequence

							disorders (Parkinson's disease, multiple sclerosis, and epilepsy; OR = 1.88), and congestive heart failure (OR = 1.46). PIM users had significantly higher hospitalization risk (1.68-fold), more outpatient visit days (1.18-fold), and higher medical costs (33% increase) than did nonusers.		
34.	Zaveri H G, 2010(51)	Ahmedabad city, India	Descriptive Prospective	407 geriatric patients aged ≥ 65 years from medicine outpatient department	Prescribed drug	PIM using 2003 Beers criteria. Using prospective proforma data collection.	**Prescribing error:** PIM prevalence Out of 407 patients, 96 patients (23.6%) received at least one drug that was potentially inappropriate. **Risk factors:** There was highly significant association between the number of drugs prescribed and frequency of use of PIMs (P< 0. 0002).	PIM prevalence: 96/407= (23.6%)	
35.	Barnett K, 2011(52)	Tayside, Scotland, UK	Cohort	65,742 elderly aged 66-99 years living in home	Prescribed drug	PIM using 2003 Beers criteria and the association between exposure to PIM and mortality. Using dispensing and prescribing database and medical record.	**Prescribing error**: PIM prevalence PIM found in 20,304 (30.9%) patients living at home. **Risk factors:** After adjustment for age, sex and polypharmacy, 1-Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy 2-Reciveing at least one PIM were not associated with increased risk of mortality (adjusted OR 0.98, 95% CI 0.92 -1.05).	PIM prevalence: 20,304/65,742= (30.9%)	Risk factors for both care home and home
36.	Chang C B, 2011(53)	Taipei, Taiwan	Cohort	193 outpatient elderly patient aged ≥ 65 years with polypharmacy (≥ 8 chronic medications) from Medication Safety Review Clinic in Taiwanese Elders (MSRC-Taiwan) study.	Prescribed drugs and dietary supplement excluding herbals	PIM using six different criteria and drug-related problem: the 2003 version of the Beers criteria (from the USA), the Rancourt (from Canada), the Laroche (from France), (STOPP; from Ireland), the Winit-Watjana (from Thailand) and the Norwegian General Practice (NORGEP) criteria (from Norway). Analyse baseline data from the MSRC-Taiwan	**Prescribing error**: PIM prevalence: The proportion of patients who had at least one PIM varied from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria). Approximately 31% (the STOPP criteria) to 42% (the NORGEP criteria) of PIMs identified were considered as drug related problems by the medication review team experts. **Risk factors:** In the bivariate analysis, the common characteristics associated with having at least one PIM in all criteria were a high number of chronic conditions and a high number of chronic medications.	PIM prevalence: (24% -73%)	

						study. Secondary data analysis.			
37.	Leikola S, 2011(54)	Finland	Cross-sectional	841,509 non-institutionalised elderly patient aged ≥ 65 years from Finland's Social Insurance Institution prescription register of all reimbursed drugs for outpatient	Prescribed and OTC medications that are reimbursed	PIM using 2003 Beers criteria.	**Prescribing error:** PIM prevalence 14.7% (n = 123,545) had received PIMs according to the Beers 2003 criteria.	PIM prevalence: 123,545/841,509= (14.7%)	
38.	Lin Y J, 2011(55)	Taiwan	Cross-sectional Retrospective analysis	327 elderly patient aged ≥ 65 years from outpatient clinic of a community health centre	Prescribed drugs	PIM using 2003 Beers criteria and risk factors of PIM use. Using data review.	**Prescribing error:** PIM prevalence The prevalence of patients having at least one PIM was 27.5% (90/327). **Risk factors:** Independent risk factors for PIMs are older age (OR = 1.05, 95% CI 1.00–1.09, p = 0.046), higher number of prescribed medications (OR = 1.06, 95% CI = 1.39–1.98, p < 0.001), and diagnosis of acute diseases (OR = 8.98, 95% CI 4.71–17.1, p < 0.001).	PIM prevalence: 90/327= (27.5%)	
39.	Woelfel J A, 2011(68)	California, USA	Cross-sectional	295 elderly aged ≥ 65 years from ambulatory population of Medicare beneficiaries	Prescribed drug	PIM using 2003 Beers criteria. Using medication review	**Prescribing error:** PIM prevalence 54 (18.3% beneficiaries were taking at least one PIM. **Risk Factors:** Number of medications was significantly greater in the PIM than the non-PIM group (p < 0.001)	PIM prevalence: 54/295= (18.3%)	
40.	Zhang Y J, 2011(56)	USA	Cohort Retrospective	3,570 Elderly community-based respondents aged ≥ 65 from 2007 Medical Expenditure Panel Survey (MEPS), a nationally representative survey of the US community-dwelling population	Prescribed drug	PIM using Zhan criteria and risk factors for PIM use. Information from MEPS database	**Prescribing error:** PIM prevalence PIM prevalence in 2007:13.84% (CI 12.52–15.17). PIM prevalence in 1996: 21.3% (CI 19.5–23.1). **Risk factors**: Older women, people taking ≥25 prescriptions, people with middle family income, people living in the South census region, and people who said they were in fair or poor health were more likely to have received an inappropriate medication during the year.	PIM prevalence: 13.84%-21.3%	
41.	Haasum Y, 2012(57)	Sweden	Cross-sectional Retrospective	1,260,843 home-dwelling elderly	Prescribed drug only	Potentially IDU (use of anticholinergic drugs,	**Prescribing error**: PIM prevalence 11.6% of the home-dwelling elderly were	Potentially IDU prevalence:	Information on both

				aged ≥ 65 year from the Swedish Prescribed Drug Register		long-acting benzodiazepines, concurrent use of ≥ 3 psychotropics, and potentially serious DDIs). Information from the Swedish Prescribed Drug Register	exposed to Potentially IDU.	145,749/1,260,843= (11.6%)	institutionalised and home dwelling. Extracted home dwelling information only.
42.	Marroquin E C, 2012(19)	Cáceres, Spain	Descriptive	471 patient aged ≥ 65 years from health centers	Consumed medications	Potentially IP using STOPP/START criteria. Using patient interview and medical chart review.	**Prescribing error:** PIM prevalence 249 patients (52.8%, 95% CI 48.3-57.3) had potentially IP according to STOPP/START criteria. STOPP: 162 patients (34.3%, 95% CI 30.2-38.8%) START: 114 patients (24.2%, 95% CI 20.5-28.2%)	Potentially IP prevalence: 249/471= [(52.8%) (95% CI 48.3-57.3)]	
43.	Nyborg G, 2012(58)	Norway	Cross-sectional Retrospective	445,900 home dwelling elderly aged ≥ 70 years from the Norwegian Prescription Database	Prescribed drug	Prevalence of and predictors for PIM use by the Norwegian General Practice (NORGEP) criteria. Survey undertaken based on data from the Norwegian Prescription Database	**Prescribing error:** PIM prevalence 34.8% of the study population was exposed to at least one PIM. **Risk factors:** The odds of receiving potentially harmful prescriptions increased with the number of doctors involved in prescribing (OR 3.52, 99% CI 3.44–3.60 for those with ≥5 compared to those with 1 or 2 prescribers). Females were at higher risk for PIMs (OR 1.6, 99% CI 1.58–1.64).	PIM prevalence: 155,341 /445,900= [(34.8%) (99%CI 34.7-35)]	
44.	Yasein N A, 2012(59)	Jordan	Cross-sectional	400 elderly aged ≥65 years from family practice clinic	Prescribed drug	Polypharmacy (≥ 5drugs) and IP using 2003 Beers criteria. Using patient file and patient interview	**Prescribing error**: PIM prevalence Inappropriate medications as determined by Beers criteria independent of diagnosis accounted for 118 (29.5%) patients.	IP prevalence: 118/400= (29.5%)	
45.	Blozik E, 2013(60)	Helsana, Switzerland	Cohort	2008: 1,059,495 2009: 1,047,939 2010: 929,791 community dwelling adult aged > 18 years from claim data of Helsana.	Prescribed drug submitted for reimbursement	Prevalence of polypharmacy and PIM using 2003 Beers criteria or the PRISCUS list. Using analysis of data based on claim data from Switzerland health insurance	**Prescribing error:** PIM prevalence: According to 2003 Beers criteria: 10.3 % of the community-dwelling population aged > 65 years received at least one medication which is PIM, and according to the PRISCUS list1: 16.0 % of persons had a PIM. When using both Beers and PRISCUS criteria, 21.1 % of the population received at least one PIM. Of those persons older than 65 years asking for reimbursement of medications, 12.9 % received	PIM prevalence: 21.1%	There are huge discrepancies in estimating the prevalence of PIM depending on the definition used.

							at least one PIM according to 2003 Beers, 20.2 % according to PRISCUS, and 26.6 % of either definition. **Risk Factors:** Women were more likely to receive a PIM: 25.5 % of females as compared to 15.4 % of males when both Beers and PRISCUS definitions were used.		
46.	Cahir C, 2013(61)	Ireland	Cohort Retrospective	931 Community dwelling elderly aged ≥ 70 years from 15 general practices	Prescribed drug and OTC	The association between potentially IP using STOPP -and health related outcomes [ADEs, health related quality of life (HRQOL) and hospital accident and emergency department (ED)]. Using patient self-report and medical record.	**Prescribing error:** PIM prevalence Prevalence of potentially IP was 40.5% (n = 377). **ADE prevalence:** In total, 674 of 859 participants (78%) were classified as having at least one ADE during the study period. **Risk Factors:** Patients with ≥2 Potentially IP indicators were: 1-Twice as likely to have an ADE (adjusted OR 2.21; 95% CI 1.02, 4.83, P < 0.05), 2- Significantly lower mean HRQOL utility (adjusted coefficient −0.09, SE 0.02, P < 0.001), 3-A two-fold increased risk in the expected rate of ED visits (adjusted Incidence Rate Ratio 1.85; 95% CI 1.32, 2.58, P <0.001).	Potentially IP prevalence: 377/931= (40.5%) ADE prevalence: 674/859= (78%)	*Consequence. Type of ADE was not mentioned
47.	Weng M C, 2013(62)	Taiwan	Cross-sectional Retrospective	780 older patients aged ≥ 65 years from the outpatient geriatric clinic	Long-term Prescribed drugs (≥ 28 days) for chronic diseases. Not OTC	Impact of number of drugs prescribed on the risk of PIM using STOPP criteria. Patient medical chart review	**Prescribing error**: PIM prevalence 302 patients (39%) had at least one PIM. **Risk factors:** Multivariate analysis revealed that PIM risk was associated with the number of medications prescribed (P < 0.001) and the presence of cardiovascular (P < 0.001) or gastrointestinal disease (P = 0.003). Patients prescribed ≥ 5 drugs [adjusted (OR) = 5.4; had significantly higher PIM risk than those prescribed ≤ 2 drugs.	PIM prevalence: 302/780= (39%)	
48.	Zimmerman n T, 2013(18)	German	Cohort longitudinal analysis	follow-up3: N = 1,942 Baseline N =3,214 1,855 elderly aged ≥75 years from primary care. Data from the prospective,	Prescribed drug	PIM using Beers, PRISCUS list. By checking medications during visits to patients' homes.	**Prescribing error:** PIM prevalence At baseline, PIM prevalence is (848) 29 % according to the PRISCUS list, which decreased to (464) 25.0 % 4.5 years later (χ^2: 7.87, p = 0.004). The Beers list yielded a prevalence of (620) 21 % at baseline, decreasing after 4.5 years to (317) 17.1 % (χ^2: 10.77, p = 0.000).	Prescribing error: PIM prevalence 17%-29%	

				multicenter, observational study "German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe),"			**Risk factors:** By PRISCUS list: The risk for PIM increase with: 1-Increasing age of the patients (OR: 1.06, CI: 1.00 to 1.13; p = 0.037), 2-The presence of depression (OR: 2.42, CI: 1.65 to 3.57; p = 0.000), 3-Increasing number of prescription drugs (OR: 1.99; CI: 1.80 to 2.18; p = 0.000). By contrast, the risk of taking PIM decrease by using PRISCUS list with the number of present illness (OR: 0.88, CI: 0.80 to 0.97; p = 0.012). As the growing number of ingested prescription drugs increased the risk for the ingestion of PIM from the Beers list (OR: 1.66, CI: 1.50 to 1.84; p = 0.000).		
49.	Baldoni A D, 2014(29)	Ribeirao Preto, Brazil	Cross-sectional	1000 elderly aged ≥ 60 years from outpatient pharmacy	Prescribed drug, self-medication (309 user) and OTC (802 user)	Prevalence and factors associated with PIM using 2003 and 2012 Beers criteria. Using structured interview questionnaire	**Prescribing error:** PIM prevalence According to Beers criteria 2003, 480 (48.0 %) participants used at least one PIM, the mean being 1.38 (SD = 0.65) PIMs/person, ranging from one to five. According to Beers criteria 2012, 592 (59.2 %) participants used at least one PIM, the mean being 1.56 (SD = 0.81) PIMs/person, ranging from one to six. **Adverse drug event (ADE):** During the interview 45.5 % of participants reported complaints related to ADEs; 94.5 % of these were caused by prescribed medication. **Risk factors:** Factors that are associated with PIMs use were female gender, self-medication, use of OTC medications, complaints related to ADEs, psychotropic medication, more than five medications. *Ten medications with the highest prevalence of self-reported ADEs complaints are Clonidine, amitriptyline, metformin, fluoxetine, dexchlorpheniramine, diclofenac, captopril, acetyl salicylic acid, simvastatin, hydrochlorothiazide. Among them, five were considered PIMs according to Beers criteria, of	PIM prevalence by Beers criteria 2003, 480/1000= (48.0 %) PIM prevalence by Beers criteria 2012, 592/1000= (59.2 %)	*Error-related adverse event

							which clonidine, amitriptyline and dexchlorpheniramine are listed in both criteria, while fluoxetine is listed only in Beers criteria 2003 and diclofenac is listed only in Beers criteria 2012.		
50.	Castillo-Paramo A, 2014(63)	Spain	Cross-sectional	272 electronic record of elderly aged ≥65 years from primary healthcare	Prescribed drugs	PIM using STOPP/START criteria and version adapted to Spanish primary healthcare and factors may modulate PIM onset. Using electronic health record and paper clinical record	**Prescribing error:** PIM prevalence The prevalence of PIM (mis- and over-prescribing) using the STOPP original criteria was 37.5% (95% CI: 31.7 – 43.2), and 50.7% (95% CI: 44.7 – 56.6) using the STOPP Spanish AP2012 version. The prevalence of under-prescribing was 45.9% (95% CI: 40.0 – 51.8) with the START original criteria, and 43.0% (95% CI: 37.1 – 48.9) with the START AP2012 version. **Risk factors:** A significant correlation was found between the number of STOPP PIM and age or number of prescriptions, and between the number of START PIM with age, CCI and number of prescriptions.	PIM prevalence: 102/272 (STOPP) = [(37.5%) (95% CI: 31.7 – 43.2)] 138/272 (STOPP AP2012) = [(50.7%)(95% CI: 44.7 – 56.6)] 125/272 (START) = (45.9%) 117/272 (START AP2012) = (43%)	
51.	Vezmar Kovacevic S, 2014(64)	Serbia Belgrade	Cross-sectional Prospective	509 elderly aged ≥ 65 years from 5 community pharmacies	Prescribed drug	PIM and PPO using STOPP/START criteria. Using patient interview and medical, biomedical record	**Prescribing error**: PIM prevalence There were 164 PIM identified in 139 patients (27.3%) by STOPP and 439 PPO, identified in 257 patient, (50.5%) by START. **Risk factors:** Patients with more than four prescriptions had a higher risk for PIM (OR 2.85, 95% CI 1.97–4.14, p <0.001 and ≥ 9 medications OR 7.43, 95% CI 3.20–17.23, p<0.001). Patients older than 74 years were more likely to have a PPO (75–84 years OR 1.47, 95% CI 1.01–2.13, p= 0.041 and ≥85 years OR 1.79, 95% CI 1.19–2.83, p = 0.009).	PIM prevalence: 139/509= (27.3%) PPO prevalence: 257/509= (50.5%)	
52.	Amos T B, 2015(65)	Emilia-Romagna, Italy	Cohort Retrospective	865,354 elderly aged ≥ 65 years community dwelling From administrative care data	Prescribed drug only	PIM using updated Maio criteria and patient characteristic related to IP. Using Regional Emilia-Romagna administrative healthcare database.	**Prescribing error:** PIM prevalence A total of 240,310 (28%) older adults were exposed to at least one PIM. **Risk factors:** The oldest group (≥85) followed by patients aged 75–84 had 53% and 25% greater odds of receiving PIM than patients 65–75 years old, respectively [OR = 1.53,95% CI: 1.50–1.55; OR = 1.25, 95% CI: 1.23–1.26, respectively]. These odds of exposure to any PIM were	PIM prevalence: 240,310/ 865,354= (28%)	

							slightly lower among males than females (OR = 0.98, 95% CI: 0.97–1.00). An increase in the number of medications prescribed to the patient corresponded with higher odds of PIM exposure. Older general practitioners (≥56), male GPs, and solo practice GPs were more likely to prescribe PIMs to their older patients.		
53.	Hedna K, 2015(66)	Sweden	Cohort retrospective	542 elderly aged ≥ 65 years from the Swedish Total Population Register (primary care)	Prescribed drug	Prevalence of Potentially IPs using STOPP criteria and to investigate the association between Potentially IPs and occurrence of ADRs. Using the Swedish Prescribed Drug Register, medical records and health administrative data	**Prescribing error:** PIM prevalence 226 patients using primary healthcare had Potentially IP. **Risk factors:** Persons prescribed Potentially IP had more than twofold-increased odds to experience ADRs (OR 2.47, 95 % CI (1.65–3.69); P <0.001), compared to that in persons without Potentially IP.	Potentially IP prevalence: 226/542= (42%)	* Error-related adverse event. The association between PIPs and occurrence of ADRs was for primary care, outpatient or inpatient and hospitalized patient.
54.	Moriarty F, 2015(67)	Ireland	Cohort Prospective	2,051 elderly aged ≥ 65 years from The Irish Longitudinal Study on ageing (TILDS). Community dwelling elderly.	Prescribed drug only	PIM and PPO using STOPP, Beers criteria, ACOVE (Assessing Care of Vulnerable Elders) indicators and START. Using face to face interview then follow up after 1 and 2 years	**Prescribing error: PIM prevalence** Baseline N%(95%CI) / Follow-up N%(95%CI) Any PIM using STOPP, Beers, ACOVE: 1,259 (61.4%) (CI 59.3-63.5) / 1,330 (64.8%) (CI 62.8-66.9) Any PPO using START,: 1,094 (53.3 %) (CI 51.2-55.5) / 1,161 (56.6%) (CI 54.5-58.8)	PIM: (36.7%-64.8%)	

							ACOVE Both PIM and PPO: 753 (36.7 %); 843(41.1 %) **Risk factors:** Female sex, age and higher number of medicines were significantly associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be significantly associated with change in PPO prevalence.		
55.	Ramia E, 2014(69)	Lebanon	Cross sectional	284 outpatient aged ≥ 18 years visiting community pharmacy	Patient on ≥ one of the chronic medications mentioned in the study	The completion of therapeutic/safety monitoring tests. Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring.	**Monitoring error:** - 185 of the patients (65%) were found to complete some, but not all, of the recommended therapeutic/safety monitoring tests - 76 of the patients (27%) completed all recommended therapeutic/safety monitoring -23 of the patients (8%) did not complete any of the recommended monitoring tests	Incomplete therapeutic/safety laboratory-test monitoring tests prevalence: 208/284= (73%)	
Other: Discrepancies									
56.	Tulner L R, 2009(70)	Amsterdam , The Netherland	Descriptive prospective	120 elderly aged >65 years from Dutch geriatric outpatient	Using more than one prescribed or OTC medications	1-Frequency and relevancy of discrepancies in drug use 2-Frequency of medication discrepancy adverse patient events (MDAPEs) 3-Contributing factors- such as increasing age, cognitive status and depressive symptoms, the number of medications used, the number of physicians visited by the patient. By comparing the medication described by the patient and caregivers with the drugs listed by their general practitioners.	**Other: Discrepancies prevalence:** At least one discrepancy (deletion, addition, or difference in dosage) between the medication lists from the patient, the GP, or the pharmacy was present in 104 patients (86.7%) involving 386 drugs. **Medication discrepancy adverse patient events:** Medication discrepancy adverse patient events were identified in 29 patients (24.2%). 7 patient had under-treatment due to deletions 9 patients had ADR due to additions 13 patient had DDI. **Risk factors:** Patients with ≥ 1 discrepancy reported using a higher mean number of drugs (5.9 vs. 4.0; $P <$ 0.05) and had more prescribing physicians in addition to their GP (1.1 vs. 0.43; $P <$ 0.05). Both the presence of discrepancies (Pearson' s 1", *0.293; P* s 0.05) and MDAPEs (Pearson's 1", 0.230; $P = 0.012$) were significantly	Discrepancies prevalence: 104/120= (86.7%) *Error-related adverse event: MDAPEs: 29/120= (24.2%)	*Error-related adverse event

							correlated with the number of medications reported by the patient. *The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (82.9%), and formulations fix dermatologic or ophthalmologic diseases (81.3%).		
57.	Cornu P, 2012(71)	Brussels, Belgium	Cohort retrospective	189 elderly aged ≥65 years discharged from acute geriatric department of a Belgain university hospital	Prescribed drug	Incidence and type of discrepancies between the discharge letter for the primary care physician and the patient discharge medication and identify possible patient-related determinants for experiencing discrepancies. Discrepancies were categorized as omitted drug, unintended continuation (discontinued home medication documented as home medication), discrepant dose, missing dose, and discrepant brand, omission of a brand name, discrepant frequency, missing frequency, or an incorrect pharmaceutical form. By comparing the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list	**Other: Discrepancies prevalence:** Almost half of these patients (n=90, 47.6%) (95% CI 40.5-54.7) had 1 or more discrepancies in medication information at discharge. *Two discrepancies (1.2%) were categorized as having the potential to cause severe patient harm. These discrepancies consisted of a wrong dose (doubled the prescribed dose) of digoxin in the patient discharge medication list and the listing of a low-molecular-weight heparin in the patient discharge medication list that was intentionally omitted in the discharge letter because of the development of heparin-induced thrombocytopenia during hospitalization. **Risk factors:** The explorative multivariate model adjusted for age, sex, length of hospital stay, and residential situation showed that when the discharge letter contained more than 5 drugs, the likelihood of experiencing 1 or more drug discrepancies was 3.22 (95% CI 1.40 to 7.42; p = 0.006) times higher than when 5 or fewer drugs were mentioned. Increasing numbers of drugs in the discharge medication list (OR 1.19; 95% CI 1.07 to 1.32; p = 0.001) and discharge letter (OR 1.18; 95% CI 1.07 to 1.32; p = 0.001) were associated with a higher risk for discrepancies.	Discrepancies prevalence: 90/189= [(47.6%) (95% CI 40.5-54.7)]	*Error-related adverse event
Preventable ADEs									
58.	Field T S, 2007(77)	USA	Cohort	30,000 elderly ≥ 65 years from ambulatory care	Prescribed drug	ADE resulting from patients error and risk factors By electronic tracking of administrative data, review medical records,	**Preventable ADE:** ADE resulting from patients error prevalence 113 individual experience ADE and potential ADE **Risk factor:** In a multivariate analysis, there was a dose–	ADE resulting from patients' error prevalence: 113/30,000 = (0.38%)	*ADE resulting from patients error

						reports from clinicians, hospital discharge summaries and ED visit	response association between patient errors leading to ADEs and potential ADEs and regularly scheduled medications; compared with zero to two medications, the OR for three to four medications was (OR 2.0; 95% CI=0.9–4.2), for five to six medications was (OR 3.1; 95% CI=1.5– 7.0), and for seven or more medications was (OR 3.3; 95% CI=1.5–7.0). The strongest association was with the CCI; compared with a score of 0, the OR for a score of 1 to 2 was (OR 3.8; 95% CI=2.1–7.0), for a score of 3 to 4 was (OR 8.6; 95% CI=4.3–17.0), and for a score of 5 or more was (OR 15.0; 95% CI=6.5–34.5).		
59.	Gandhi T K, 2010(22)	Boston and Indianapolis ,USA	Cross-sectional	68,013 outpatient, mean age 48 and 47 years	Prescribed drug	ADE. Using electronic health record screening, chart review and ADE monitor	**Preventable ADE** incidence: The overall rate was 138 ADEs/1000 person-years across the two sites. Preventable ADEs rate 15 /1000 person-years across two sites. *Most commonly drugs associated with preventable ADE were the angiotensin-converting enzyme (ACE) inhibitors and beta blockers.	Preventable ADEs rate 15 /1000 person-years across two sites.	*Preventable ADE
60.	Obreli Neto P R, 2012(28)	Ourinhos microregion, Brazil	Cohort prospective	433 elderly aged ≥ 60 years from the primary public health system	Prescribed drugs both within and across prescriptions	DDI-related ADR incidence and factors. Using phone or face-to-face structured interview DDI screening tool: DDI checker Programs (DrugDigest®, Drugs®, Micromedex® and Medscape®)	**Preventable ADE:** DDI-related ADR incidence: Occurred in 30 patients (6.9 %). Gastrointestinal bleeding occurred in 37 % of the DDI-related ADR cases, followed by hyperkalemia (17 %) and myopathy (13 %). Seventeen DDI-related ADRs were classified as severity level 2, and hospital admission was necessary in 11 cases. *Warfarin was the most commonly involved drug (37%cases), followed by acetylsalicylic acid (17 %), digoxin (17 %), and spironolactone (17 %). **Risk Factors:** The multiple logistic regression showed that the following were associated with the occurrence of DDI-related ADRs: Age ≥80 years [OR 4.4; 95 % CI 3.0–6.1, p<0.01], CCI ≥4 (OR 1.3; 95 % CI 1.1–1.8, p<0.01), Consumption of five or more drugs (OR 2.7; 95 % CI 1.9– 3.1, p<0.01), Use of warfarin (OR 1.7; 95 % CI 1.1–1.9,	Incidence of DDI-related ADR 30/433= (6.9%)	*Error-related adverse event

							p<0.01)		

Abbreviations: ACE: Angiotensin-converting enzyme. ACOVE: Assessing Care of Vulnerable Elders. ADE: Adverse Drug Event. ADI: Adverse Drug Interaction. CI: Confidence Interval. DDI: Drug-Drug Interaction. ED: emergency department. GP: general practitioners. HEDIS: Health Plan Employer Data and Information Set. IPET: Improved Prescribing in the Elderly Tool. IDU: Inappropriate Drug Use. IP: Inappropriate Prescribing. MAI: Medication Appropriate Index. MDAPE: Medication Discrepancy Adverse Patient Event. OTC: Over-the-Counter. OR: Odds Ratio. PDDI: Potential drug-disease interaction. PIM: Potentially Inappropriate Medicine. PPO: Potential Prescribing Omissions. STOPP: Screening Tool of Older Person's Prescriptions. START: Screening Tool to Alert doctors to Right Treatment.

Table 2: Systematic review quality assessment

A. Joanna Briggs Institute critical appraisal checklist for descriptive/case series and cross-sectional

Was study based on a random or pseudo- random sample?
Were the criteria for inclusion in the sample clearly defined?
Were confounding factors identified and strategies to deal with them stated?
Were outcomes assessed using objective criteria?
If comparisons are being made, was there sufficient descriptions of the groups?
Was follow up carried out over a sufficient time period?
Were the outcomes of people who withdrew described and included in the analysis?
Were outcomes measured in a reliable way?
Was appropriate statistical analysis used?
Y = Yes, No = N, Unclear = U, Not applicable = NA

		1	2	3	4	5	6	7	8	9	Overall appraised	
1	Ramia E, 2014 (69) Adult	Y	Y	N	N	NA	NA	Y	Y	Y	High	Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring, may cause

												recall bias
2	Sorensen L, 2006 (76) Adult	Y	Y	N- Risk factors related to patient not studied	Y	NA	NA	Y	Y	Y	High	
3	Vuong T, 2006 (25) Adult	U	Y	N	Y	NA	NA	N	Y	Y, percentage was used but statistics was not described in the full text.	High	Unclear sampling strategy
4	Adams R J, 2009(72) Adult	Y	Y	Y (but for all type of adverse event)	N (self-reported adverse events)	NA	NA	N	Y	Y	High	Risk of recall bias and attribution with self-reported adverse events and
5	Gandhi T K, 2010 (22) Adult	U	Y	N	Y	Y	NA	NA	Y	Y	High	
6	Lu C Y, 2011(20)	Y	Y	Y	N (subjective patient-reported	Y	NA	NA (secondary analysi	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient-

	Adult				medication error)			s)				reported medication error pp
7	Sears K, 2012 (21) Adult	Y	Y	Y	N (subjective self-reported medication error)	Y	NA	NA (secondary analysis)	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient self-reported medication error
8	Koper D, 2013(23) Adult	N (convenience)	Y	N	Y	NA	NA	NA (100% participant)	Y	Y	High	Selection bias
9	Dallenbach, 2007 (24) Adult-DDI	N (consecutive)	N	N	Y	NA	NA	NA (retrospective)	Y	Y	Moderate	
10	Indermitte J, 2007 (32) Adult-DDI	Y (pharmacy choose). No (first 12 customer)	Y	N	Y	NA	NA	Y	Y	Y	High	
11	Mahmood, 2007 (33) Adult-DDI	Y	Y	N	Y	NA	NA	NA (retrospective)	Y	Y	High	Patients may actually be on other drugs so may not

												catch all the DDI.
12	Guthrie B, 2015 (37) Adult-DDI	Y	Y	Y (but for both own home and care home)	Y	Y	NA	NA (secondary analysis)	Y	Y	High	Risk factors for both own home and care home.
13	Martins S D O, 2006 (39) Elderly -PIM	N (1st came to pharmacy carrying prescription for 2 or more drugs)	Y	Y, but not all	Y	Y	NA	N	Y	Y	High	Self-reported data from elderly concerning drug use may lead to information bias.
14	Pugh M J V, 2006 (40) Elderly -PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	May underestimate the exposure because they do not account for OTC
15	Saab Y B, 2006(41) Elderly -PIM	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported data from elderly concerning drug use may decrease accuracy

16	Bregnhoj L, 2007 (43) Elderly -PIM	N (Each GP was asked to recruit 6 patients who were randomly selected)	Y	N	Y	NA	NA	Y	Y	Y	High	Selection bias
17	Johnell K, 2008 (44) Elderly -PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Did not look for comorbidity as a risk factor because data from Swedish Prescribing Drug Register
18	Haider S I, 2009 (46) Elderly -PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
19	Lai H Y, 2009 (47) Elderly – PIM	Y	Y	Y	Y	NA	NA	NA (secondary analysis)	Y	Y	High	Did not address comorbidity as a risk factor

20	Ryan C, 2009 (49) Elderly – PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	May underestimate the outcome because they do not account for OTC
21	Zaveri H G, 2010 (51) Elderly -PIM	U	Y	Y	Y	NA	NA	N	Y	Y	High	Not enough information in the article
22	Leikola S, 2011 (54) Elderly -PIM	Y	Y	N	Y	NA	NA	NA	Y	Y	High	May underestimate the outcome because database lacks diagnostic patient data, therefore used the Beers 2003 criteria independent of diagnoses and the data provide no information on the use

												of PIMs that are not reimbursable. Nine PIMs that were not reimbursable in Finland in 2007: triazolam, belladonna alkaloids, diphenhydramine, hydroxyzine, ferrous sulfate, bisacodyl, nitrofurantoin and clonidine.
23	Lin Y J, 2011 (55) Elderly -PIM	U	Y	Y	Y	NA	NA	NA	Y	Y	High	
24	Woelfel J A, 2011 (68) Elderly -PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
25	Haasum Y,	Y	Y	N	Y	Y	NA	NA (secon	Y	Y	High	

	2012 (57) Elderly -PIM							dary data analysis)				
26	Nyborg G, 2012 (58) Elderly -PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	
27	Yasein N A, 2012 (59) Elderly -PIM	N	Y	N	Y	Y	NA	N	Y	Y	Moderate	
28	Marroquin E C, 2012 (19) Elderly -PIM	N (convenience sample)	Y	N	Y	NA	NA	N	Y	Y	Moderate	Sampling strategy. Subjective information on socioeconomic and clinical variables may decrease accuracy
29	Weng M C, 2013 (62) Elderly -PIM	Y	Y	Y	Y	Y	NA	N	Y	Y	High	Sampling strategy

30	Baldoni A O, 2014 (29) Elderly -PIM	UC	Y	Y	Y	Y	NA	Y	Y	Y	High	
31	Castillo-paramo A, 2014 (63) Elderly -PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Electronic health record use limitations (incomplete record and quality of data)
32	Vezmar Kovacevic S, 2014 (64) Elderly -PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	
33	Nobili A, 2009 (36) Elderly- DDI	Y	Y	Y	Y	NA	NA	NA (administrative database)	Y	Y	High	The use of administrative database limit looking for comorbidity as a confounder.
34	Secoli S-R 2010 Elderly-DDI	U	Y	Y	Y	NA	NA	NA	Y	Y	High	May underestimate the true DDI prevalence

												because they do not account for OTC
35	Obreli Neto P R, 2012 (27) Elderly-DDI	Y	Y	Y	Y	NA	NA	NA (data from primary healthcare system)	Y	Y	High	May under estimate the DDI prevalence because 1- Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interactions involving combinations of three or more drugs so. 2- did not account for OTC
36	Pit S W, 2008 (74) Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	

37	Tulner L R, 2009 (70) Elderly	N (consecutive)	Y	Y	Y	NA	NA	Y	Y	Y	High	Information on medication described by the patient and caregivers may not always be accurate
38	Obreli Neto P R, 2011(26) Elderly DDI	Y	Y	N	Y	NA	NA	NA	Y	Y	High	
39	Mira J J, 2012 (73) Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported medication error from elderly concerning drug use may have recall bias
40	Mand P, 2014 (31) Elderly	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	

B. Critical Appraisal Skills Program (CASP) for cohort study

1 Did the study address a clearly focused issue?

2 Was the cohort recruited in an acceptable way?

3 Was the exposure accurately measured to minimise bias?

4 Was the outcome accurately measured to minimise bias?

5(a) Have the authors identified all important confounding factors?

List the ones you think might be important, that the author missed

5(b) Have they taken account of the confounding factors in the design and/or analysis?

6(a) Was the follow up of subjects complete enough?

6(b) Was the follow up of subjects long enough?

7 What are the results of this study?

8 How precise are the results?

9 Do you believe the results?

10 Can the results be applied to the local population?

11 Do the results of this study fit with other available evidence?

12 What are the implications of this study for practice?

Yes= Y, No=N, can't tell

	Study design: Cohort														
	Reference	**Quality domains**													
		1	**2**	**3**	**4**	**5 (a)**	**5 (b)**	**6(a)**	**6 (b)**	**7**	**8**	**9**	**10**	**11**	**12**	**Overall quality**
		Are the results of the study valid?								**What are the results?**			**Will the results help locally?**			
1	Maio V, 2006(38) PIM	Y	Y	Y	Y	Y- Age, gender, geographic location, number of medication, number of chronic condition and income None	N	Y	Y (1 year) retrospective	PIM prevalence 18%. Older age, polypharmacy, and greater number of chronic conditions were significant predictors of PIM use.	P value <0.05, 95 % CI	Y	Y	Y	-	Moderate

2	Zuckerman I H, 2006(42) PIM	Y	Y	Y	Y	Y-but used for irrelevant outcome -	Y	Y	Y (2 years)	Inappropriate medication use prevalence 41.9%	P= 0.01, 99% CI	Y	Can't tell (generalisability)	Y	Limited information from the database. Confounding factors were for the nursing home admission rather than for PIM.	Moderate
3	Field T S, 2007(77) Elderly	Y	Y	Y	Y	Y-Age, gender, comorbidity, number of medications None	Y	Y	Y (1 year)	ADE resulting from patients' error prevalence: 0.38%	P value <0.05	Y	Y	Y	Possible drug-related incidence for which necessary information was not documented in the medical record was not considered.	High

4	Gagne J J, 2008(34) DDI	Y	Y	Y	Y	Y- Age, gender, geographic location, comorbidity, number of medication prescribed. None	Y	Y	Y (1 year)	DDI: prevalence 53%	95% CI	Y	Y	Y	Applying the US list of clinically important DDI to Italy may underestimate the prevalence as it captured only 12 out of the 25 DDI original list. Unable to extract risk factors data as it for all age group.	High
5	Berdot S, 2009(45) Elderly PIM	Y	Y	Y	Y	Y-but for irrelevant outcome -	Y	Y	Y (4 years)	PMI prevalence 31.6%	95%CI, P value <0.05	Y	Y	Y	Self-report and data from healthcare insurance plan are not perfect for actual drug consumption. Recall bias. Confounding factors were for the risk of falls rather than for PIM.	High

6	Lapi F, 2009(35) Elderly PIM	Y	Y	Y	Y	Y- Comorbidity, polypharmacy, stroke, heart failure Age, gender	Y	Y	Y (1 year)	1999: IP prevalence: (5.1%) Potential DDI prevalence: (30.5%) Potential Major DDI: (5.6%) Polypharmacy, aws a predictors of PIM use.	P-value <0.05, 95% CI	Y	N	Y	Self-reported diagnosis and medication use may cause recall bias. Beers' list cannot be fully applied to Italy, it most reflect US drug market.	Moderate
7	Ryan C, 2009 (48) Elderly PIM	Y	Y	Y	Y	N -	Can't tell	Y	Y (6 month)	Medicine prescribed inappropriately Beers 2003: 13% IPET: 10.4%	Can't tell	Y	Y	Y	-	Low

8	Akazawa M, 2010(50) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, polypharmacy (>5 drugs), hospitalisation , comorbidities. None	Y	Y	Y (1 year)	Prevalence of PIM 43.6%. Inpatient service use, polypharmacy, and comorbidities were significant predictors of PIM use.	95%CI, P value <0.05	Y	Y	Y	Medical information cannot be taken from claim data, unobserved confounder. PIM not associated with age as several other studies.	High
9	Barnett K, 2011(52) Elderly PIM	Y	Y	Y	Y	Y- Age, sex, polypharmacy and place of residence. Comorbidity	Y	Y	Y(2yesrs)	PIM prevalence 30.9%. Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy	95%CI	Y	Y	Y	Comorbidity not accounted for. Risk factors for both care home and home	High
10	Chang C B, 2011(53) Elderly PIM	Y	Y	Y	Y	Y- Age, sex, education, number of chronic medication, number of chronic conditions, and number of ED visits.	Y	Y	Y (12,24 Week)	PIM: 24% - 73%. Number of chronic drugs and number of chronic conditions was a common risk factor in all criteria	P value < 0.05	Y	Y	Y	May underestimated the prevalence because several drugs in Taiwan was not available in the sex	High

						None									criteria	
11	Zhang Y J, 2011(56) Elderly PIM	Y	Y	Y	Y	Y- Race, gender, family income, educational level, census region, number of prescription, self-rated health status. None	Y	Y	Can't tell	Prevalence of PIM was from [(13.84%) (95% CI 12.52-15.17)] to [(21.3%) (95% CI 19.5-23.1)]	95%CI, P value <0.05	Y	Y	Y	Recall bias due to self-reported survey. Did not assess DDI, drug-disease interaction and under-use so may underestimate the prevalence	Moderate
12	Cornu P, 2012(71) Elderly	Y	Y	Y	Y	Y- Age, gender, residential situation before admission, residential situation after discharge, number of drugs in the discharge letter or list. Comorbidity	Y	Y	Y (from admission to discharge)	Almost half of these patients [(47.6%) (95% CI 40.5-54.7)] had 1 or more discrepancies in medication information at discharge.	95%CI, P value <0.05	Y	Can't tell	Y	Was done in one centre that may have different procedure of discharge	Moderate
13	Mosher H J, 2012(75)	Y	Y	Y	Y	Y- Health literacy	Y	Y	Y (3 and 12 months)	ADEs occurred in 51	P value <0.05	Y	Can't tell	Y	Results may be biased due	Moderate

	Elderly					Age, number of medications, comorbidity				patients (16.5%) of the patients within the first 3 months of the study, which increased, to 119 patients (38.4%) over the full 12-month follow-up period.					to sampling strategy	
14	Obreli Neto P R , 2012 (28) DDI	Y	Y	Y	Y	Y None	Y	Y	Y (4months)	Incidence of DDI-related ADR (6.9%)	95%CI, P value <0.05	Y	Y	N	Recall bias from weekly meeting with patient. Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interaction involving combinations of three or more drugs so the risk of DDI may be underestimated	Moderate

15	Blozic E, 2012 (60) Adult	Y	Y	Y	Y	Y- gender Age, number of medications, number of disease	Y	Y	Y (3 years)	Prevalence of PIM 21.1%	95% CI	Y	Y	Y	-	High
16	Cahir C, 2013(61) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, socioeconomic status, private health insurance, co-morbidity, number of repeat drug, social support and network, adherence. None	Y	Y	Y (6 months) retrospective study	Prevalence of potentially IP was 40.5%	95%CI	Y	N	Y	Recall bias due to self-reported ADE.	Moderate
17	Zimmermann T, 2013(18) Elderly PIM	Y	Y	Y	Y	Y- Gender age, number of medications, number of disease, depression, education None	Y	Y	Y (4.5 years)	At baseline PIM prevalence is (848) 29% according to the PRISCUS list, which decreased to (464) 25.0% 4.5 years later and 21% according to the Beers list decreasing	95%CI, P value <0.05, OR and CI for risk factors	Y	Y	Y	-	High

										after 4.5 years to (317) 17.1%						
18	Amos T B, 2015(65) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, geographic location, number of medication. Number of chronic conditions	Y	Y	Y (1 year) retrospective study	PIM prevalence 28 % and older age, female, number of medications increase risk of PIM	95%CI, P value <0.05	Y	Cant 'tell	Y	May underestimate the true PIM prevalence because they do not account for OTC	Moderate
19	Hedna K, 2015(66) Elderly PIM	Y	Y	Y	Y	N Age, gender, number of medication, number of chronic condition	Y	Y	Y (3 months) retrospective	Potentially IP Prevalence 42%. ADR caused by potentially IP.	95% CI, P value <0.05	Y	Cant 'tell	Y	Undetected confounders.	Moderate
20	Moriarty F, 2015(67) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, number of medication, number of chronic condition, level of education.	Y	Y	Y (1 year)	PIM prevalence (36.7%-64.8%). Female, age and higher number of medicines were	95% CI	Y	Y	Y	Lack of information on OTC from the pharmacy claim data.	High

						None			associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be associated with change in PPO prevalence.						

Table 3: Medication errors patient-related risk factors

Risk factor	Number of studies with positive association	Number of controlled studies	Controlled for	Specific information	OR or RR (95% or 99% CI) p-value
Age ≥ 75 years	13 (18, 27, 31, 36, 38, 46, 47, 49, 55, 63-65, 67)	10	NA	≥ 80 years	OR 1.021 (95% CI 1.018-1.023) p<0.001.(47)
			Adjusted for age, sex, number of regular medicine and diagnosed chronic condition	Older age	OR 1.03 (95% CI 1.02-1.04) p<0.05.(67)
			NA	Older age	OR 1.05 (95% CI 1-1.09) p=0.046.(55)
			NA	Older age	OR 1.06 (95% CI 1.0-1.13) p=0.037.(18)
			NA	≥ 75 years	OR 1.10 (95% CI 1.05-1.15) p<0.001.(31)
			NA	≥ 85 years	OR 1.18 (95% CI 1.16-1.20) p<0.05.(38)
			Adjusted for sex, age and number of chronic drugs	≥ 85 years	OR 1.52 (95% CI 1.46-1.6).(36)
			NA	≥ 85 years	OR 1.53 (95% CI 1.5-1.55) p< 0.01.(65)
			NA	≥ 85 years	OR 1.79 (95% CI 1.19-2.83) p=0.009.(64)

			Adjusted for sex, age	≥ 75 years	OR 4.03 (95% CI 3.79-4.28) p<0.001.(27)
Comorbidity or Number of disease or Chronic condition drug group (CCDG) score ≥ 4	10 (18, 20, 27, 38, 41, 50, 53, 67, 73, 74)	3	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of chronic conditions	PPO: OR 1.47 (95% CI 1.39-1.56) p<0.05.(67)
			NA	CCDG score ≥ 4	OR 1.76 (95% CI 1.72-1.81) P<0.05.(38)
			Adjusted for age, sex	Diagnosed disease ≥ 3	OR 6.43 (95% CI 3.25-12.44) p<0.001.(27)
Charlson Comorbidity Index (CCI)	3 (46, 49, 63)	1	NA	CCI < 2	RR 2.885 (95% CI 1.972-4.22) p=0.(63)
Female gender	10 (27, 29, 41, 46, 47, 56, 58, 60, 65, 67)	4	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition		PIM: OR 1.27 (95% CI 1.07-1.5) p<0.05.(67)
			Adjusted		OR 1.6 (99% CI 1.58-1.64).(58)
			Adjusted for age, sex, education level, partnership, per capita		Beers 2003: OR 2.5 (95% CI 1.9-3.5)

			income and occupation		Beers 2012: OR 1.8 (95% CI 1.3-2.5).(29)
			Adjusted for sex, age		OR 2.49 (95% CI 2.29-2.75) p<0.001.(27)
Health literacy or Low education	2 (46, 75)	1	Adjusted for age, sex, type of residential area and comorbidity		OR 1.09 (95% CI 1.07-1.17).(46)
Hospital admission	2 (20, 50)	1	NA		OR 3.35 (95% CI 2.43-4.62) p<0.05.(50)
Middle family income	1 (56)	NA	NA		
Polypharmacy	26 (18, 27, 29-31, 35, 36, 38-40, 47, 49-51, 53, 55, 56, 62-65, 67, 68, 70, 71, 74)	18	NA	Higher number of prescribed medications	OR 1.06 (95% CI 1.39-1.98) p<0.001.(55)
			Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of prescribed medications	PIM: OR 1.2 (95% CI1.17-1.24) p<0.05 PPO: OR 1.04 (95% CI 1.01-1.07) p<0.05.(67)
			NA	≥ 4 medications	OR 1.91 (95% CI 1.83-2.0) p<0.001.(31)
			NA	Higher number of prescribed medications	OR 1.99 (95% CI 1.80-2.18) p=0.000.(18)
			Adjusted for age, sex, education level, partnership, per capita income and occupation	≥ 5 medications	Beers 2003: OR 2.9 (95% CI 2.1-3.8) Beers 2012: OR 2.7 (95% CI 2-3.6).(29)
			Adjusted for disability, coronary artery disease, heart failure and other comorbidities	≥ 5 medications	IP: OR 2.9 (95% CI 1.5-5.8) Potential major DDI: 3.8 (95% CI 1.7-8.2).(35)

			Adjusted for age, sex, number of chronic conditions and number or drug consumed	≥ 3 medications	OR 3.21 (95% CI 2.78-3.59) p<0.001.(27)
			Adjusted for age, sex, length of hospital stay, and residential situation	≥ 5 medications	OR 3.22 (95% CI 1.40-7.42) p=0.006.(71)
			NA	≥ 6 medications	OR 3.37 (95% CI 2.08-5.48) p<0.001.(30)
			NA	≥ 7 medications	OR 4.528 (95% CI 4.52-4.54) p<0.001.(47)
			Adjusted for age, sex, CCI, history of cardiovascular disorder, history of digestive disorder	≥ 5 medications	OR 5.4 (95% CI 3-9.7) p<0.001.(62)
			Adjusted for sex, age and number of chronic drugs	≥ 6 medications	OR 5.59 (95% CI 5.39-5.80).(36)
			NA	≥ 5 medications	OR 5.69 (95% CI 5.0-6.48) p<0.05.(50)
			NA	≥ 6 medications	STOPP: RR 6.837 (95% CI 4.155-11.247) START: RR 2.051 (95% CI 1.25-3.367).(63)
			NA	≥ 10 medications	OR 7.33 (95% CI 7.15-7.51) p<0.05.(38)
			NA	≥ 9 medications	OR 7.43 (95% CI 3.20-17.23) p<0.001.(64)
			NA	≥ 10 medications	Male: OR 8.2 (95% CI 8-8.4) Female: OR 9.6 (95% CI 8.2-11.2).(40)
			NA	≥ 10 medications	OR 11.45 (95% CI 11.2 -11.7) p<0.01.(65)

Table 4: Medication errors healthcare professional-related risk factors

Risk factor	Number of studies with positive association	Number of controlled studies	Adjusted for	OR or RR or Beta (95% or 99% CI) p-value
Age ≥ 51 years	2 (47, 65)	2	NA	OR 1.03 (95% CI 1.01 -1.06) p<0.01.(65)
			NA	OR 1.238 (95% CI 1.235-1.242) p<0.001.(47)
More than one physician involved in their care	5 (27, 58, 70, 73, 74)	3	NA	Beta 0.7 (95% CI 0.5-1.0) p=0.034.(73)
			Adjusted for age, sex, number of chronic conditions and number or drug consumed	OR 1.39 (95% CI 1.17-1.67) p<0.001.(27)
			Adjusted for age and number of prescriber	OR 3.52 (99% CI 3.44-3.60).(58)
Male general practitioner	2 (47, 65)	2	NA	OR 1.07 (95% CI 1.05-1.10) p<0.01.(65)
			NA	OR 1.206 (95% CI 1.202-1.210) p<0.001.(47)
Frequent changes in prescription	1 (73)	1	NA	Beta 0.4 (95% CI 0.2-0.9) p=0.019.(73)
Not considering the prescription of other physicians	1 (73)	1	NA	Beta 1.9 (95% CI 1.1-3.2) p=0.013.(73)
Inconsistency in the information	1 (73)	1	NA	Beta 4.4 (95% CI 1.3-14.8) p=0.013.(73)
Outpatient clinic visit	1 (40)	1	NA	1.4 (Male 95% CI 1.3-1.4) (Female 95% CI 1.3-1.6).(40)

Family medicine/ general practice specialty	3 (47, 50, 65)	3	NA	OR 1.06 (95% CI 1.03-1.10) p<0.01.(65)
			NA	OR 1.267 (95% CI 1.265-1.269) p<0.001.(47)
			NA	OR 1.46 (95% CI 1.28-1.65) p<0.05.(50)

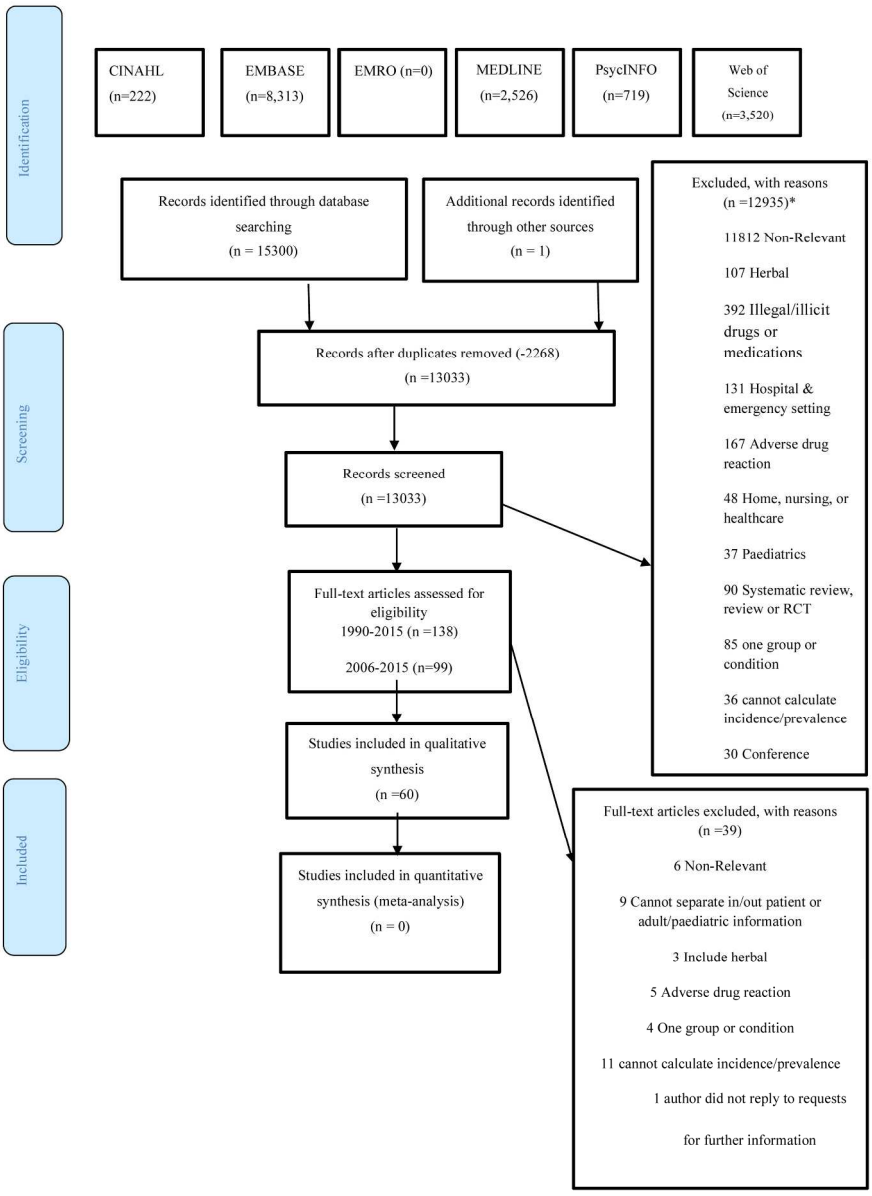

Figure 1: PRISMA flow diagram. (From: Moher D, Liberati A, Tetzlaff J. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement).
*Articles may be duplicated between the excluded groups

189x260mm (300 x 300 DPI)

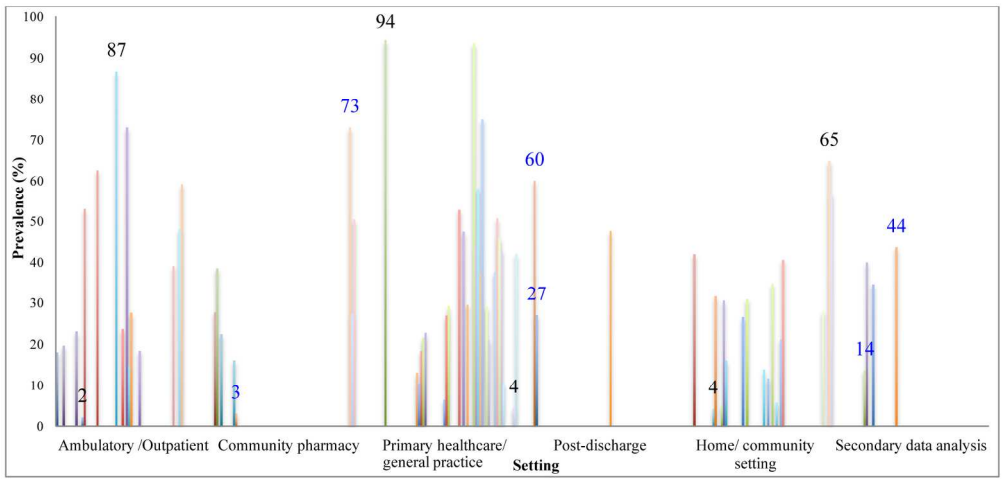

Figure 2: Medication errors prevalence estimates according to settings.

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Appendix 1: Search strategies

A. MEDLINE

1. Medication Errors/ae, cl, mt [Adverse Effects, Classification, Methods]
2. "Drug-Related Side Effects and Adverse Reactions"/
3. adverse drug event*.mp.
4. medication error*.mp.
5. Patient Safety/
6. drug safety.mp.
7. medication safety.mp.
8. prescribed medication*.mp.
9. prescribed drug*.mp.
10. Nonprescription Drugs/
11. over the counter medication*.mp.
12. patient error*.mp.
13. medication management.mp.
14. Medication Therapy Management/

15. drug related problem*.mp.

16. medication related problem*.mp.

17. preventable adverse drug event*.mp.

18. preventable adverse event*.mp.

19. potential adverse event*.mp.

20. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. household*.mp.

23. residence*.mp.

24. residential home.mp.

25. ambulatory care.mp.

26. Outpatients/

27. self care/ or self medication/ or self manage*.mp.

28. After-Hours Care/

29. out of hours medical care.mp.

30. Homebound Persons/

31. home visit.mp.

32. face to face home interview.mp.

33. face to face interview.mp.

34. Primary Health Care/

35. General Practice/

36. Family Practice/

37. Patient-Centered Care/

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. ((after or post) adj2 hospital discharge).mp.

40. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. Epidemiology/

42. Prevalence/

43. Incidence/

44. risk factor*.mp.

45. follow up.mp.

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. observational.mp.

50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51. 21 and 40 and 50

52. limit 51 to (humans and yr="1990 -2015")

B. EMBASE

1. adverse drug event*.mp.

2. medication error/

3. patient safety/

4. drug safety/

5. medication safety.mp.

6. prescription drug/

7. prescribed medication*.mp.

8. non prescription drug/

9. over the counter medication*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10. patient error*.mp.

11. medication therapy management/

12. medication management.mp.

13. drug related problem*.mp.

14. medication related problem*.mp.

15. preventable adverse drug event*.mp.

16. preventable adverse event*.mp.

17. potential adverse drug event*.mp.

18. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. household*.mp.

21. residence*.mp.

22. ambulatory care/

23. outpatient care/ or outpatient/

24. self care/

25. self medication/

26. self manage*.mp.

27. after hours care.mp.

28. out of hours medical care.mp.

29. home visit.mp.

30. interview/ or face to face interview.mp.

31. primary health care/

32. general practice/

33. patient centered care.mp. or patient care/

34. family practice.mp.

35. ((after or post) adj2 hospital discharge).mp.

36. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

37. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. epidemiology/

39. prevalence/

40. incidence/

41. risk factor*.mp.

42. follow up/

43. observational method/

44. cross-sectional study/ or cross sectional.mp.

45. cohort.mp.

46. case control study/ or case control.mp.

47. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. 19 and 37 and 47

49. limit 48 to (human and yr="1990 -2015")

C. PsycINFO

1. medication error*.mp.

2. adverse drug event*.mp.

3. drug related adverse event*.mp.

4. patient safety.mp.

5. drug safety.mp.

6. medication safety.mp.

7. exp Prescription Drugs/ or exp "Prescribing (Drugs)"/

8. prescribed medication*.mp.

9. exp Nonprescription Drugs/

10. over the counter medication*.mp.

11. patient error*.mp.

12. medication management.mp.

13. medication therapy management.mp.

14. drug related problem*.mp.

15. medication related problem*.mp.

16. preventable adverse event*.mp.

17. preventable adverse drug event*.mp.

18. potential adverse event*.mp.

19. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21. household*.mp.

22. residence*.mp.

23. residential home.mp.

24. ambulatory care.mp.

25. exp Outpatients/

26. self care.mp.

27. exp Self Medication/

28. exp Self Management/

29. after hours care.mp.

30. home visit.mp.

31. exp Home Visiting Programs/

32. exp Interviews/ or face to face interview.mp.

33. exp Primary Health Care/

34. exp General Practitioners/ or general practice.mp.

35. family practice.mp.

36. patient centered care.mp.

37. ((after or post) adj2 hospital discharge).mp.

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp Epidemiology/

41. incidence.mp.

42. prevalence.mp.

43. risk factor*.mp.

44. follow up.mp.

45. exp Observation Methods/

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. 20 and 39 and 49

51. limit 50 to (human and yr="1990 -2015")

D. Web of Science

#5	#4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#4	TS=(follow up) OR TS=(cross sectional) OR TS=(cohort) OR TS=(case control) OR TS=(observational study) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#3	TS=(epidemiology) OR TS=(incidence) OR TS=(prevalence) OR TS=(risk factor*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#2	**TOPIC:** (household) *OR* **TOPIC:** (residence) *OR* **TOPIC:** (ambulatory) *OR* **TOPIC:** (community) *OR* **TOPIC:** (outpatient) *OR* **TOPIC:** (general practice) *OR* **TOPIC:** (family practice) *OR* **TOPIC:** (primary health care) *OR* **TOPIC:** (patient centered care) *OR* **TOPIC:** (self care) *OR*

	TOPIC: (self manage*) *OR* **TOPIC:** (self medication*) *OR* **TOPIC:** (after hours care) *OR* **TOPIC:** (after hospital discharge) *OR* **TOPIC:** (post hospital discharge) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#1	**TOPIC:** (medication error*) *OR* **TOPIC:** (adverse drug event*) *OR* **TOPIC:** (drug related adverse event*) *OR* **TOPIC:** (medication related adverse event*) *OR* **TOPIC:** (patient safety) *OR* **TOPIC:** (drug safety) *OR* **TOPIC:** (patient error*) *OR* **TOPIC:** (drug related problem*) *OR* **TOPIC:** (preventable adverse drug event*) *OR* **TOPIC:** (potential adverse drug event*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015

E. CINAHL

S25	S21 AND S22 AND S23 Limiters – Published Date: 19900101-20151031

S24	S21 AND S22 AND S23
S23	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S22	S8 OR S9 OR S10 OR S11 OR S12 OR S13
S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S20	(MH "Case Control Studies")
S19	"cohort"
S18	(MH "Cross Sectional Studies")
S17	(MH "Prospective Studies")
S16	(MH "Risk Factors")
S15	(MH "Incidence")
S14	(MH "Prevalence")
S13	(MH "Family Practice") OR "general practice"
S12	(MH "Primary Health Care")
S11	(MH "Self Care")
S10	(MH "Ambulatory Care")
S9	(MH "Outpatients")

S8	"household*"
S7	"medication therapy management"
S6	"drug related problem*"
S5	"over the counter medication*"
S4	"prescribed medication*"
S3	"drug safety"
S2	(MH "Adverse Drug Event")
S1	(MH "Medication Errors")

F. Global Health Library (EMRO)

(Adverse drug event* OR medication error* OR patient error*) AND (outpatient OR ambulatory OR general practice OR family practice OR household OR community OR home visit OR after hospital discharge) AND (prevalence OR incidence OR risk factor* OR cross sectional OR cohort OR case control)

G. Google scholar

(Medication error* OR adverse drug event*) AND (home* OR ambulatory OR community OR outpatient OR general practice OR after discharge) AND (prevalence OR incidence OR risk factor* OR Cross sectional OR cohort OR case control)

2- Experts in the field was contacted by email:

	Date	Replay or not	Result
1- Tahir M khan from Malaysia	11/8/2015	Yes	(Medication error in the Southeast Asian countries) systematic review study
2- Azmi Hassali from Malaysia	11/8/2015	Yes	Referred to Tahir M khan
3- Izham M Ibrahim from Malaysia	11/8/2015	No	-
4- David Bates	11/8/2015	No	-

5- Tejal Gandhi	11/8/2015	No	-
6- Kathleen Walsh	11/8/2015	Yes	Published papers

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	49(table2)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8, 27(table 1)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: **www.prisma-statement.org**.

BMJ Open

What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019101.R2
Article Type:	Research
Date Submitted by the Author:	13-Feb-2018
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology, General practice / Family practice, Global health
Keywords:	medication errors, adverse drug events, error-related adverse drug events, prevalence, incidence, risk factor

What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature

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Keywords: medication errors, adverse drug events, error-related adverse drug events, drug related problems, prevalence, incidence, risk factor, primary care, ambulatory care, home setting, and adult.

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Abstract

Objectives: To investigate the epidemiology of medication errors and error-related adverse events in adults in primary care, ambulatory care and patients' homes.

Design: Systematic review.

Data source: Six international databases were searched for publications between 1/1/2006-31/12/2015.

Data extraction and analysis: Two researchers independently extracted data from eligible studies and assessed the quality of these using established instruments. Synthesis of data was informed by an appreciation of the medicines' management process and the conceptual framework from the International Classification for Patient Safety (ICPS).

Results: 60 studies met the inclusion criteria, of which 53 studies focused on medication errors, three on error-related adverse events and four on risk factors only. The prevalence of prescribing errors was reported in 46 studies: prevalence estimates ranged widely from 2-94%. Inappropriate prescribing was the most common type of error reported. Only one study reported the prevalence of monitoring errors, finding that incomplete therapeutic/safety laboratory-test monitoring occurred in 73% of patients. The incidence of preventable adverse drug events (ADEs) was estimated as 15/1000 person-years, the prevalence of drug-drug interaction (DDI) -related adverse drug reactions (ADR) as 7% and the prevalence of preventable ADE as 0.4%. A number of patient, healthcare professional and medication-related risk factors were identified, including the number of medications used by the patient, increased patient age, the number of comorbidities, use of anticoagulants, cases where more than one physician was involved in patients' care and care being provided by family physicians/general practitioners (GP).

Conclusion: A very wide variation in the medication-error and error-related adverse events rates is reported in the studies, this reflecting heterogeneity in the populations studied, study designs employed and outcomes evaluated. This review has identified important limitations and discrepancies in the methodologies used and gaps in the literature on the epidemiology and outcomes of medication errors in community settings.

Strengths

- This is the first systematic review on the epidemiology of medication errors and medication associated harm in community settings. The use of the International Classification for Patient Safety (ICPS) conceptual framework helped with framing and organising the findings from this systematic review.
- A rigorous and transparent process has been employed, which included no language restrictions in undertaking searches, independent screening of titles, abstracts and full text papers, independent data extraction and critical appraisal of included studies by two reviewers.

Limitations

- Outcomes have been reported in a variety of ways using different tools and methodology which made it difficult to undertake any quantitative pooled summary of the results.
- Despite the comprehensiveness of the searches, we found no data regarding errors during medication dispensing and administration. This might be due to the lack of 'dispensing error' and 'administration error' terms in our search strategy, although 'medication therapy management' was included as a more over-arching search term.
- There is at present no agreed, consistently applied set of confounders that should be taken into account when trying to make causal inferences.

Introduction

Patient safety is a public concern in healthcare systems across the world.(1) Medication errors (ME) and error-related adverse drug events (ADEs) are common and are responsible for considerable patient harm.(1) More specifically, ADEs can lead to morbidity, hospitalisation, increased healthcare costs and, in some cases, death.(1) It has been estimated that 5-6% of all hospitalisations are drug-related,(2, 3) with one estimate suggesting that ADEs causing hospital admission in the United Kingdom (UK) occur in around 10% of inpatients; approximately half of these ADEs are believed to be preventable.(4) The cost of medication errors worldwide has been estimated as US$ 42 billion/year.(5)

Since the release of *To Err is Human: Building a Safer Health System* by the Institute of Medicine (IOM; now the National Academy of Medicine)(6), which focused on acute care settings, most patient safety research has been conducted in hospital settings.(7, 8) Given that international and national policy drivers are for patients to be increasingly managed in primary, ambulatory and home settings in order to realise the goals of more accessible, patient-centred and efficient healthcare,(9) there is an increased sense of urgency to further focus attention on community care contexts, particularly in relation to medication safety. With an aging population, particularly in economically-developed countries, as well as the use of polypharmacy, there is a need to empower patients, particularly those with chronic diseases, to self-care safely.

The aim of this systematic review was to investigate the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts (i.e. primary care, ambulatory and home settings). Box 1 provides definitions of the key terms employed in this review.

Adverse drug event (ADE): Bates et al. (1995) define ADE as, *"an injury resulting from medical intervention related to a drug."*(10) Some ADEs are caused by underlying medication errors and therefore they are preventable.
Medication error: The National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) defines a medication error as: *"any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health-care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use".*(11) Medication errors can result from any step of the medication-use process: selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration, or monitoring.(1)
Non-prescription drugs: Medicines that can be sold legally without a drug prescription.
Over-the-counter (OTC) drug: The FDA defines OTC drugs *as "drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription*".(12)
Prescription drug: Drugs that cannot be sold legally without a prescription.

Box 1: Key definitions.

Methods

Protocol and reporting

The study protocol was developed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and was registered in PROSPERO.(13, 14) The detailed systematic review protocol has also been published.(15)

Eligibility criteria/ study selection:

Studies conducted in adults (≥18 years) who were looked after in the community and living in their own or family homes without home healthcare or nursing home were eligible for inclusion in this review. The studied patients could have been self-managing, receiving care in primary care or ambulatory care settings, or any combination of the above. Studies were included if they were population-based, cross-sectional or cohort studies, which were suitable to estimate the incidence and prevalence of medication errors or ADEs. These study designs and case-control studies were considered eligible to study risk factors for the development of error-related ADEs. Studies with prescribed and/or over-the-counter (OTC) medications as the exposure of interest were eligible.

Paediatric studies (<18 years) and studies on patients receiving care in hospital at home settings (i.e. continuous medical and/or nursing care provided to patients in their own homes), in nursing homes, as hospitalised in-patients or in emergency departments (ED) were excluded. Randomised controlled trials (RCT) were excluded since these could not be used to reliably assess the incidence and/or prevalence of the outcomes of interest. Existing reviews were also excluded since the focus was on the primary literature. Incompletely reported studies, e.g. in the form of abstracts, were not eligible for inclusion. Studies on illegal substance abuse, herbal products and those focusing on particular medications, were also excluded.

No restriction on the language of publication was employed.

Data sources and search strategy

Search terms were developed based on the systematic review protocol.(15) The search terms and detailed search strategies are presented in Appendix 1. In summary, these involved identifying search terms (and their synonyms) in relation to medication safety, community care settings and study design, and combining these concepts with the Boolean operator AND to identify studies that intersected all three search concepts of interest. Examples of the search terms used included: for the outcome: medication safety, medication error, preventable adverse drug event, patient error; for the setting: ambulatory care, outpatient, self-care, primary healthcare and general practice; and for the study design: cohort study, cross sectional study and observational study. Six biomedical databases were searched, including the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Eastern Mediterranean Regional Office

of the World Health Organization (WHO EMRO), MEDLINE, PsycINFO, and Web of Science between 01 January 2006 and 31 December 2015. Google Scholar was searched for additional studies. An international panel of experts was also contacted to identify unpublished work and research in progress (Appendix 1). The reference list of all included studies was further reviewed for additional possible eligible studies.

The databases were searched by Ghadah Assiri (GA). The title and abstracts were then independently screened for eligible studies according to the above detailed selection criteria by GA and a second reviewer, Nada Shebl (NS). The corresponding authors of the eligible articles were contacted if additional information was needed. Disagreements were resolved by discussion between the reviewers or by arbitration by a third reviewer, Aziz Sheikh (AS), if a decision could not be reached. Full-text articles were retrieved from selected studies and reviewed according to the selection criteria. Each copy of the selected studies was retrieved and the reason for excluding other studies was clearly noted.

Data extraction and risk of bias assessment

Data were independently extracted and recorded onto a customised data extraction sheet by two reviewers [GA and NS, or GA and Mansour Mahmoud (MM)]. Discrepancies were resolved by discussion or by arbitration by an additional reviewer (AS), if necessary.

Key information such as study design, study type (retrospective, prospective), population of interest, exposure of interest, outcomes of interest and main findings were extracted.

The risk of bias assessment was independently carried out on each study by two reviewers [GA and NS, or GA and Nouf Aloudah (NA)] using the Critical Appraisal Skills Program (CASP) quality assessment tool for cohort and case-control studies,(16) and cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Descriptive Studies.(17) Any disagreements were resolved by consensus or by arbitration by a third reviewer (AS) if a decision could not be reached. Each study was given an overall grading as being at high, medium, or low risk of bias.

Data synthesis

Data were summarised in detailed data tables, which included information on the incidence, prevalence, relative risk and odds ratios (ORs), together with 95% confidence intervals, for each study (where available). A descriptive and narrative synthesis of the extracted data was undertaken.

The definition of incidence rate used in this review is: *"the number of patients with one or more [medication error or preventable ADE] (numerator) divided by the total number of patients at risk per time unit (denominator)."*(18) The definition of prevalence rate used in the data extraction is: *"the number of patients experiencing one or more [medication error or preventable ADE] (numerator) divided by the total number of patients in the study population (denominator)."*(19) The prevalence rate per population was either reported and extracted directly from the included study or calculated from data provided in the study.

We worked with the definitions of medication errors and error-related ADEs employed in individual studies. These errors may have occurred anywhere in the medicines' management process.(1) Medication errors were described according to: i). the stage in the medicines' management process when the error occurred i.e. prescribing, dispensing, administration and monitoring;(1) and ii). the type of error that occurred in each stage according to the conceptual framework for the International Classification for Patient Safety (ICPS) definitions (Box 2).(20)

1- Administration error
"Any discrepancy between how the medication is given to the patient and the administration directions from the physician or hospital guidelines"(1)
2- Prescribing error
"*Medication error occurring during the prescription of a medicine that is about writing the drug order or taking the therapeutic decision, appreciated by any non intentional deviation from standard reference such as: the actual scientific knowledge, the appropriate practices usually recognized, the summary of the characteristics of the medicine product, or the mentions according to the regulations. A prescribing error notably can concern: the choice of the drug (according to the indications, the contraindications, the known allergies and patient characteristics, interactions whatever nature it is with the existing therapeutics, and the other*

factors), dose, concentration, drug regimen, pharmaceutical form, route of administration, duration of treatment, and instructions of use; but also the failure to prescribe a drug needed to treat an already diagnosed pathology, or to prevent the adverse effects of other drugs".(20)
Inappropriate prescribing "*The use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition. Inappropriate prescribing also includes the use of medicines at a higher frequency and for longer than clinically indicated, the use of multiple medicines that have recognized drug–drug interactions and drug–disease interactions, and importantly, the under-use of beneficial medicines that are clinically indicated but not prescribed for ageist or irrational reasons*".(21)
3- Monitoring error "*Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed theory*".(20)
4- Dispensing error "*Deviation from the prescriber's order, made by staff in the pharmacy when distributing medications to nursing units or to patients in an ambulatory pharmacy setting*".(20)
5- Other: discrepancies "*Any differences between the medication described by the patient and caregivers with the drugs listed by their general practitioners (GP) or between the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list*".(22, 23)

Box 2: Classification of definitions used in this systematic review.

Risk factors were categorised as patient, healthcare professional and medication-related risk factors.

Changes from the original protocol

The following changes were made from the plans described in the research protocol:(15) i). due to the large quantity of studies found during the initial search and because of medications and practice changes over the years, only studies published in the last 10 years were included: 01 January 2006 to 31 December 2015; ii). only studies with the incidence or prevalence rate per number of patients were included; and iii). meta-analysis was not possible due to the heterogeneity of outcomes, methods and definitions.

Results

A total of 13,033 potentially eligible studies were identified after removing duplicates, of which 59 studies met the inclusion criteria. One additional study was identified through hand-searching. Therefore, a total of 60 studies were included in the systematic review (Figure 1).

One study was available only in German, and one in Spanish. Those two papers were retrieved and translated into English by native speakers.(24, 25)

The key characteristics of all included studies are presented in Table 1. The quality assessments of these studies are summarised in Table 2.

Nine studies were conducted in Asia, four in Australia, 32 in Europe, eight in the North America, five in South America, and two were conducted across continents [one study covering two Australian countries, three European countries, one North American country and one South American country,(26) and one study across two Australian countries, four European countries, one North American country and one South American country].(27) 19 studies were conducted in primary healthcare or general practice contexts, 15 studies in home or community settings, 16 studies in ambulatory care or outpatient settings, five studies in community pharmacies and two studies in post-discharge settings, while three studies used secondary data analysis.

Eleven studies enrolled adults in all age groups (>18 years), three studies reported the mean age only,(28-30) one enrolled those of 55 years or older,(31) five enrolled those aged 60 years or older ,(32-36) and the majority of studies (n=40 studies, 67%) enrolled

patients of 65 years or older. If the study included adult and paediatric data, only relevant adult data were extracted.

The quality of the cross-sectional or descriptive studies using the JBI Critical Appraisal Checklist was high for nine studies, moderate for 10 studies and low for one study. The quality of the cohort studies using the CASP quality assessment tool was high for 37 studies and moderate for three studies.

Different methods of medication errors and error-related adverse events identification were used in the studies, including data review (electronic/paper-based medical record review, lab review, prescription review), database analysis, patient survey (face-to-face or telephone interview and survey or questionnaire), patient self-report and home visits.

Medication errors

Incidence and/or prevalence

We found no study reporting data on the incidence of medication errors. Estimates of community setting medication error prevalence were available from 53 studies.(22-27, 29, 30, 32, 33, 35-77)

Self-reported medication errors

The period prevalence of self-reported medication errors was measured in four cross-sectional studies by Adams R J (2009), Lu C Y (2011), Sears K (2012) and Mira J J (2013).(26, 27, 76, 77) In the first three studies, the period prevalence was reported as 2%, 6% and 6% respectively,(26, 27, 76) while in Mira's study, 75% of elderly patients with multiple comorbidities and polypharmacy (five or more drugs) reported having made at least one mistake with their medication (including errors related to dose, similar appearance of medications, and lack of understanding of the physician's instructions).(77) In this study, in 5% of cases, errors due to drug confusion had very severe consequences, requiring a visit to the emergency services or hospital admission.(77) That wide differences in prevalence were seen between the first three studies and the last may be due to population factors. Mira's study population comprised of older poly-medicated patients with multiple comorbidities. This elderly group had a greater risk of error, while the first three studies had populations including any patient over 18 years.

Medication error according to medicines' management process

1- Prescribing errors:

The point or period prevalence of prescribing errors was reported in 46 studies. In these studies, prescribing errors included errors in drug indications, drug-disease interactions, drug-drug interactions (DDI) and dosing error, as well as inappropriate prescribing, which was the most common error reported.

Indication

Koper D et al. (2013) found that, on average, 2.7 medications per patient were not indicated, with a total of 94% of patients having medications prescribed by the general practitioner, but not mentioned in the indication of the UpToDate®.(29)

Drug-disease interactions or contra-indications

Drug-disease interactions were measured in one study by Mand P (2014) with a prevalence of 10%.(37)

Drug-drug interactions

The prevalence of DDIs was measured in 11 studies and ranged from 2 - 58%.(29, 30, 32, 33, 36, 38-43) This could in part have been due to the fact that different DDI screening tools were used, namely: DDI compendia and (ePocrates RX), Thompson Micromedex program, database Pharmavista, program BotPlus of the General Council of Pharmacists' Official Colleges, British National Formulary 2010, Italian computerised interaction database, DrugDigest®, Drugs®, Micromedex® and Medscape®.

Inappropriate prescribing

A- The prevalence of potentially inappropriate medication (PIM) was measured in 37 studies in the elderly age group only (≥65 years) and ranged from 5 - 94%.(24, 25, 29, 32, 35, 41, 44-74) This extremely wide range of inappropriate prescribing prevalence estimates is likely to be, at least in part, due to the different detection tools used, namely: Beers 2003, the 2006 Health Plan Employer Data and Information Set (HEDIS), Improved Prescribing in the Elderly Tool (IPET), Medication Appropriate Index (MAI), PRISCUS and Screening Tool of Older Person's Prescriptions (STOPP)

criteria. Johnell K (2008) and Haider S I (2009) mentioned two other specific criteria.(50, 52)

B- The prevalence of potential prescribing omission (PPO) was measured in five studies for the elderly age group only (≥65 years) ranging from (23 - 57%).(25, 55, 69, 70, 73) PPO was detected by Screening Tool to Alert doctors to Right Treatment (START) and Assessing Care of Vulnerable Elders (ACOVE).

Dosing errors

Koper D (2013) found that over- and/or under-dosing was found in 44% of patients.(29)

2- **Monitoring errors:** Monitoring errors were measured in one study by Ramia E (2014), who found that 73% of patients had incomplete therapeutic/safety laboratory-test monitoring tests.(75)

3- **Other errors: discrepancy**

One study found that at least one discrepancy between the medication lists from the pharmacy, the general practitioner (GP), or the patient was present in 86.7% of patients.(22) In another study, almost half of the patients (47.6%; 95% CI 40.5-54.7) had one or more discrepancies in medication information at discharge.(23)

The reported point or period prevalence of medication errors in the community settings, including self-reported medication errors, prescribing errors (indication, drug-disease interaction, DDI, dosing error and inappropriate prescribing), monitoring error and discrepancies, had a very wide range from 2 - 94%. Figure 2 shows the medication errors prevalence estimates stratified according to the settings. The highest prevalence was in primary healthcare or general practice (94%).

Risk factors

Risk factors for medication errors were either related to patients, healthcare professionals and/or medications.

Patient-related risk factors

Patient-related risk factors for the development of medication errors were discussed in 33 studies.(22-24, 26, 33, 35-37, 41, 42, 44-47, 52, 53, 55-57, 59, 61, 62, 64, 66, 68-71, 73, 74, 77-79)

Seven risk factors related to patients were addressed in the included studies: polypharmacy, increased age, number of diseases or comorbidities, female, low level of education, hospital admission and middle family income (Table 3).

Several definitions of polypharmacy existed, ranging from prescription of at least three to six medications concurrently. Twenty-six studies showed a positive association between medication error and polypharmacy,(22-24, 33, 35-37, 41, 42, 44-46, 53, 55-57, 59, 61, 62, 68-71, 73, 74, 78) of which 18 mentioned the estimated OR ranging from 1.06 to 11.45.(23, 24, 33, 35-37, 41, 42, 44, 46, 53, 56, 61, 68-71, 73)

Older age (≥ 75 years) was associated with medication errors in 13 studies, (24, 33, 37, 42, 44, 52, 53, 55, 61, 69-71, 73) of which 10 mentioned the OR ranging from 1.02 to 4.03. (24, 33, 37, 42, 44, 53, 61, 70, 71, 73)

Healthcare professional-related risk factors

Nine risk factors related to healthcare professionals for the development of medication errors were identified: more than one physician involved in their care, family medicine/GP speciality, age ≥ 51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits (see Table 4).(22, 33, 46, 53, 56, 64, 71, 77, 78)

Medication-related risk factors

Medication-related risk factors for the development of medication error were: multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication,(31), no medication administration routine, poor adherence and patients confused by generic and trade names.(80) In one study by Johnell K (2008), multi-dose drug dispensing users (i.e. medicines machine-packed into unit-dose bags for each time of administration) were more exposed to all indicators of potentially inappropriate drug.(50)

Receiving anticoagulant therapy (OR 2.38; 95% CI 2.15-2.64) was strongly associated in one study to potential drug-disease interactions.(37)

The use of OTC and/or prescribed drugs was a risk factor in two additional studies.(35, 47) The use of OTC medications was associated with PIM; the OR after adjusting for

age, sex, education level, partnership, per capita income and occupation was (2.5; 95% CI 1.7-3.6) using Beers 2003 and (1.8; 95% CI 1.2-2.5) using Beers 2012.(35)

Error-related adverse events

Error-related adverse events or preventable ADEs were mentioned in six studies.(22, 23, 28, 34, 35, 81) The most frequently reported consequences were ED visits and hospitalisation.

Two methods for detecting ADE were applied: an ADE monitor (i.e. using computerised programs composed of rules that identified incidents suggesting that an ADE might be present),(28) and using trigger tools to detect ADEs.(81)

Incidence and/or prevalence

One study estimated preventable ADE incidence as 15/1000 person-years.(28) Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers were the most common medications associated with preventable ADE.(28) The estimate of the prevalence of preventable ADE was calculated from five studies as detailed below.(22, 23, 34, 35, 81)

All stages of medicines' management process

Field T S (2007) found the prevalence of error caused by patients leading to an adverse event to be 0.38% i.e. less than 1% of the overall population experienced a medication related adverse event. He found that the majority of patient errors-related adverse events (n=129) occurred in modifying the medication regimen (42%), administering the medication (32%), or not following clinical advice about medication use (22%).(81) The medications associated with more than 10 preventable ADEs were anticoagulants/anti-platelets, cardiovascular drugs, diuretics, hypoglycaemics and non-opioid analgesics.(81)

Error-related adverse events according to medicines' management process

1- Prescribing errors

DDI: Obreli Neto P R (2012) found that DDI-related adverse drug reaction (ADR) occurred in 7% of patients.(34) Warfarin, digoxin, spironolactone and acetylsalicylic acid were the drugs most commonly associated with DDI-related ADRs.(34)

PIM: 46% of participants reported complaints related to ADEs by interview; 95% of these were caused by prescribed medications.(35)

Use of inappropriate drugs was associated with an increased risk of nursing home admission, hospitalisation, more outpatient visit days, ED visits, and having ADEs or ADRs.(48, 56, 67, 72)

2- Other errors

Adverse events (under-treatment due to deletions, ADR due to additions and DDI) related to discrepancy between the medication lists from the patient, the GP, or the pharmacy were identified in 24% of patients.(22) Two discrepancies were categorised as having the potential to cause severe patient harm.(23)

Risk factors

Risk factors for the error-related adverse events were discussed in three studies only.(22, 34, 81)

Patient- related risk factors

Field T S (2007) found that the number of regularly scheduled medications (seven or more medications (OR 3.3; 95% CI 1.5-7.0) and a Charlson Comorbidity Index (CCI) score of five or more (OR 15.0; 95% CI 6.5-34.5) were both associated with higher risk of patient error leading to preventable ADE.(81) Obreli Neto P R (2012) found that an age of 80 years or more (OR 4.4; 95 % CI 3.0–6.1, p<0.01), a CCI of four or more (OR 1.3; 95% CI 1.1-1.8, p<0.01) and consumption of five or more medications (OR 2.7; 95% CI 1.9-3.1, p<0.01), were associated with the occurrence of DDI-related ADRs.(34) In addition, Tulner L R (2009) found that the number of medications was significantly positively correlated with medication discrepancy adverse patient events (MDAPEs).(22)

Medication-related risk factors

The use of medication with narrow therapeutic indices such as warfarin were associated with an increased risk of DDI-related ADRs (OR 1.7; 95% CI 1.1-1.9, p<0.01).(34)

Discussion

Summary of main findings

We sought to critically review previous studies conducted in the community of the incidence/prevalence of medication errors and associated adverse events and to identify the main risk factors. We identified 60 studies carried out in various countries providing a comprehensive assessment of the available evidence on the epidemiology of medication errors and error-related ADEs in community settings.

No relevant studies on the incidence of medication errors in these settings were found. The reported point or period prevalence of medication errors in community settings had a very wide range (i.e. 2-94%). This wide range appears, at least in part, to be due to the inconsistency in the definitions of the medication errors used in the studies, differences in populations studied, methodologies employed for error detection, and different outcome measures. More than half (37 studies) of the resulting studies were regarding the prescription of inappropriate drugs within the prescribing error stage in an elderly age group using different criteria. The comparison of those criteria is challenging due to the difference in medication use, consumption and availability of those medications to patients between countries. Further work is needed to review errors occurring at administration and dispensing stages of the medicines' management process.

As for preventable ADEs, which may in some cases occur as a result of medication errors, only one study reported error-related adverse events incidence, measured as 15/1000 person-years.(28) The prevalence of preventable ADE was further reported in five other studies and varied according to the medication error type that resulted in the adverse event.

The most common patient-related risk factors for both medication errors and preventable ADEs mentioned were the number of medications used by the patient and the increased age of patients.

Strengths and limitations

The main strengths of this systematic review are that a rigorous and transparent process has been employed, which included no language restrictions, an independent screening of

titles and abstracts, independent data extraction and critical appraisal of included studies by two reviewers. It is the first review undertaken within community settings. The use of the ICPS conceptual framework,(20) which provides a comprehensive definition of each concept and type of error in the medicines' management process, is a further strength.

However, several limitations need to be considered. Firstly, despite the thorough process, no data were found regarding the dispensing error stage. This might be due to the lack of a 'dispensing error' key-term in our search strategy, although 'medication therapy management' as a key-term was included. However, 10 studies on dispensing errors were excluded because they failed to satisfy the inclusion criteria on one or more counts. Secondly, no data were found regarding the administration error stage. However, 14 studies on administration errors were also excluded for the same previous reason. Thirdly, this systematic review had different outcomes reported in a variety of ways using different tools and methodology that made combining results in one meta-analysis difficult. Lastly, the studies addressed risk factors adjusted for different confounders, which makes it difficult to generate comparable estimates and/or make causal inferences about whether the harm resulted from the medication error.

Comparison of the findings with previous studies

The definitional variation issue is supported by another two reviews.(82, 83) Other systematic reviews focusing on the safety of primary care contexts only have identified studies with vastly different prevalence estimates of the rates of medication errors. These reflect differences in definitions, sampling strategy and populations studied; none have investigated the risk factors for medication errors.(84, 85)

Implications for research, policy and practice

There is a need for: i). improvement in the quality of research in this area. It is important that all researchers provide a standardised set of outcome measures of medication errors or internationally accepted terminology and definitions of key concepts; ii). training and monitoring of healthcare professionals with the involvement of medication safety pharmacists in the community; iii). empowering and educating the patients and the public, particularly those with chronic diseases and polypharmacy to increase their knowledge of medication safety with a record of the current medication list for each patient; iv). patient use of tools and technology particularly for monitoring and follow-up; and v). encourage

the reporting of medication errors, administration errors and dispensing errors.(86) This would strengthen the quality of research, improve the development of strategies to detect and prevent these errors and provide a safer environment for the community to self-care safely.

Conclusions

We found a very wide variation in the medication error and error-related adverse events rate between studies, which, at least in part, reflects differences in their definitions, methodologies employed for error detection or clinical heterogeneity i.e. differences in populations studied and different outcome measures. Most of the studies were conducted on elderly populations in economically-developed countries. There is therefore clearly a need to extend this work to low- and middle-income countries, particularly give the WHO's recent launch of a Global Medication Safety Challenge.(86, 87) Furthermore, most studies focused only on inappropriate prescribing with relatively little attention to other stages such as administration and dispensing. The most common patient and medication-related risk factors for both medication errors and preventable ADEs were the number of medications used by the patient, increased age and receiving anticoagulant therapy. The most common healthcare professional-related risk factors for medication error was when more than one practitioner was involved in the care of patients and care provision by family medicine and GP specialities.

This study has identified important limitations and discrepancies in the methodology used to study medication errors and error-related adverse drug events in community settings. These findings need to be considered in the context of designing future research related to medication safety. More research is needed in the areas of incidence of medication errors, administration error and dispensing errors and reporting. Researchers should use a more consistent set of definitions and outcomes in order to facilitate collation and synthesis of data.

Ethics and dissemination

The systematic review protocol was published in the British Medical Journal (BMJ) Open on 31 August 2016 and is registered with PROSPERO - an international prospective register of systematic reviews.(14, 15) It is reported using Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA). *Systematic Review Registration: (PROSPERO 2016: CRD42016048126).*

Contributorship

GA conceived the idea for this review, conducted the systematic literature search, study inclusion, data extraction and quality assessment. NS participated in the study inclusion, data extraction and quality assessment. MM participated in data extraction. NA participated in data extraction and quality assessment. GA led the writing and drafting of the manuscript, and this was commented on critically by AS, EG, HA and NS.

Funding

The systematic review protocol is a part of GA's Ph.D. study at the University of Edinburgh. King Saud University, College of Pharmacy funded the scholarship. AS is supported by the Farr Institute.

Conflicts of interest

None known.

Acknowledgments

We are grateful to Marshall Dozier for her help with formulating the search strategy; Kathrin Cresswell and Andrea Fuentes Pacheco for non-English studies translation; experts in the field for unpublished and in progress work and experts within the Farr Institute. The project was financially supported through Prince Abdullah bin Khalid Celiac Disease Research Chair, vice dean ship of research chairs, King Saud University and the University of Edinburgh.

Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Figures

Figure 1: PRISMA flow diagram. (From: Moher D, Liberati A, Tetzlaff J. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement).

*Articles may be duplicated between the excluded groups.

Figure 2: Medication errors prevalence estimates according to settings.

Table 1: Systematic review data extraction table

Key characteristics of included studies									
	Author Year	**Country/ city**	**Study Design/type**	**Population of interest**	**Exposure of interest**	**Outcome of interest**	**Main finding**	**Conclusion n/N (%)**	**Additional notes**
Self- reported medication errors									
1.	Adams R J, 2009(76)	Australia	Cross-sectional	Analysis of data from 3,522 adults participating in Stage 2 of the North West Adelaide Health Study aged ≥18 years	Unclear	Self-reported adverse event (medication, diagnosis and others). Using survey.	Of the total 3522 survey participants, 148 (4.2%) reported an adverse event causing harm in the previous 12 months, giving an annual incidence of 4.2% (95% Confidence Interval (CI), 3.4%–5.0%). Medication error: The main types of adverse events perceived as causing harm were **medication error** (reported by 46% of the 148 participants reporting adverse events).	Medication error prevalence 68/3,522= (1.9%)	Subjective data rather than objective
2.	Lu C Y, 2011(26)	Australia, Canada, New Zealand, the United Kingdom, the United States, Germany and the Netherlands	Cross-sectional (secondary analysis)	11,910 respondent adult aged ≥ 18 years. Data from the 2007 Commonwealth Fund International Health Policy Survey.	Prescribed drug	Self-reported medication error and compare factors associated with medication errors across the 7 countries. Using survey.	**Self-reported medication errors prevalence:** 752 respondents had medication error. [Australia=7.4%; Canada=5.7%; New Zealand=5.9%; UK=5.2%; U.S= 7%; Germany=5.2%; Netherland=8%]. Risk factors across countries included seeing multiple specialists, multiple chronic conditions, hospitalisation and multiple emergency room visits.	Medication error prevalence: 752/11,910= (6.3%)	Prevalence for medication error alone from table 1, while the risk factors for both medical and medication error.
3.	Sears K, 2012(27)	Australia, Canada, France, Germany, the Netherlands, New Zealand, the United Kingdom and the	Descriptive (Secondary/retrospective analysis)	9,944 adults aged ≥ 18 years from the community setting	Taking medication regularly	Patient-related risk factors associated with self-reported medication errors. Using telephone survey.	**Medication error prevalence:** 570 respondents with medication errors occurring in the community setting. Approximately 4 out of every 5 self-reported medication errors occurred in the community setting.	Medication error prevalence: 570/9,944= (5.7%)	Risk factors for both hospital and community setting.

		United States							
4.	Mira J J, 2013(77)	Alicante, Spain	Cross-sectional	382 elderly aged ≥65 years from primary care. Patients on polypharmacy (5 or more drugs) and with comorbidity: [cardiovascular (51.6%); diabetes (34.3%)]	Prescribed and self-medications .	Frequency of mistakes in communication between the physician and the patient and their medication error in the last year. Using semi-structured interviews.	**Medication error prevalence:** 75.1% of the patient reported having made at least one mistake with the medication in the last year. **Risk factors:** Multiple comorbidities (P = 0.006), frequent changes in prescription (P = 0.02), not considering the prescriptions of other physicians (P = 0.01), inconsistency in the messages (P = 0.01), being treated by various different physicians at the same time (P = 0.03), a feeling of not being listened to (P < 0.001) or loss of trust in the physician (P < 0.001). *The error due to drug confusion had very severe consequences, requiring a visit to the emergency service or hospital admission.	Medication error prevalence: 287/382= (75%)	*Consequence
Risk factors									
5.	Sorensen L, 2006(80)	4 states of Australia	Cross sectional, prospective	204 general practice patients living in their own home aged 37-99 years.	Prescribed drugs	Prevalence and interrelationships of medication-related risk factors for poor patient health outcomes identifiable through 'in-home' visit observations.	**Risk factors:** Prevalence of nominal medication-related risk factors and health outcomes among the sample of 204 patients 1-Multiple medication storage locations used = 17(8.3%), 2- Expired medication present = 40 (19.6%), 3- Discontinued medication repeats retained = 43(21%), 4- Hoarding of medications = 43 (21%), 5- Therapeutic duplication present= 50 (24.5%), Administration error: 6- No medication administration routine = 56 (27.5%), 7- Poor adherence = 107 (52.5%), 8- Confused by generic and trade names = 114 (55.9%).		
6.	Vuong T, 2006(31)	Melbourne, Australia	Descriptive	142 discharged adult aged ≥ 55 years who were returning to independent care at home Patient at risk of medication misadventure	Discharge prescribed drugs	Unnecessary medicine stored at home as a risk factor. Using home visit within 5 days of discharge.	Unnecessary medicine stored at home prevalence 85/142= (60%) 85 (60%) of 142 patients who received a home visit allowed removal of medicines that had expired or no longer required. **Prescribing error:** drug duplication prevalence: Thirty-two (27%) patients allowed removal of 82 duplicate packs of the same item that was no longer required.	Unnecessary medicine stored at home prevalence: 85/142= (60%)	No information on how many patients had unnecessary medicine. Information available is on the patient allowed to remove unnecessary

							A total of 390 medicines were removed with a mean of 4.6 medicines per patient (range 1–21).		medicine.
7.	Pit S W, 2008(78)	New South Wales, Australia.	Cross-sectional Study	849 elderly aged ≥ 65 years from general practice	Self-medications	Prevalence of self-reported risk factors for medication misadventures Tool used: Medication Risk Assessment Form (patient survey)	**Risk factors:** 1- Using at least one medication for more than 6 months (95%). 2-More than one doctor involved in their care (59%) 3- Had three or more health conditions (57%) 4- Used five or more medicines (54%). 5- Adverse drug reactions (ADRs), in the last month 39% of participants experienced difficulties sleeping, felt drowsy or dizzy (34%), had a skin rash (28%), leaked urine (27%), had stomach problems (22%) or had been constipated (22%).		*ADR as a risk factor for medication misadventure may not be related to the use of medication in all cases
8.	Mosher H J, 2012(79)	Iowa, USA	Cohort prospective	310 elderly aged ≥65 years who were cognitively intact from a Veterans Administration primary care clinic	Taking 5 or more non-topical medications	Association of health literacy with medication knowledge, adherence, and Adverse Drug Events (ADEs). Using interview and chart review	Total 310 patients **Prevalence of ADEs** ADEs occurred in 51 patients (16.5%) of the patients within the first 3 months of the study, which increased, to 119 patients (38.4%) over the full 12-month follow-up period. **Risk factor:** Association of health literacy with ADEs: The incidence of ADEs at 3 and 12 months appeared higher among patients with low health literacy, but this was not statistically significant.	Low health literacy increase the risk of ADEs	
Medicines' management process:									
9.	Koper D, 2013(29)	Austria	Descriptive	169 patient form general practice taking 5 or more medicines. Mean age: 76.4 ± 8.5 SD years. Of the 169 patient, 158 were elderly aged ≥ 65 years	Prescribed and OTC drug	Medication errors including non-evidence based medications, dosing errors and potentially dangerous interactions in all patients. Potential interactions were identified using the Lexi-Interact® database. PIMs in subgroup of elderly patient according to the PRISCUS list. Using case report form filled by the general practitioners (GP)	**Prescribing error prevalence:** Indication: 158 of the 169 patients (93.5%) had at least one non-evidence-based medication. Dosing error: 74 of the 169 patients (43.8%) had at least one dosing error. Drug-drug interaction (DDI) prevalence: Category D interactions: 99 patients (58%) had at least one category D interaction. Category X interactions: 4 patients (2.4%) had at least one category X interaction. PIM prevalence 59 of seniors (37.3%) had at least one medication that was inappropriate.	Medication error prevalence: 1- non-evidence based medications: 158/169= (93.5%) 2-dosing error 74/169= (43.8%) 3-category D drug interaction 99/168= (58%). category X drug interaction 4/168= (2.4%) 4- PIMs 59/158=37.3%	A medication was classified as non-evidence based if the indication for use indicated by the (GP) was not mentioned in any peer-reviewed chapter of UpToDate®

10.	Mand P, 2014(37)	Germany	Descriptive retrospective	24,619 elderly aged ≥65 years from family practice with at least one diagnosis named in the Beers list	Prescribed drug	Potential drug-disease interaction (PDDI) frequency and whether there are gender- or age-related differences. Analysis from electronic patient records.	**Prescribing error:** contraindication or drug-disease interaction prevalence: 10.4% of elderly were exposed to at least one PDDI. **Risk factors:** 1-Patients over 75 years (Odds Ratio (OR) 1.10; CI: 1.05 – 1.15) 2-Number of drugs prescribed (> 4 drugs: OR 1.91, CI: 1.83 – 2.00) 3-Blood clotting disorders/receiving anticoagulant therapy (OR 2.38, CI: 2.15 – 2.64) showed the strongest association with PDDI.	PDDI prevalence 2,560/24,619= (10.4%)	
11.	Gagne J J, 2008(40)	Regione Emilia-Romagna, Italy	Cohort Retrospective	4,222,165 Regional Emilia-Romagna residents. Outpatient aged from 0 to ≥85 years	Prescribed drug	Clinically important potential DDI. Risk factors. Outpatient prescription data from the Regional Emilia-Romagna. DDI screening tool: a list of clinically important potential DDIs included 12 drug pairs that could be captured using the Regional Emilia-Romagna database.	**Prescribing error:** DDI prevalence: Exposed to potential DDI adult (19 - ≥85 year) = 7,893. Unexposed adult= 7013. Total= 14,906.	DDI prevalence: 7,893/14,906= (53%)	Risk factors for all age group including paediatrics. All age group included so results should be considered cautiously.
12.	Dallenbach M F, 2007(30)	Geneva, Switzerland	Descriptive Retrospective file review	591 outpatients. Mean age 39 years.	Prescription drug and drug currently taking	Clinically significant adverse drug interactions (ADI). Prescription review. DDI screening tool: DDI compendia and (ePocrates RX) with clinical decision support	**Prescribing error:** DDI prevalence: In 135 of the consultations, a potentially clinically significant ADI was identified.	DDI prevalence: 135/591= (23%)	
13.	Obreli Neto P R, 2011(32)	Brazil	Cross-sectional	2,627 elderly aged (60-88 years) from the primary healthcare	Prescribed drug	Potential risks in drug prescriptions: DDI, Potentially Inappropriate Medicine (PIM). Using prescription review.	**Prescribing error:** DDI prevalence: Using (DrugDigest®) showed that 4.7% and 28.4% of elderly presented at least one potential DDI classified as major and moderate respectively. Using (Medscape®) showed that 3.4% and 19.3% of elderly presented at least one potential	DDI prevalence: (3.1%)-(29.1%) PIM prevalence: (26.9%)	

						DDI screening tool: (DrugDigest®, Medscape®, and Micromedex®) PIM using Beers criteria 2003.	DDI classified as major and moderate respectively. Using (Micromedex®, showed that 3.1% and 29.1% of elderly presented at least one potential DDI classified as major and moderate respectively. **Prescribing error:** PIM prevalence 26.9% of the patients had prescriptions with at least one PIM.		
14.	Secoli S R, 2010(36)	Sao Paulo, Brazil	Cross-sectional	2,143 community-dwelling elderly aged ≥ 60 years. Data were obtained from the SABE (Health, Well-Being, and Aging) survey.	≥2 prescribed drug use	Potential DDIs and identify associated factors. Using home interview. DDI screening tool: Micromedex ® Healthcare Series.	**Prescribing error:** DDI prevalence: 568/2143= 26.5% **Risk factors:** The use of six or more medications (OR 3.37; 95% CI 2.08, 5.48) or having hypertension (OR 2.56; 95% CI 1.73, 3.79), diabetes (OR 1.73; 95% CI 1.22, 2.44) or heart problems (OR 3.36; 95% CI 2.11, 5.34) significantly increased the risk of Potential DDI.	DDI prevalence: 568/2,143= (26.5%)	
15.	Obreli Neto P R, 2012(33)	5 cities of Brazil	Cross-sectional	12,343 elderly aged ≥ 60 years from the primary public health system	Prescription for 2 or more drugs (Prescribed both within and across prescriptions)	Potential DDIs (presence of a minimum 5-days overlap in supply of an interacting drug pair) and predictor of DDI. Using medical prescriptions and patients' medical records review. DDI screening tool: DDI checker Programs (DrugDigest®, Drugs®, Micromedex® and Medscape®)	12,343 patients [(5,855 (exposed); 6,488(unexposed)] **Prescribing error:** DDI prevalence: 47.4% **Risk factors:** Female sex (OR = 2.49 [95% CI 2.29–2.75]), diagnosis of ≥ 3 diseases (OR = 6.43 [95% CI 3.25–12.44]), and diagnosis of hypertension (OR = 1.68 [95% CI 1.23–2.41]) were associated with potential DDIs. Age was associated with an increasing risk of DDIs. Number of prescribers, number of drugs consumed, ATC codes, and drugs that act on CYP450 presented positive associations with potential DDIs in univariate and multivariate analyses of drug therapy characteristics.	DDI prevalence: 5,855/12,343= (47.4%)	
16.	Indermitte J, 2007(38)	Switzerland	Descriptive	434 passer-by customers aged ≥18 years from community pharmacies	Prescription only medicines and OTC drug	Potential drug interactions. 1-Observation of customer contacts and interviews with passer-by customers purchasing selected OTC drugs. 2- Telephone interviews with regular customers treated with selected	**Prescribing error:** DDI prevalence: Observation of passer-by customers Of 1183 passer-by customers observed, 164 purchased at least one of the selected OTC drugs. One hundred and two (62.2%) of those subjects were interviewed. Forty-three (42.2%) mentioned taking prescribed drugs, and three of them were exposed to potential drug interactions of moderate severity.	DDI prevalence: 3/102= (3%) 69/434= (16%) 116/434= (26.7%)	

						prescription only medicines identified in community pharmacies' databases. DDI screening tool: database Pharmavista	Telephone interview with regular customers Out of 592 regular customers selected from the community pharmacy database, 434 (73.3%) could be interviewed. Prevalence of DDI in regular customers Sixty-nine (15.9%) of them were exposed to a potential drug interaction between purchased OTC drug for self-medication and their prescription only medicines. Furthermore, 116 (26.7%) regular customers were exposed to potential drug interactions within their prescribed drugs and in 28 (6.5%) multiple (>2) potential drug interactions were found.		
17.	Mahmood M, 2007(39)	USA	Cross-sectional retrospective	2,795,345 patients who filled prescriptions for medications involved potential DDI from 128 Veterans Affairs medical centres. Ambulatory care clinic	Prescribed drug	Clinically important DDI. Database analysis of pharmacy records. DDI screening tool: a list of 25 potential DDI.	**Prescribing error:** DDI prevalence: The overall rate of potential DDIs was 21.54 per 1000 veterans exposed to the object or precipitant medications of interest.	DDI prevalence: (2.15%)	Age not mentioned.
18.	Lapi F, 2009(41)	Dicomano, Italy	Cohort, a Two-Wave, Population-Based Survey	568 community-dwelling elderly aged ≥65 years	Prescription and nonprescription drugs used at least 1 week before enrolment.	Suboptimal prescribing: Inappropriate medication = 1991 Beers' criteria (13 items out of the original 39 (33.3%) Beers' list medications were considered) DDI screening tool: Micromedex_ Drug-Reax_ system. Using population based survey.	**Prescribing error**: Potential DDI Prevalence was significantly higher in 1999 compared to 1995 (30.5% vs. 20.1%; p < 0.001). Inappropriate prescriptions were significantly higher in 1995 compared to 1999 (9.1% vs. 5.1%; p 0.004). 1995 / 1999 / P-value Inappropriate medication: 47 (9.1%) / 26 (5.1%) / 0.004 DDI: 97 (20.1%) / 147 (30.5%) / <0.001 Major DDI: 20 (4.7%) / 24 (5.6%) / 0.585 **Risk factors:** Polypharmacy always predicted a substantial increase in the risk of the PIM and DDI.	Potential DDI prevalence: (30.5%) p < 0.001 Inappropriate medication prevalence: (5.1%), P=0.004	

19.	Nobili A, 2009(42)	Lecco, Italy	Cross-sectional Retrospective	58,800 community dwelling elderly aged ≥ 65 years registered under the Local Health Authority of Lecco.	Receiving at least two co-administered prescriptions	DDIs and associated risk factors (age, sex and number of prescriptions). DDI screening tool: Italian computerized interaction database. Analysed all prescriptions dispensed from 1 January 2003 to 31 December 2003.	**Prescribing error:** DDI prevalence: 9,427 elderly people (16%) were exposed to drug combinations with the potential for 13 932 severe DDIs. Mean number of DDI per patient was 0.2 (range 0–9). **Risk factors:** Age and number of chronic drugs were associated with an increasing risk of DDIs. The adjusted OR increased from 1.07 (95% CI 1.3–1.11) in patients aged 70–74 years to 1.52 (95% CI 1.46–1.60) in those aged 85 or older. Elderly taking more than five chronic drugs had a statistically significant higher risk of potentially severe DDIs (OR = 5.59; 95% CI 5.39–5.80) than those receiving less than 3 (reference category) or 3–5 chronic drugs (OR = 2.71; 95% CI 2.63–2.80).	Potentially severe DDI prevalence = 9,427/58,800 = (16%)	Only the interactions identified as severe were considered in these analyses.
20.	Guthrie B, 2015(43)	Scotland, UK	Cross-sectional	311,881 resident aged ≥ 20 years from the community-dispensed prescribing data. (General Practice) Living in own home 308,660.	Prescribed drugs	Potentially serious DDI. Patient characteristics associated with the presence of potentially serious DDI. DDI screening tool: Analysis community-dispensed prescribing data using British National Formulary 2010.	**Prescribing error**: DDI prevalence 40,689 adults (13%) had potentially serious DDI in 2010 [for both resident living in own home and care home]. Number of patient with potentially serous DDI for residence living in their own home in 2010= 13,615	DDI prevalence: 13,615 /308,660= (4.4%)	Resident living in both care home or own home. Risk factors for own home and care home
21.	Maio V, 2006(44)	Milia, Romagna. Italy	Cohort Retrospective	849,425 elderly outpatient aged ≥65 years from the Emilia Romagna outpatient prescription claims database	Prescribed drugs	PIM using the 2002 Beers' criteria and factors associated with PIM. Prescription review.	**Prescribing error:** PIM prevalence: A total of 152,641 (18%) elderly had one or more occurrences of PIM prescribing. **Risk factors:** 1-Older age (≥85 years) (OR 1.18, 95% CI 1.16-1.2, P value <0.05) 2- ≥ 10 drugs prescribed (OR 7.33, 95% CI 7.15-7.51, P value <0.05) 3- ≥ 4 chronic conditions (OR 1.76, 95% CI 1.72-1.81, P value <0.05)	PIM prevalence: 152,641/849,425= (18%)	
22.	Martins, S D O, 2006(45)	Lisbon, Portugal	Cross-sectional	213 elderly aged ≥65 years from 12 community pharmacies	Prescription and home medications	Inappropriate drug use (IDU) by 1997 Beers and 2003 Beers Explicit criteria.	**Prescribing error:** PIM prevalence: Using the 1997 Beers Explicit criteria, 75 occurrences of inappropriate medicines were detected in 59 patients (27.7%). Using the 2003 Beers Explicit criteria inappropriate medication	IDU prevalence: 59/213= (27.7%) using 1997 Beers. IDU prevalence: 82/213= (38.5%)	

						Using survey	was detected in 82 patients (38.5%). **Risk factors:** The occurrence of inappropriate medicines was significantly associated with the consumption of a high number of drugs	using 2003 Beers.	
23.	Pugh M J V, 2006(46)	Austin, Texas USA	Cross-sectional, retrospective	1,096,361outpatient elderly aged ≥ 65 years using national data from the Veterans Health Administration.	Prescribed drug only	Potentially inappropriate prescribing (IP) included in the 2006 Health Plan Employer Data and Information Set (HEDIS) criteria and to determine if patient risk factors are similar to those found using Beers criteria. Using database	**Prescribing error:** IP prevalence: Overall, 19.6% of older veterans were exposed to HEDIS 2006 drugs. **Risk factors:** 1- Patients receiving ≥10 medications were at greatest risk of exposure in men (OR 8.2, 95% CI 8-8.4) and women (OR 9.6, 95% CI 8.2-11.2). 2- Patient with more outpatient clinic visits (≥10) were at greater risk regardless of gender (OR 1.4, 95% CI 1.3-1.6) 3- Diagnosis with other mental illness (e.g., depression, anxiety) alone or in combination with serious mental illness was associated with higher risk of potentially IP for women (OR 1.3, 95% CI 1.1-1.5).	Potentially IP prevalence: 214,887/1,096,361= (19.6%)	
24.	Saab Y B, 2006(47)	Lebanon	Descriptive	277 elderly aged ≥65 years from 10 community pharmacies	Prescription and/or over-the-counter (OTC) medications	IDU (Beers criteria, Missing doses, inappropriate frequency of administration, poor memory, drug-disease interaction, DDI, inappropriate dose, duplicated therapy, discontinuation of therapy, adverse effect, and inappropriate indication). Factors that predict potentially inappropriate drug intake. Review patient profile using community pharmacy data and in-person interviews.	**Prescribing error:** PIM prevalence: The prevalence of elderly outpatient with at least one inappropriate medication: 165/277 (59.6%) [Include 5 patient had ADR] Inappropriate medication use was most frequently identified in terms of Beers' criteria (22.4%), missing doses (18.8), and incorrect frequency of administration (13%). Drug-disease interaction in 28 patients (10.1%) DDI 14 (5.1%) Duplicate therapy 12 (4.3%) **Risk factors:** Female sex (65.7% vs. 53.3% for males, p = 0.03). There were also significant associations between the likelihood of use of an inappropriate drug and (1) increased number of medical illnesses (p < 0.00002); (2) consumption of an OTC drug and/or prescription drug (p = 0.048 and p = 0.0035, respectively); and (3) consumption of both OTC and prescription drugs (p < 0.0002).	IDU prevalence: 62/277= (22.4%) using Beers' criteria	Just extracted the IDU by Beers criteria because the IDU include 5 cases of ADR and some patients had more than one IDU. Risk factors for all type of IDU.
25.	Zuckerman	USA	Cohort	487,383	Prescribed	Inappropriate medication	**Prescribing error**: PIM prevalence:	Inappropriate	

	I H, 2006(48)		retrospective	community dweller elderly aged ≥ 65 years. Data from MarketScan Medicare Supplemental and Coordination of Benefits database	drug	use using Beers criteria.	204,083 elderly used inappropriate medication. Use of inappropriate drugs was associated with a 31% increase in risk of nursing home admission, compared with no use of inappropriate drugs (adjusted relative risk 1.31, 99%CI 1.26–1.36).	medication use prevalence: 204,083/487,383= (41.9%)	
26.	Bregnhoj L, 2007(49)	Copenhage, Denmark	Cross-sectional	212 elderly aged ≥65 years with polypharmacy (≥ 5 drugs) patient from primary care	Subsidised and non-subsidised medications prescribed	IP measured by the Medication Appropriate Index (MAI: 10 criteria are indication, effectiveness, dosage, directions practicality, directions correctness, drug–drug interaction, drug–disease interaction, duplication, duration and expense). Patients exposed to polypharmacy were identified via the database recording the drug subsidy system of Danish pharmacies and questionnaire.	**Prescribing error**: IP prevalence: The main part of the patients namely 94.3% had one or more inappropriate ratings among their medications.	IP prevalence: 200/212= (94.3%)	
27.	Johnell K, 2008(50)	Sweden	Cross-sectional	731,105 People aged ≥75 years from the Swedish Prescribed Drug Register (secondary data analysis)	Prescribed drug only and multi-dose drug dispensing	Whether the use of multi-dose drug dispensing is associated with potential IDU (IDU) (i.e. anticholinergic drugs, long acting benzodiazepines, concurrent use of ≥ 3 psychotropic drugs, and combinations of drugs that may lead to potentially serious DDIs). Information from the Swedish Prescribed Drug Register.	**Prescribing error:** PIM prevalence: Prevalence of potential IDU in Multi-dose dispensing users: 40.3% (women: 41%, men 38.5%) Prevalence of potential IDU In prescription users: 13.6% (women: 15%, men 11.5%) The multi-dose users had higher prevalence of all indicators of potential inappropriate drug than prescription users. 1-The younger elderly (aged 75-79 years) who used multi-dose drug dispensing had the highest frequency of all indicators of potential IDU. 2-Most indicators of IDU were more common in women than men. 3- Multi-dose drug dispensing among 75- to 79-year-olds was even more strongly associated with any IDU, anticholinergic drugs, three or more psychotropic drugs in both men and women, and long-acting benzodiazepines	PIM prevalence: multi-dose dispensing users: 292,737/731,105= (40%) Prescription users: 994, 30.3/731,105= (13.6%)	Multi-dose drug dispensing means that patients get their drugs machine dispensed into one unit for each dose occasion and packed in disposable bags.

							among men.		
28.	Berdot S, 2009(51)	Dijon, Bordeaux, Montpellier . France	Cohort Prospective	6,343 community dwelling elderly aged ≥ 65 years	Prescribed drug	PIM using 1997 and 2003 Beers criteria, Fick and Laroche. Face to face interview using standardised questionnaire.	**Prescribing error:** PIM prevalence: One-third (31.6%) of the study participants reported using at least one inappropriate medication at study entry.	PIM prevalence: 2,004 / 6,343= (31.6%) p <0.001	
29.	Haider S I, 2009(52)	Sweden	Cross-sectional register-based study	626,258 Older people aged 75-89 year from the Swedish Prescribed Drug Register (secondary data analysis)	Prescribed drug only	If low education associated with potential IDU (i.e. anticholinergic drugs, long acting benzodiazepines, concurrent use of ≥ 3 psychotropic drugs, and clinically relevant potential drug–drug interaction (DDI)). Information from the Swedish Prescribed Drug Register.	**Prescribing error:** PIM prevalence: The proportion of participants reporting use of at least one potential IDU was 34.6%. **Risk factors:** Subjects with low education had a higher probability of potential IDU (OR 1.09, 95% CI 1.07–1.17). Older age, being a woman, and higher Charlson Comorbidity Index (CCI) were associated with the highest frequencies of potential IDU.	IDU prevalence: 216,685/626,258= (34.6%)	
30.	Lai H Y, 2009 (53)	Taiwan	Descriptive	2,133,864 patient aged ≥ 65 years between 2001-2004 from ambulatory care. National Health Insurance claim database	Prescribed drug	PIM prescribing using updated 2003 Beers criteria and the characteristics of and risk factors for such prescribing.	**Prescribing error:** PIM prevalence A mean of 63.8% of the older population received a PIM at least once a year in 2001–2004. Details: In 2001: 1,974,869 patients of which 1,297,425 had inappropriate prescription. (65.7) In 2002: 2,026,737 patients of which 1,312,147 had inappropriate prescription. (64.7) 2003: 2,077,677 patients of which 1,295,227 had inappropriate prescription. (62.3) 2004: 2,133,864 patients of which 1,333,792 had inappropriate prescribing (62.5)] **Risk factors:** The only patient characteristic associated with an increased likelihood of the prescribing of PIM was female sex (male sex: (OR 0.982 [95% CI, 0.980-0.983]), (p < 0.001) and when ≥4 drugs were prescribed (P < 0.001). Physician characteristics associated with a greater likelihood of the prescribing of PIM was: 1-Male sex (OR 1.206; 95% CI, 1.202–1.210, P < 0.001);	PIM prevalence: 2001: (65.7%) 2002: (64.7%) 2003: (62.3%) 2004: 1,333,792/2,133,864 = (62.5%)	

							2-Older age (43–50 years: OR 1.021; 95% CI, 1.018–1.025, P < 0.001; ≥51 years: OR 1.238; 95% CI, 1.235–1.242, P < 0.001); 3-Family medicine/ general practice (OR 1.267; 95% CI, 1.265–1.269, P < 0.001).		
31.	Ryan C, 2009(54)	Ireland	Cohort Prospective	500 patient aged ≥ 65 years from primary care	Prescribed drug	IP using 2003 Beers' criteria and improved prescribing in the elderly tool (IPET). Screening patients' medical records (electronic and paper).	**Prescribing error:** PIM prevalence 65 patients (13%) and 52 patients (10.4%) had at least one medicine prescribed inappropriately using 2003 Beers and IPET criteria respectively.	IP prevalence: Beers 2003: 65 /500= (13%) IPET: 52/500= (10.4%)	
32.	Ryan C, 2009(55)	Cork, Southern Ireland	Descriptive case record review	1,329 elderly aged ≥ 65 years from primary care	Prescribed drugs	A-1- PIM using 2003 Beers and Screening Tool of Older Person's Prescriptions (STOPP) criteria 2- Potential prescribing omissions (PPO) using Screening Tool to Alert doctors to Right Treatment (START) criteria B- Relationship between age and number of prescription drugs and IP. Case record through paper and electronic record review.	**Prescribing error:** PIM prevalence IP rate identified by Beers' criteria in 18.3% (243) of patients IP rate identified by STOPP was 21.4% (284). PPO was identified in 22.7% (302) of patients using the START tool. **Risk factors:** A significant correlation was found between the occurrence of PIM and 1-The number of medicines prescribed when calculated using Beers' criteria (r_s = 0.270, P < 0.01) and STOPP (r_s = 0.356, P < 0.01) using Spearman's ρ correlation test. 2-Age using Beers' criteria (r_s = 0.068, P < 0.01) and STOPP (r_s = 0.071, P < 0.01). 3-Increasing CCI score identified by STOPP (r_s = 0.210, P < 0.01).	PIM prevalence: Beers': 243/1329= (18.3%) STOPP: 284/1329= (21.4%) PPO prevalence: START: 302/1329= (22.7%)	Spearman's ρ correlation test.
33.	Akazawa M, 2010(56)	Tokyo, Japan	Cohort Retrospective	6,628 elderly patient aged ≥ 65 years from health insurance claim data (secondary data analysis)	Prescribed drugs	PIM using modified Beers criteria in Japan. Drug utilization review using medical and pharmacy claim from database of (Japan Medical Data Center).	**Prescribing error:** PIM prevalence 43.6% (2,889/6,628) were prescribed at least one PIM. **Risk factors:** Factors positively associated with PIM prescriptions at a significance level of 5% included the following: Hospital admission (OR = 3.35, 95% CI 2.43-4.62); polypharmacy (OR = 5.69, 95% CI 5-6.48); prescriptions from a hospital (OR = 1.19), general medicine practitioner (OR = 1.46), or psychiatrist/neurologist (OR = 2.33); and comorbid conditions including peptic ulcer disease without bleeding (OR = 4.18 , 95% CI 3.52-4.97), depression (OR = 3.69), cardiac	PIM prevalence: 2,889/6,628= (43.6%)	*Consequence

							arrhythmias (OR = 1.93), other neurologic disorders (Parkinson's disease, multiple sclerosis, and epilepsy; OR = 1.88), and congestive heart failure (OR = 1.46). PIM users had significantly higher hospitalization risk (1.68-fold), more outpatient visit days (1.18-fold), and higher medical costs (33% increase) than did nonusers.		
34.	Zaveri H G, 2010(57)	Ahmedabad city, India	Descriptive Prospective	407 geriatric patients aged ≥ 65 years from medicine outpatient department	Prescribed drug	PIM using 2003 Beers criteria. Using prospective proforma data collection.	**Prescribing error:** PIM prevalence Out of 407 patients, 96 patients (23.6%) received at least one drug that was potentially inappropriate. **Risk factors:** There was highly significant association between the number of drugs prescribed and frequency of use of PIMs (P< 0. 0002).	PIM prevalence: 96/407= (23.6%)	
35.	Barnett K, 2011(58)	Tayside, Scotland, UK	Cohort	65,742 elderly aged 66-99 years living in home	Prescribed drug	PIM using 2003 Beers criteria and the association between exposure to PIM and mortality. Using dispensing and prescribing database and medical record.	**Prescribing error**: PIM prevalence PIM found in 20,304 (30.9%) patients living at home. **Risk factors:** After adjustment for age, sex and polypharmacy, 1-Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy 2-Reciveing at least one PIM were not associated with increased risk of mortality (adjusted OR 0.98, 95% CI 0.92 -1.05).	PIM prevalence: 20,304/65,742= (30.9%)	Risk factors for both care home and home
36.	Chang C B, 2011(59)	Taipei, Taiwan	Cohort	193 outpatient elderly patient aged ≥ 65 years with polypharmacy (≥ 8 chronic medications) from Medication Safety Review Clinic in Taiwanese Elders (MSRC-Taiwan) study.	Prescribed drugs and dietary supplement excluding herbals	PIM using six different criteria and drug-related problem: the 2003 version of the Beers criteria (from the USA), the Rancourt (from Canada), the Laroche (from France), (STOPP; from Ireland), the Winit-Watjana (from Thailand) and the Norwegian General Practice (NORGEP) criteria (from Norway). Analyse baseline data	**Prescribing error**: PIM prevalence: The proportion of patients who had at least one PIM varied from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria). Approximately 31% (the STOPP criteria) to 42% (the NORGEP criteria) of PIMs identified were considered as drug related problems by the medication review team experts. **Risk factors:** In the bivariate analysis, the common characteristics associated with having at least one PIM in all criteria were a high number of chronic conditions and a high number of chronic medications.	PIM prevalence: (24% -73%)	

						from the MSRC-Taiwan study. Secondary data analysis.			
37.	Leikola S, 2011(60)	Finland	Cross-sectional	841,509 non-institutionalised elderly patient aged ≥ 65 years from Finland's Social Insurance Institution prescription register of all reimbursed drugs for outpatient	Prescribed and OTC medications that are reimbursed	PIM using 2003 Beers criteria.	**Prescribing error:** PIM prevalence 14.7% (n = 123,545) had received PIMs according to the Beers 2003 criteria.	PIM prevalence: 123,545/841,509= (14.7%)	
38.	Lin Y J, 2011(61)	Taiwan	Cross-sectional Retrospective analysis	327 elderly patient aged ≥ 65 years from outpatient clinic of a community health centre	Prescribed drugs	PIM using 2003 Beers criteria and risk factors of PIM use. Using data review.	**Prescribing error:** PIM prevalence The prevalence of patients having at least one PIM was 27.5% (90/327). **Risk factors:** Independent risk factors for PIMs are older age (OR = 1.05, 95% CI 1.00–1.09, p = 0.046), higher number of prescribed medications (OR = 1.06, 95% CI = 1.39–1.98, p < 0.001), and diagnosis of acute diseases (OR = 8.98, 95% CI 4.71–17.1, p < 0.001).	PIM prevalence: 90/327= (27.5%)	
39.	Woelfel J A, 2011(74)	California, USA	Cross-sectional	295 elderly aged ≥ 65 years from ambulatory population of Medicare beneficiaries	Prescribed drug	PIM using 2003 Beers criteria. Using medication review	**Prescribing error:** PIM prevalence 54 (18.3% beneficiaries were taking at least one PIM. **Risk Factors:** Number of medications was significantly greater in the PIM than the non-PIM group (p < 0.001)	PIM prevalence: 54/295= (18.3%)	
40.	Zhang Y J, 2011(62)	USA	Cohort Retrospective	3,570 Elderly community-based respondents aged ≥ 65 from 2007 Medical Expenditure Panel Survey (MEPS), a nationally representative survey of the US community-dwelling population	Prescribed drug	PIM using Zhan criteria and risk factors for PIM use. Information from MEPS database	**Prescribing error:** PIM prevalence PIM prevalence in 2007:13.84% (CI 12.52–15.17). PIM prevalence in 1996: 21.3% (CI 19.5–23.1). **Risk factors**: Older women, people taking ≥25 prescriptions, people with middle family income, people living in the South census region, and people who said they were in fair or poor health were more likely to have received an inappropriate medication during the year.	PIM prevalence: 13.84%-21.3%	
41.	Haasum Y,	Sweden	Cross-sectional	1,260,843 home-	Prescribed	Potentially IDU (use of	**Prescribing error**: PIM prevalence	Potentially IDU	Information on

	2012(63)		Retrospective	dwelling elderly aged ≥ 65 year from the Swedish Prescribed Drug Register	drug only	anticholinergic drugs, long-acting benzodiazepines, concurrent use of ≥ 3 psychotropics, and potentially serious DDIs). Information from the Swedish Prescribed Drug Register	11.6% of the home-dwelling elderly were exposed to Potentially IDU.	prevalence: 145,749/1,260,843= (11.6%)	both institutionalised and home dwelling. Extracted home dwelling information only.
42.	Marroquin E C, 2012(25)	Cáceres, Spain	Descriptive	471 patient aged ≥ 65 years from health centers	Consumed medications	Potentially IP using STOPP/START criteria. Using patient interview and medical chart review.	**Prescribing error:** PIM prevalence 249 patients (52.8%, 95% CI 48.3-57.3) had potentially IP according to STOPP/START criteria. STOPP: 162 patients (34.3%, 95% CI 30.2-38.8%) START: 114 patients (24.2%, 95% CI 20.5-28.2%)	Potentially IP prevalence: 249/471= [(52.8%) (95% CI 48.3-57.3)]	
43.	Nyborg G, 2012(64)	Norway	Cross-sectional Retrospective	445,900 home dwelling elderly aged ≥ 70 years from the Norwegian Prescription Database	Prescribed drug	Prevalence of and predictors for PIM use by the Norwegian General Practice (NORGEP) criteria. Survey undertaken based on data from the Norwegian Prescription Database	**Prescribing error:** PIM prevalence 34.8% of the study population was exposed to at least one PIM. **Risk factors:** The odds of receiving potentially harmful prescriptions increased with the number of doctors involved in prescribing (OR 3.52, 99% CI 3.44–3.60 for those with ≥5 compared to those with 1 or 2 prescribers). Females were at higher risk for PIMs (OR 1.6, 99% CI 1.58–1.64).	PIM prevalence: 155,341 /445,900= [(34.8%) (99%CI 34.7-35)]	
44.	Yasein N A, 2012(65)	Jordan	Cross-sectional	400 elderly aged ≥65 years from family practice clinic	Prescribed drug	Polypharmacy (≥ 5drugs) and IP using 2003 Beers criteria. Using patient file and patient interview	**Prescribing error**: PIM prevalence Inappropriate medications as determined by Beers criteria independent of diagnosis accounted for 118 (29.5%) patients.	IP prevalence: 118/400= (29.5%)	
45.	Blozik E, 2013(66)	Helsana, Switzerland	Cohort	2008: 1,059,495 2009: 1,047,939 2010: 929,791 community dwelling adult aged > 18 years from claim data of Helsana.	Prescribed drug submitted for reimbursement	Prevalence of polypharmacy and PIM using 2003 Beers criteria or the PRISCUS list. Using analysis of data based on claim data from Switzerland health insurance	**Prescribing error:** PIM prevalence: According to 2003 Beers criteria: 10.3 % of the community-dwelling population aged > 65 years received at least one medication which is PIM, and according to the PRISCUS list1: 16.0 % of persons had a PIM. When using both Beers and PRISCUS criteria, 21.1 % of the population received at least one PIM. Of those persons older than 65 years asking for	PIM prevalence: 21.1%	There are huge discrepancies in estimating the prevalence of PIM depending on the definition used.

							reimbursement of medications, 12.9 % received at least one PIM according to 2003 Beers, 20.2 % according to PRISCUS, and 26.6 % of either definition. **Risk Factors:** Women were more likely to receive a PIM: 25.5 % of females as compared to 15.4 % of males when both Beers and PRISCUS definitions were used.		
46.	Cahir C, 2013(67)	Ireland	Cohort Retrospective	931 Community dwelling elderly aged ≥ 70 years from 15 general practices	Prescribed drug and OTC	The association between potentially IP using STOPP -and health related outcomes [ADEs, health related quality of life (HRQOL) and hospital accident and emergency department (ED)]. Using patient self-report and medical record.	**Prescribing error:** PIM prevalence Prevalence of potentially IP was 40.5% (n = 377). **ADE prevalence:** In total, 674 of 859 participants (78%) were classified as having at least one ADE during the study period. **Risk Factors:** Patients with ≥2 Potentially IP indicators were: 1-Twice as likely to have an ADE (adjusted OR 2.21; 95% CI 1.02, 4.83, P < 0.05), 2- Significantly lower mean HRQOL utility (adjusted coefficient −0.09, SE 0.02, P < 0.001), 3-A two-fold increased risk in the expected rate of ED visits (adjusted Incidence Rate Ratio 1.85; 95% CI 1.32, 2.58, P <0.001).	Potentially IP prevalence: 377/931= (40.5%) ADE prevalence: 674/859= (78%)	*Consequence. Type of ADE was not mentioned
47.	Weng M C, 2013(68)	Taiwan	Cross-sectional Retrospective	780 older patients aged ≥ 65 years from the outpatient geriatric clinic	Long-term Prescribed drugs (≥ 28 days) for chronic diseases. Not OTC	Impact of number of drugs prescribed on the risk of PIM using STOPP criteria. Patient medical chart review	**Prescribing error**: PIM prevalence 302 patients (39%) had at least one PIM. **Risk factors:** Multivariate analysis revealed that PIM risk was associated with the number of medications prescribed (P < 0.001) and the presence of cardiovascular (P < 0.001) or gastrointestinal disease (P = 0.003). Patients prescribed ≥ 5 drugs [adjusted (OR) = 5.4; had significantly higher PIM risk than those prescribed ≤ 2 drugs.	PIM prevalence: 302/780= (39%)	
48.	Zimmerman n T, 2013(24)	German	Cohort longitudinal analysis	follow-up3: N = 1,942 Baseline N =3,214 1,855 elderly aged ≥75 years from primary care. Data from the	Prescribed drug	PIM using Beers, PRISCUS list. By checking medications during visits to patients' homes.	**Prescribing error:** PIM prevalence At baseline, PIM prevalence is (848) 29 % according to the PRISCUS list, which decreased to (464) 25.0 % 4.5 years later (χ^2: 7.87, p = 0.004). The Beers list yielded a prevalence of (620) 21 % at baseline, decreasing after 4.5 years to	Prescribing error: PIM prevalence 17%-29%	

				prospective, multicenter, observational study "German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe),"			(317) 17.1 % (χ^2: 10.77, p = 0.000). **Risk factors:** By PRISCUS list: The risk for PIM increase with: 1-Increasing age of the patients (OR: 1.06, CI: 1.00 to 1.13; p = 0.037), 2-The presence of depression (OR: 2.42, CI: 1.65 to 3.57; p = 0.000), 3-Increasing number of prescription drugs (OR: 1.99; CI: 1.80 to 2.18; p = 0.000). By contrast, the risk of taking PIM decrease by using PRISCUS list with the number of present illness (OR: 0.88, CI: 0.80 to 0.97; p = 0.012). As the growing number of ingested prescription drugs increased the risk for the ingestion of PIM from the Beers list (OR: 1.66, CI: 1.50 to 1.84; p = 0.000).		
49.	Baldoni A D, 2014(35)	Ribeirao Preto, Brazil	Cross-sectional	1000 elderly aged ≥ 60 years from outpatient pharmacy	Prescribed drug, self-medication (309 user) and OTC (802 user)	Prevalence and factors associated with PIM using 2003 and 2012 Beers criteria. Using structured interview questionnaire	**Prescribing error:** PIM prevalence According to Beers criteria 2003, 480 (48.0 %) participants used at least one PIM, the mean being 1.38 (SD = 0.65) PIMs/person, ranging from one to five. According to Beers criteria 2012, 592 (59.2 %) participants used at least one PIM, the mean being 1.56 (SD = 0.81) PIMs/person, ranging from one to six. **ADE:** During the interview 45.5 % of participants reported complaints related to ADEs; 94.5 % of these were caused by prescribed medication. **Risk factors:** Factors that are associated with PIMs use were female gender, self-medication, use of OTC medications, complaints related to ADEs, psychotropic medication, more than five medications. *Ten medications with the highest prevalence of self-reported ADEs complaints are Clonidine, amitriptyline, metformin, fluoxetine, dexchlorpheniramine, diclofenac, captopril, acetyl salicylic acid, simvastatin, hydrochlorothiazide. Among them, five were	PIM prevalence by Beers criteria 2003, 480/1000= (48.0 %) PIM prevalence by Beers criteria 2012, 592/1000= (59.2 %)	*Error-related adverse event

							considered PIMs according to Beers criteria, of which clonidine, amitriptyline and dexchlorpheniramine are listed in both criteria, while fluoxetine is listed only in Beers criteria 2003 and diclofenac is listed only in Beers criteria 2012.		
50.	Castillo-Paramo A, 2014(69)	Spain	Cross-sectional	272 electronic record of elderly aged ≥65 years from primary healthcare	Prescribed drugs	PIM using STOPP/START criteria and version adapted to Spanish primary healthcare and factors may modulate PIM onset. Using electronic health record and paper clinical record	**Prescribing error:** PIM prevalence The prevalence of PIM (mis- and over-prescribing) using the STOPP original criteria was 37.5% (95% CI: 31.7 – 43.2), and 50.7% (95% CI: 44.7 – 56.6) using the STOPP Spanish AP2012 version. The prevalence of under-prescribing was 45.9% (95% CI: 40.0 – 51.8) with the START original criteria, and 43.0% (95% CI: 37.1 – 48.9) with the START AP2012 version. **Risk factors:** A significant correlation was found between the number of STOPP PIM and age or number of prescriptions, and between the number of START PIM with age, CCI and number of prescriptions.	PIM prevalence: 102/272 (STOPP) = [(37.5%) (95% CI: 31.7 – 43.2)] 138/272 (STOPP AP2012) = [(50.7%)(95% CI: 44.7 – 56.6)] 125/272 (START) = (45.9%) 117/272 (START AP2012) = (43%)	
51.	Vezmar Kovacevic S, 2014(70)	Serbia Belgrade	Cross-sectional Prospective	509 elderly aged ≥ 65 years from 5 community pharmacies	Prescribed drug	PIM and PPO using STOPP/START criteria. Using patient interview and medical, biomedical record	**Prescribing error**: PIM prevalence There were 164 PIM identified in 139 patients (27.3%) by STOPP and 439 PPO, identified in 257 patient, (50.5%) by START. **Risk factors:** Patients with more than four prescriptions had a higher risk for PIM (OR 2.85, 95% CI 1.97–4.14, p <0.001 and ≥ 9 medications OR 7.43, 95% CI 3.20–17.23, p<0.001). Patients older than 74 years were more likely to have a PPO (75–84 years OR 1.47, 95% CI 1.01–2.13, p= 0.041 and ≥85 years OR 1.79, 95% CI 1.19–2.83, p = 0.009).	PIM prevalence: 139/509= (27.3%) PPO prevalence: 257/509= (50.5%)	
52.	Amos T B, 2015(71)	Emilia-Romagna, Italy	Cohort Retrospective	865,354 elderly aged ≥ 65 years community dwelling From administrative care data	Prescribed drug only	PIM using updated Maio criteria and patient characteristic related to IP. Using Regional Emilia-Romagna administrative healthcare database.	**Prescribing error:** PIM prevalence A total of 240,310 (28%) older adults were exposed to at least one PIM. **Risk factors:** The oldest group (≥85) followed by patients aged 75–84 had 53% and 25% greater odds of receiving PIM than patients 65–75 years old, respectively [OR = 1.53,95% CI: 1.50–1.55; OR = 1.25, 95% CI: 1.23–1.26, respectively].	PIM prevalence: 240,310/ 865,354= (28%)	

							These odds of exposure to any PIM were slightly lower among males than females (OR = 0.98, 95% CI: 0.97–1.00). An increase in the number of medications prescribed to the patient corresponded with higher odds of PIM exposure. Older GP (≥56), male GPs, and solo practice GPs were more likely to prescribe PIMs to their older patients.		
53.	Hedna K, 2015(72)	Sweden	Cohort retrospective	542 elderly aged ≥ 65 years from the Swedish Total Population Register (primary care)	Prescribed drug	Prevalence of Potentially IPs using STOPP criteria and to investigate the association between Potentially IPs and occurrence of ADRs. Using the Swedish Prescribed Drug Register, medical records and health administrative data	**Prescribing error:** PIM prevalence 226 patients using primary healthcare had Potentially IP. **Risk factors:** Persons prescribed Potentially IP had more than twofold-increased odds to experience ADRs (OR 2.47, 95 % CI (1.65–3.69); P <0.001), compared to that in persons without Potentially IP.	Potentially IP prevalence: 226/542= (42%)	* Error-related adverse event. The association between PIPs and occurrence of ADRs was for primary care, outpatient or inpatient and hospitalized patient.
54.	Moriarty F, 2015(73)	Ireland	Cohort Prospective	2,051 elderly aged ≥ 65 years from The Irish Longitudinal Study on ageing (TILDS). Community dwelling elderly.	Prescribed drug only	PIM and PPO using STOPP, Beers criteria, Assessing Care of Vulnerable Elders (ACOVE) indicators and START. Using face to face interview then follow up after 1 and 2 years	**Prescribing error: PIM prevalence** Baseline N%(95%CI) / Follow-up N%(95%CI) Any PIM using STOPP, Beers, ACOVE: 1,259 (61.4%) (CI 59.3-63.5) / 1,330 (64.8%) (CI 62.8-66.9) Any PPO using: 1,094 (53.3 %) (CI 51.2- / 1,161 (56.6%) (CI 54.5-58.8)	PIM: (36.7%-64.8%)	

							START, ACOVE: 55.5) / Both PIM and PPO: 753 (36.7 %), 843(41.1 %) **Risk factors:** Female sex, age and higher number of medicines were significantly associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be significantly associated with change in PPO prevalence.		
55.	Ramia E, 2014(75)	Lebanon	Cross sectional	284 outpatient aged ≥ 18 years visiting community pharmacy	Patient on ≥ one of the chronic medications mentioned in the study	The completion of therapeutic/safety monitoring tests. Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring.	**Monitoring error:** - 185 of the patients (65%) were found to complete some, but not all, of the recommended therapeutic/safety monitoring tests - 76 of the patients (27%) completed all recommended therapeutic/safety monitoring -23 of the patients (8%) did not complete any of the recommended monitoring tests	Incomplete therapeutic/safety laboratory-test monitoring tests prevalence: 208/284= (73%)	
Other: Discrepancies									
56.	Tulner L R, 2009(22)	Amsterdam , The Netherland	Descriptive prospective	120 elderly aged >65 years from Dutch geriatric outpatient	Using more than one prescribed or OTC medications	1-Frequency and relevancy of discrepancies in drug use 2-Frequency of medication discrepancy adverse patient events (MDAPEs) 3-Contributing factors- such as increasing age, cognitive status and depressive symptoms, the number of medications used, the number of physicians visited by the patient. By comparing the medication described by the patient and caregivers with the drugs listed by their GP.	**Other: Discrepancies prevalence:** At least one discrepancy (deletion, addition, or difference in dosage) between the medication lists from the patient, the GP, or the pharmacy was present in 104 patients (86.7%) involving 386 drugs. **Medication discrepancy adverse patient events:** MDAPES were identified in 29 patients (24.2%). 7 patient had under-treatment due to deletions 9 patients had ADR due to additions 13 patient had DDI. **Risk factors:** Patients with ≥ 1 discrepancy reported using a higher mean number of drugs (5.9 vs. 4.0; P < 0.05) and had more prescribing physicians in addition to their GP (1.1 vs. 0.43; P< 0.05). Both the presence of discrepancies (Pearson' s 1", 0.293; P s 0.05) and MDAPEs (Pearson's 1",	Discrepancies prevalence: 104/120= (86.7%) *Error-related adverse event: MDAPEs: 29/120= (24.2%)	*Error-related adverse event

							0.230; P = 0.012) were significantly correlated with the number of medications reported by the patient. *The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (82.9%), and formulations fix dermatologic or ophthalmologic diseases (81.3%).		
57.	Cornu P, 2012(23)	Brussels, Belgium	Cohort retrospective	189 elderly aged ≥65 years discharged from acute geriatric department of a Belgain university hospital	Prescribed drug	Incidence and type of discrepancies between the discharge letter for the primary care physician and the patient discharge medication and identify possible patient-related determinants for experiencing discrepancies. Discrepancies were categorized as omitted drug, unintended continuation (discontinued home medication documented as home medication), discrepant dose, missing dose, and discrepant brand, omission of a brand name, discrepant frequency, missing frequency, or an incorrect pharmaceutical form. By comparing the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list	**Other: Discrepancies prevalence:** Almost half of these patients (n=90, 47.6%) (95% CI 40.5-54.7) had 1 or more discrepancies in medication information at discharge. *Two discrepancies (1.2%) were categorized as having the potential to cause severe patient harm. These discrepancies consisted of a wrong dose (doubled the prescribed dose) of digoxin in the patient discharge medication list and the listing of a low-molecular-weight heparin in the patient discharge medication list that was intentionally omitted in the discharge letter because of the development of heparin-induced thrombocytopenia during hospitalization. **Risk factors:** The explorative multivariate model adjusted for age, sex, length of hospital stay, and residential situation showed that when the discharge letter contained more than 5 drugs, the likelihood of experiencing 1 or more drug discrepancies was 3.22 (95% CI 1.40 to 7.42; p = 0.006) times higher than when 5 or fewer drugs were mentioned. Increasing numbers of drugs in the discharge medication list (OR 1.19; 95% CI 1.07 to 1.32; p = 0.001) and discharge letter (OR 1.18; 95% CI 1.07 to 1.32; p = 0.001) were associated with a higher risk for discrepancies.	Discrepancies prevalence: 90/189= [(47.6%) (95% CI 40.5-54.7)]	*Error-related adverse event
Preventable ADEs									
58.	Field T S, 2007(81)	USA	Cohort	30,000 elderly ≥ 65 years from ambulatory care	Prescribed drug	ADE resulting from patients error and risk factors By electronic tracking of administrative data,	**Preventable ADE:** ADE resulting from patients error prevalence 113 individual experience ADE and potential ADE **Risk factor:**	ADE resulting from patients' error prevalence: 113/30,000 = (0.38%)	*ADE resulting from patients error

						review medical records, reports from clinicians, hospital discharge summaries and ED visit	In a multivariate analysis, there was a dose–response association between patient errors leading to ADEs and potential ADEs and regularly scheduled medications; compared with zero to two medications, the OR for three to four medications was (OR 2.0; 95% CI=0.9–4.2), for five to six medications was (OR 3.1; 95% CI=1.5– 7.0), and for seven or more medications was (OR 3.3; 95% CI=1.5–7.0). The strongest association was with the CCI; compared with a score of 0, the OR for a score of 1 to 2 was (OR 3.8; 95% CI=2.1–7.0), for a score of 3 to 4 was (OR 8.6; 95% CI=4.3–17.0), and for a score of 5 or more was (OR 15.0; 95% CI=6.5–34.5).		
59.	Gandhi T K, 2010(28)	Boston and Indianapolis ,USA	Cross-sectional	68,013 outpatient, mean age 48 and 47 years	Prescribed drug	ADE. Using electronic health record screening, chart review and ADE monitor	**Preventable ADE** incidence: The overall rate was 138 ADEs/1000 person-years across the two sites. Preventable ADEs rate 15 /1000 person-years across two sites. *Most commonly drugs associated with preventable ADE were the angiotensin-converting enzyme (ACE) inhibitors and beta blockers.	Preventable ADEs rate 15 /1000 person-years across two sites.	*Preventable ADE
60.	Obreli Neto P R, 2012(34)	Ourinhos microregion, Brazil	Cohort prospective	433 elderly aged ≥ 60 years from the primary public health system	Prescribed drugs both within and across prescriptions	DDI-related ADR incidence and factors. Using phone or face-to-face structured interview DDI screening tool: DDI checker Programs (DrugDigest®, Drugs®, Micromedex® and Medscape®)	**Preventable ADE:** DDI-related ADR incidence: Occurred in 30 patients (6.9 %). Gastrointestinal bleeding occurred in 37 % of the DDI-related ADR cases, followed by hyperkalemia (17 %) and myopathy (13 %). Seventeen DDI-related ADRs were classified as severity level 2, and hospital admission was necessary in 11 cases. *Warfarin was the most commonly involved drug (37%cases), followed by acetylsalicylic acid (17 %), digoxin (17 %), and spironolactone (17 %). **Risk Factors:** The multiple logistic regression showed that the following were associated with the occurrence of DDI-related ADRs: Age ≥80 years [OR 4.4; 95 % CI 3.0–6.1, p<0.01], CCI ≥4 (OR 1.3; 95 % CI 1.1–1.8, p<0.01), Consumption of five or more drugs (OR 2.7; 95 % CI 1.9– 3.1, p<0.01),	Incidence of DDI-related ADR 30/433= (6.9%)	*Error-related adverse event

							Use of warfarin (OR 1.7; 95 % CI 1.1–1.9, p<0.01)		

Abbreviations: ACE: Angiotensin-converting enzyme. ACOVE: Assessing Care of Vulnerable Elders. ADE: Adverse Drug Event. ADI: Adverse Drug Interaction. Adverse Drug Reaction: ADR. CI: Confidence Interval. DDI: Drug-Drug Interaction. ED: emergency department. GP: general practitioners. HEDIS: Health Plan Employer Data and Information Set. IPET: Improved Prescribing in the Elderly Tool. IDU: Inappropriate Drug Use. IP: Inappropriate Prescribing. MAI: Medication Appropriate Index. MDAPE: Medication Discrepancy Adverse Patient Event. OTC: Over-the-Counter. OR: Odds Ratio. PDDI: Potential drug-disease interaction. PIM: Potentially Inappropriate Medicine. PPO: Potential Prescribing Omissions. STOPP: Screening Tool of Older Person's Prescriptions. START: Screening Tool to Alert doctors to Right Treatment.

Table 2: Systematic review quality assessment

A. Joanna Briggs Institute critical appraisal checklist for descriptive/case series and cross-sectional

Was study based on a random or pseudo- random sample?
Were the criteria for inclusion in the sample clearly defined?
Were confounding factors identified and strategies to deal with them stated?
Were outcomes assessed using objective criteria?
If comparisons are being made, was there sufficient descriptions of the groups?
Was follow up carried out over a sufficient time period?
Were the outcomes of people who withdrew described and included in the analysis?
Were outcomes measured in a reliable way?
Was appropriate statistical analysis used?
Y = Yes, No = N, Unclear = U, Not applicable = NA

		1	2	3	4	5	6	7	8	9	Overall appraised	
1	Ramia E, 2014 (75) Adult	Y	Y	N	N	NA	NA	Y	Y	Y	High	Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring, may cause

												recall bias
2	Sorensen L, 2006 (80) Adult	Y	Y	N- Risk factors related to patient not studied	Y	NA	NA	Y	Y	Y	High	
3	Vuong T, 2006 (31) Adult	U	Y	N	Y	NA	NA	N	Y	Y, percentage was used but statistics was not described in the full text.	High	Unclear sampling strategy
4	Adams R J, 2009(76) Adult	Y	Y	Y (but for all type of adverse event)	N (self-reported adverse events)	NA	NA	N	Y	Y	High	Risk of recall bias and attribution with self-reported adverse events and
5	Gandhi T K, 2010 (28) Adult	U	Y	N	Y	Y	NA	NA	Y	Y	High	
6	Lu C Y, 2011(26)	Y	Y	Y	N (subjective patient-reported	Y	NA	NA (secondary analysi	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient-

	Adult				medication error)			s)				reported medication error pp
7	Sears K, 2012 (27) Adult	Y	Y	Y	N (subjective self-reported medication error)	Y	NA	NA (secondary analysis)	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient self-reported medication error
8	Koper D, 2013(29) Adult	N (convenience)	Y	N	Y	NA	NA	NA (100% participant)	Y	Y	High	Selection bias
9	Dallenbach, 2007 (30) Adult-DDI	N (consecutive)	N	N	Y	NA	NA	NA (retrospective)	Y	Y	Moderate	
10	Indermitte J, 2007 (38) Adult-DDI	Y (pharmacy choose). No (first 12 customer)	Y	N	Y	NA	NA	Y	Y	Y	High	
11	Mahmood, 2007 (39) Adult-DDI	Y	Y	N	Y	NA	NA	NA (retrospective)	Y	Y	High	Patients may actually be on other drugs so may not

												catch all the DDI.
12	Guthrie B, 2015 (43) Adult-DDI	Y	Y	Y (but for both own home and care home)	Y	Y	NA	NA (secondary analysis)	Y	Y	High	Risk factors for both own home and care home.
13	Martins S D O, 2006 (45) Elderly -PIM	N (1st came to pharmacy carrying prescription for 2 or more drugs)	Y	Y, but not all	Y	Y	NA	N	Y	Y	High	Self-reported data from elderly concerning drug use may lead to information bias.
14	Pugh M J V, 2006 (46) Elderly -PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	May underestimate the exposure because they do not account for OTC
15	Saab Y B, 2006(47) Elderly -PIM	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported data from elderly concerning drug use may decrease accuracy

16	Bregnhoj L, 2007 (49) Elderly -PIM	N (Each GP was asked to recruit 6 patients who were randomly selected)	Y	N	Y	NA	NA	Y	Y	Y	High	Selection bias
17	Johnell K, 2008 (50) Elderly -PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Did not look for comorbidity as a risk factor because data from Swedish Prescribing Drug Register
18	Haider S I, 2009 (52) Elderly -PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
19	Lai H Y, 2009 (53) Elderly – PIM	Y	Y	Y	Y	NA	NA	NA (secondary analysis)	Y	Y	High	Did not address comorbidity as a risk factor

20	Ryan C, 2009 (55) Elderly – PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	May underestimate the outcome because they do not account for OTC
21	Zaveri H G, 2010 (57) Elderly -PIM	U	Y	Y	Y	NA	NA	N	Y	Y	High	Not enough information in the article
22	Leikola S, 2011 (60) Elderly -PIM	Y	Y	N	Y	NA	NA	NA	Y	Y	High	May underestimate the outcome because database lacks diagnostic patient data, therefore used the Beers 2003 criteria independent of diagnoses and the data provide no information on the use

												of PIMs that are not reimbursable. Nine PIMs that were not reimbursable in Finland in 2007: triazolam, belladonna alkaloids, diphenhydramine, hydroxyzine, ferrous sulfate, bisacodyl, nitrofurantoin and clonidine.
23	Lin Y J, 2011 (61) Elderly -PIM	U	Y	Y	Y	NA	NA	NA	Y	Y	High	
24	Woelfel J A, 2011 (74) Elderly -PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
25	Haasum Y,	Y	Y	N	Y	Y	NA	NA (secon	Y	Y	High	

	2012 (63) Elderly -PIM							dary data analysis)				
26	Nyborg G, 2012 (64) Elderly -PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	
27	Yasein N A, 2012 (65) Elderly -PIM	N	Y	N	Y	Y	NA	N	Y	Y	Moderate	
28	Marroquin E C, 2012 (25) Elderly -PIM	N (convenience sample)	Y	N	Y	NA	NA	N	Y	Y	Moderate	Sampling strategy. Subjective information on socioeconomic and clinical variables may decrease accuracy
29	Weng M C, 2013 (68) Elderly -PIM	Y	Y	Y	Y	Y	NA	N	Y	Y	High	Sampling strategy

30	Baldoni A O, 2014 (35) Elderly -PIM	UC	Y	Y	Y	Y	NA	Y	Y	Y	High	
31	Castillo-paramo A, 2014 (69) Elderly -PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Electronic health record use limitations (incomplete record and quality of data)
32	Vezmar Kovacevic S, 2014 (70) Elderly -PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	
33	Nobili A, 2009 (42) Elderly- DDI	Y	Y	Y	Y	NA	NA	NA (administrative database)	Y	Y	High	The use of administrative database limit looking for comorbidity as a confounder.
34	Secoli S-R 2010 Elderly-DDI	U	Y	Y	Y	NA	NA	NA	Y	Y	High	May underestimate the true DDI prevalence

												because they do not account for OTC
35	Obreli Neto P R, 2012 (33) Elderly-DDI	Y	Y	Y	Y	NA	NA	NA (data from primary healthcare system)	Y	Y	High	May under estimate the DDI prevalence because 1- Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interactions involving combinations of three or more drugs so. 2- did not account for OTC
36	Pit S W, 2008 (78) Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	

37	Tulner L R, 2009 (22) Elderly	N (consecutive)	Y	Y	Y	NA	NA	Y	Y	Y	High	Information on medication described by the patient and caregivers may not always be accurate
38	Obreli Neto P R, 2011(32) Elderly DDI	Y	Y	N	Y	NA	NA	NA	Y	Y	High	
39	Mira J J, 2012 (77) Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported medication error from elderly concerning drug use may have recall bias
40	Mand P, 2014 (37) Elderly	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	

B. Critical Appraisal Skills Program (CASP) for cohort study

1 Did the study address a clearly focused issue?

2 Was the cohort recruited in an acceptable way?

3 Was the exposure accurately measured to minimise bias?

4 Was the outcome accurately measured to minimise bias?

5(a) Have the authors identified all important confounding factors?

List the ones you think might be important, that the author missed

5(b) Have they taken account of the confounding factors in the design and/or analysis?

6(a) Was the follow up of subjects complete enough?

6(b) Was the follow up of subjects long enough?

7 What are the results of this study?

8 How precise are the results?

9 Do you believe the results?

10 Can the results be applied to the local population?

11 Do the results of this study fit with other available evidence?

12 What are the implications of this study for practice?

Yes= Y, No=N, can't tell

	Study design: Cohort														
	Reference	**Quality domains**													
		1	**2**	**3**	**4**	**5 (a)**	**5 (b)**	**6(a)**	**6 (b)**	**7**	**8**	**9**	**10**	**11**	**12**	**Overall quality**
		Are the results of the study valid?								**What are the results?**			**Will the results help locally?**			
1	Maio V, 2006(44) PIM	Y	Y	Y	Y	Y- Age, gender, geographic location, number of medication, number of chronic condition and income None	N	Y	Y (1 year) retrospective	PIM prevalence 18%. Older age, polypharmacy, and greater number of chronic conditions were significant predictors of PIM use.	P value <0.05, 95 % CI	Y	Y	Y	-	Moderate

2	Zuckerman I H, 2006(48) PIM	Y	Y	Y	Y	Y-but used for irrelevant outcome -	Y	Y	Y (2 years)	Inappropriate medication use prevalence 41.9%	P= 0.01, 99% CI	Y	Can't tell (generalisability)	Y	Limited information from the database. Confounding factors were for the nursing home admission rather than for PIM.	Moderate
3	Field T S, 2007(81) Elderly	Y	Y	Y	Y	Y-Age, gender, comorbidity, number of medications None	Y	Y	Y (1 year)	ADE resulting from patients' error prevalence: 0.38%	P value <0.05	Y	Y	Y	Possible drug-related incidence for which necessary information was not documented in the medical record was not considered.	High

4	Gagne J J, 2008(40) DDI	Y	Y	Y	Y	Y- Age, gender, geographic location, comorbidity, number of medication prescribed. None	Y	Y	Y (1 year)	DDI: prevalence 53%	95% CI	Y	Y	Y	Applying the US list of clinically important DDI to Italy may underestimate the prevalence as it captured only 12 out of the 25 DDI original list. Unable to extract risk factors data as it for all age group.	High
5	Berdot S, 2009(51) Elderly PIM	Y	Y	Y	Y	Y-but for irrelevant outcome -	Y	Y	Y (4 years)	PMI prevalence 31.6%	95%CI, P value <0.05	Y	Y	Y	Self-report and data from healthcare insurance plan are not perfect for actual drug consumption. Recall bias. Confounding factors were for the risk of falls rather than for PIM.	High

6	Lapi F, 2009(41) Elderly PIM	Y	Y	Y	Y	Y- Comorbidity, polypharmacy, stroke, heart failure Age, gender	Y	Y	Y (1 year)	1999: IP prevalence: (5.1%) Potential DDI prevalence: (30.5%) Potential Major DDI: (5.6%) Polypharmacy, aws a predictors of PIM use.	P-value <0.05, 95% CI	Y	N	Y	Self-reported diagnosis and medication use may cause recall bias. Beers' list cannot be fully applied to Italy, it most reflect US drug market.	Moderate
7	Ryan C, 2009 (54) Elderly PIM	Y	Y	Y	Y	N -	Can't tell	Y	Y (6 month)	Medicine prescribed inappropriately Beers 2003: 13% IPET: 10.4%	Can't tell	Y	Y	Y	-	Low

8	Akazawa M, 2010(56) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, polypharmacy (>5 drugs), hospitalisation , comorbidities. None	Y	Y	Y (1 year)	Prevalence of PIM 43.6%. Inpatient service use, polypharmacy, and comorbidities were significant predictors of PIM use.	95%CI, P value <0.05	Y	Y	Y	Medical information cannot be taken from claim data, unobserved confounder. PIM not associated with age as several other studies.	High
9	Barnett K, 2011(58) Elderly PIM	Y	Y	Y	Y	Y- Age, sex, polypharmacy and place of residence. Comorbidity	Y	Y	Y(2yesrs)	PIM prevalence 30.9%. Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy	95%CI	Y	Y	Y	Comorbidity not accounted for. Risk factors for both care home and home	High
10	Chang C B, 2011(59) Elderly PIM	Y	Y	Y	Y	Y- Age, sex, education, number of chronic medication, number of chronic conditions, and number of ED visits.	Y	Y	Y (12,24 Week)	PIM: 24% - 73%. Number of chronic drugs and number of chronic conditions was a common risk factor in all criteria	P value < 0.05	Y	Y	Y	May underestimated the prevalence because several drugs in Taiwan was not available in the sex	High

						None									criteria	
11	Zhang Y J, 2011(62) Elderly PIM	Y	Y	Y	Y	Y- Race, gender, family income, educational level, census region, number of prescription, self-rated health status. None	Y	Y	Can't tell	Prevalence of PIM was from [(13.84%) (95% CI 12.52-15.17)] to [(21.3%) (95% CI 19.5-23.1)]	95%CI, P value <0.05	Y	Y	Y	Recall bias due to self-reported survey. Did not assess DDI, drug-disease interaction and under-use so may underestimate the prevalence	Moderate
12	Cornu P, 2012(23) Elderly	Y	Y	Y	Y	Y- Age, gender, residential situation before admission, residential situation after discharge, number of drugs in the discharge letter or list. Comorbidity	Y	Y	Y (from admission to discharge)	Almost half of these patients [(47.6%) (95% CI 40.5-54.7)] had 1 or more discrepancies in medication information at discharge.	95%CI, P value <0.05	Y	Can't tell	Y	Was done in one centre that may have different procedure of discharge	Moderate
13	Mosher H J, 2012(79)	Y	Y	Y	Y	Y- Health literacy	Y	Y	Y (3 and 12 months)	ADEs occurred in 51	P value <0.05	Y	Can't tell	Y	Results may be biased due	Moderate

	Elderly					Age, number of medications, comorbidity				patients (16.5%) of the patients within the first 3 months of the study, which increased, to 119 patients (38.4%) over the full 12-month follow-up period.					to sampling strategy	
14	Obreli Neto P R , 2012 (34) DDI	Y	Y	Y	Y	Y None	Y	Y	Y (4months)	Incidence of DDI-related ADR (6.9%)	95%CI, P value <0.05	Y	Y	N	Recall bias from weekly meeting with patient. Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interaction involving combinations of three or more drugs so the risk of DDI may be underestimated	Moderate

15	Blozic E, 2012 (66) Adult	Y	Y	Y	Y	Y- gender Age, number of medications, number of disease	Y	Y	Y (3 years)	Prevalence of PIM 21.1%	95% CI	Y	Y	Y	-	High
16	Cahir C, 2013(67) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, socioeconomic status, private health insurance, co-morbidity, number of repeat drug, social support and network, adherence. None	Y	Y	Y (6 months) retrospective study	Prevalence of potentially IP was 40.5%	95%CI	Y	N	Y	Recall bias due to self-reported ADE.	Moderate
17	Zimmermann T, 2013(24) Elderly PIM	Y	Y	Y	Y	Y- Gender age, number of medications, number of disease, depression, education None	Y	Y	Y (4.5 years)	At baseline PIM prevalence is (848) 29% according to the PRISCUS list, which decreased to (464) 25.0% 4.5 years later and 21% according to the Beers list decreasing	95%CI, P value <0.05, OR and CI for risk factors	Y	Y	Y	-	High

										after 4.5 years to (317) 17.1%						
18	Amos T B, 2015(71) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, geographic location, number of medication. Number of chronic conditions	Y	Y	Y (1 year) retrospective study	PIM prevalence 28 % and older age, female, number of medications increase risk of PIM	95%CI, P value <0.05	Y	Cant 'tell	Y	May underestimate the true PIM prevalence because they do not account for OTC	Moderate
19	Hedna K, 2015(72) Elderly PIM	Y	Y	Y	Y	N Age, gender, number of medication, number of chronic condition	Y	Y	Y (3 months) retrospective	Potentially IP Prevalence 42%. ADR caused by potentially IP.	95% CI, P value <0.05	Y	Cant 'tell	Y	Undetected confounders.	Moderate
20	Moriarty F, 2015(73) Elderly PIM	Y	Y	Y	Y	Y- Age, gender, number of medication, number of chronic condition, level of education.	Y	Y	Y (1 year)	PIM prevalence (36.7%-64.8%). Female, age and higher number of medicines were	95% CI	Y	Y	Y	Lack of information on OTC from the pharmacy claim data.	High

						None			associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be associated with change in PPO prevalence.						

Table 3: Medication errors patient-related risk factors

Risk factor	Number of studies with positive association	Number of controlled studies	Controlled for	Specific information	OR or RR (95% or 99% CI) p-value
Age ≥ 75 years	13 (24, 33, 37, 42, 44, 52, 53, 55, 61, 69-71, 73)	10	NA	≥ 80 years	OR 1.021 (95% CI 1.018-1.023) p<0.001.(53)
			Adjusted for age, sex, number of regular medicine and diagnosed chronic condition	Older age	OR 1.03 (95% CI 1.02-1.04) p<0.05.(73)
			NA	Older age	OR 1.05 (95% CI 1-1.09) p=0.046.(61)
			NA	Older age	OR 1.06 (95% CI 1.0-1.13) p=0.037.(24)
			NA	≥ 75 years	OR 1.10 (95% CI 1.05-1.15) p<0.001.(37)
			NA	≥ 85 years	OR 1.18 (95% CI 1.16-1.20) p<0.05.(44)
			Adjusted for sex, age and number of chronic drugs	≥ 85 years	OR 1.52 (95% CI 1.46-1.6).(42)
			NA	≥ 85 years	OR 1.53 (95% CI 1.5-1.55) p< 0.01.(71)
			NA	≥ 85 years	OR 1.79 (95% CI 1.19-2.83) p=0.009.(70)

			Adjusted for sex, age	≥ 75 years	OR 4.03 (95% CI 3.79-4.28) p<0.001.(33)
Comorbidity or Number of disease or Chronic condition drug group (CCDG) score ≥ 4	10 (24, 26, 33, 44, 47, 56, 59, 73, 77, 78)	3	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of chronic conditions	PPO: OR 1.47 (95% CI 1.39-1.56) p<0.05.(73)
			NA	CCDG score ≥ 4	OR 1.76 (95% CI 1.72-1.81) P<0.05.(44)
			Adjusted for age, sex	Diagnosed disease ≥ 3	OR 6.43 (95% CI 3.25-12.44) p<0.001.(33)
Charlson Comorbidity Index (CCI)	3 (52, 55, 69)	1	NA	CCI < 2	RR 2.885 (95% CI 1.972-4.22) p=0.(69)
Female gender	10 (33, 35, 47, 52, 53, 62, 64, 66, 71, 73)	4	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition		PIM: OR 1.27 (95% CI 1.07-1.5) p<0.05.(73)
			Adjusted		OR 1.6 (99% CI 1.58-1.64).(64)
			Adjusted for age, sex, education level, partnership, per capita		Beers 2003: OR 2.5 (95% CI 1.9-3.5)

			income and occupation		Beers 2012: OR 1.8 (95% CI 1.3-2.5).(35)
			Adjusted for sex, age		OR 2.49 (95% CI 2.29-2.75) p<0.001.(33)
Health literacy or Low education	2 (52, 79)	1	Adjusted for age, sex, type of residential area and comorbidity		OR 1.09 (95% CI 1.07-1.17).(52)
Hospital admission	2 (26, 56)	1	NA		OR 3.35 (95% CI 2.43-4.62) p<0.05.(56)
Middle family income	1 (62)	NA	NA		
Polypharmacy	26 (22-24, 33, 35-37, 41, 42, 44-46, 53, 55-57, 59, 61, 62, 68-71, 73, 74, 78)	18	NA	Higher number of prescribed medications	OR 1.06 (95% CI 1.39-1.98) p<0.001.(61)
			Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of prescribed medications	PIM: OR 1.2 (95% CI1.17-1.24) p<0.05 PPO: OR 1.04 (95% CI 1.01-1.07) p<0.05.(73)
			NA	≥ 4 medications	OR 1.91 (95% CI 1.83-2.0) p<0.001.(37)
			NA	Higher number of prescribed medications	OR 1.99 (95% CI 1.80-2.18) p=0.000.(24)
			Adjusted for age, sex, education level, partnership, per capita income and occupation	≥ 5 medications	Beers 2003: OR 2.9 (95% CI 2.1-3.8) Beers 2012: OR 2.7 (95% CI 2-3.6).(35)
			Adjusted for disability, coronary artery disease, heart failure and other comorbidities	≥ 5 medications	IP: OR 2.9 (95% CI 1.5-5.8) Potential major DDI: 3.8 (95% CI 1.7-8.2).(41)

			Adjusted for age, sex, number of chronic conditions and number or drug consumed	≥ 3 medications	OR 3.21 (95% CI 2.78-3.59) p<0.001.(33)
			Adjusted for age, sex, length of hospital stay, and residential situation	≥ 5 medications	OR 3.22 (95% CI 1.40-7.42) p=0.006.(23)
			NA	≥ 6 medications	OR 3.37 (95% CI 2.08-5.48) p<0.001.(36)
			NA	≥ 7 medications	OR 4.528 (95% CI 4.52-4.54) p<0.001.(53)
			Adjusted for age, sex, CCI, history of cardiovascular disorder, history of digestive disorder	≥ 5 medications	OR 5.4 (95% CI 3-9.7) p<0.001.(68)
			Adjusted for sex, age and number of chronic drugs	≥ 6 medications	OR 5.59 (95% CI 5.39-5.80).(42)
			NA	≥ 5 medications	OR 5.69 (95% CI 5.0-6.48) p<0.05.(56)
			NA	≥ 6 medications	STOPP: RR 6.837 (95% CI 4.155-11.247) START: RR 2.051 (95% CI 1.25-3.367).(69)
			NA	≥ 10 medications	OR 7.33 (95% CI 7.15-7.51) p<0.05.(44)
			NA	≥ 9 medications	OR 7.43 (95% CI 3.20-17.23) p<0.001.(70)
			NA	≥ 10 medications	Male: OR 8.2 (95% CI 8-8.4) Female: OR 9.6 (95% CI 8.2-11.2).(46)
			NA	≥ 10 medications	OR 11.45 (95% CI 11.2 -11.7) p<0.01.(71)

Table 4: Medication errors healthcare professional-related risk factors

Risk factor	Number of studies with positive association	Number of controlled studies	Adjusted for	OR or RR or Beta (95% or 99% CI) p-value
Age ≥ 51 years	2 (53, 71)	2	NA	OR 1.03 (95% CI 1.01 -1.06) p<0.01.(71)
			NA	OR 1.238 (95% CI 1.235-1.242) p<0.001.(53)
More than one physician involved in their care	5 (22, 33, 64, 77, 78)	3	NA	Beta 0.7 (95% CI 0.5-1.0) p=0.034.(77)
			Adjusted for age, sex, number of chronic conditions and number or drug consumed	OR 1.39 (95% CI 1.17-1.67) p<0.001.(33)
			Adjusted for age and number of prescriber	OR 3.52 (99% CI 3.44-3.60).(64)
Male general practitioner	2 (53, 71)	2	NA	OR 1.07 (95% CI 1.05-1.10) p<0.01.(71)
			NA	OR 1.206 (95% CI 1.202-1.210) p<0.001.(53)
Frequent changes in prescription	1 (77)	1	NA	Beta 0.4 (95% CI 0.2-0.9) p=0.019.(77)
Not considering the prescription of other physicians	1 (77)	1	NA	Beta 1.9 (95% CI 1.1-3.2) p=0.013.(77)
Inconsistency in the information	1 (77)	1	NA	Beta 4.4 (95% CI 1.3-14.8) p=0.013.(77)
Outpatient clinic visit	1 (46)	1	NA	1.4 (Male 95% CI 1.3-1.4) (Female 95% CI 1.3-1.6).(46)

Family medicine/ general practice specialty	3 (53, 56, 71)	3	NA	OR 1.06 (95% CI 1.03-1.10) p<0.01.(71)
			NA	OR 1.267 (95% CI 1.265-1.269) p<0.001.(53)
			NA	OR 1.46 (95% CI 1.28-1.65) p<0.05.(56)

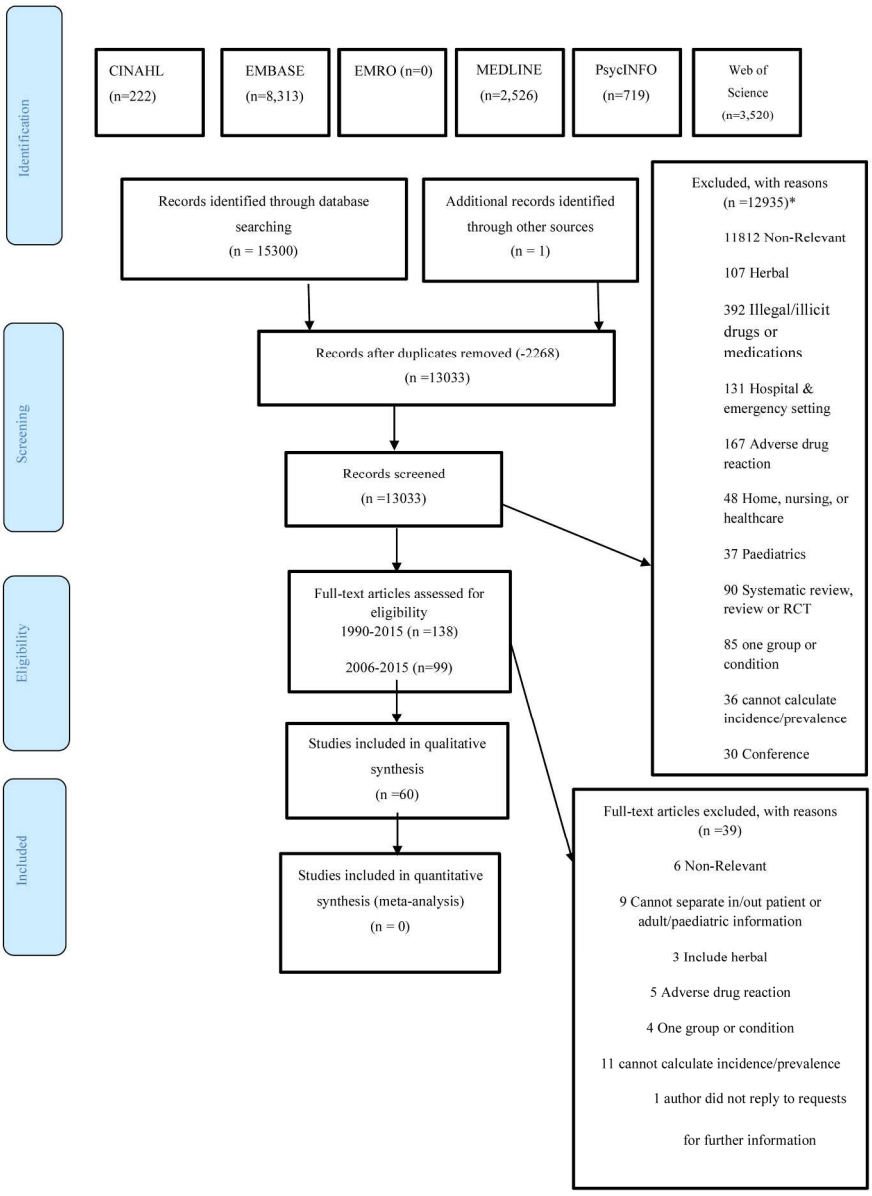

Figure 1: PRISMA flow diagram. (From: Moher D, Liberati A, Tetzlaff J. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement).
*Articles may be duplicated between the excluded groups

189x260mm (300 x 300 DPI)

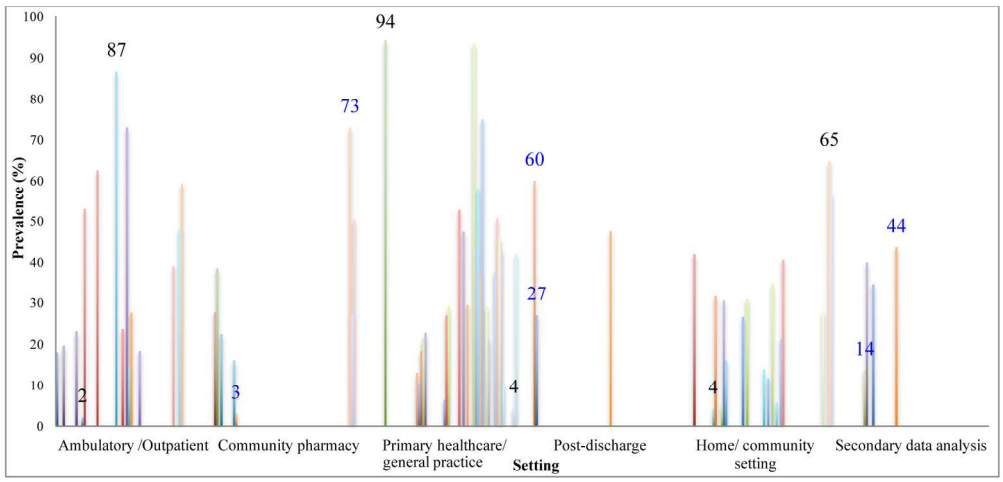

Figure 2: Medication errors prevalence estimates according to settings.

179x85mm (300 x 300 DPI)

Appendix 1: Search strategies

A. MEDLINE

1. Medication Errors/ae, cl, mt [Adverse Effects, Classification, Methods]
2. "Drug-Related Side Effects and Adverse Reactions"/
3. adverse drug event*.mp.
4. medication error*.mp.
5. Patient Safety/
6. drug safety.mp.
7. medication safety.mp.
8. prescribed medication*.mp.
9. prescribed drug*.mp.
10. Nonprescription Drugs/
11. over the counter medication*.mp.
12. patient error*.mp.
13. medication management.mp.
14. Medication Therapy Management/

15. drug related problem*.mp.

16. medication related problem*.mp.

17. preventable adverse drug event*.mp.

18. preventable adverse event*.mp.

19. potential adverse event*.mp.

20. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. household*.mp.

23. residence*.mp.

24. residential home.mp.

25. ambulatory care.mp.

26. Outpatients/

27. self care/ or self medication/ or self manage*.mp.

28. After-Hours Care/

29. out of hours medical care.mp.

30. Homebound Persons/

31. home visit.mp.

32. face to face home interview.mp.

33. face to face interview.mp.

34. Primary Health Care/

35. General Practice/

36. Family Practice/

37. Patient-Centered Care/

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. ((after or post) adj2 hospital discharge).mp.

40. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. Epidemiology/

42. Prevalence/

43. Incidence/

44. risk factor*.mp.

45. follow up.mp.

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. observational.mp.

50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51. 21 and 40 and 50

52. limit 51 to (humans and yr="1990 -2015")

B. EMBASE

1. adverse drug event*.mp.

2. medication error/

3. patient safety/

4. drug safety/

5. medication safety.mp.

6. prescription drug/

7. prescribed medication*.mp.

8. non prescription drug/

9. over the counter medication*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10. patient error*.mp.

11. medication therapy management/

12. medication management.mp.

13. drug related problem*.mp.

14. medication related problem*.mp.

15. preventable adverse drug event*.mp.

16. preventable adverse event*.mp.

17. potential adverse drug event*.mp.

18. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. household*.mp.

21. residence*.mp.

22. ambulatory care/

23. outpatient care/ or outpatient/

24. self care/

25. self medication/

26. self manage*.mp.

27. after hours care.mp.

28. out of hours medical care.mp.

29. home visit.mp.

30. interview/ or face to face interview.mp.

31. primary health care/

32. general practice/

33. patient centered care.mp. or patient care/

34. family practice.mp.

35. ((after or post) adj2 hospital discharge).mp.

36. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

37. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. epidemiology/

39. prevalence/

40. incidence/

41. risk factor*.mp.

42. follow up/

43. observational method/

44. cross-sectional study/ or cross sectional.mp.

45. cohort.mp.

46. case control study/ or case control.mp.

47. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. 19 and 37 and 47

49. limit 48 to (human and yr="1990 -2015")

C. PsycINFO

1. medication error*.mp.

2. adverse drug event*.mp.

3. drug related adverse event*.mp.

4. patient safety.mp.

5. drug safety.mp.

6. medication safety.mp.

7. exp Prescription Drugs/ or exp "Prescribing (Drugs)"/

8. prescribed medication*.mp.

9. exp Nonprescription Drugs/

10. over the counter medication*.mp.

11. patient error*.mp.

12. medication management.mp.

13. medication therapy management.mp.

14. drug related problem*.mp.

15. medication related problem*.mp.

16. preventable adverse event*.mp.

17. preventable adverse drug event*.mp.

18. potential adverse event*.mp.

19. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21. household*.mp.

22. residence*.mp.

23. residential home.mp.

24. ambulatory care.mp.

25. exp Outpatients/

26. self care.mp.

27. exp Self Medication/

28. exp Self Management/

29. after hours care.mp.

30. home visit.mp.

31. exp Home Visiting Programs/

32. exp Interviews/ or face to face interview.mp.

33. exp Primary Health Care/

34. exp General Practitioners/ or general practice.mp.

35. family practice.mp.

36. patient centered care.mp.

37. ((after or post) adj2 hospital discharge).mp.

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp Epidemiology/

41. incidence.mp.

42. prevalence.mp.

43. risk factor*.mp.

44. follow up.mp.

45. exp Observation Methods/

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. 20 and 39 and 49

51. limit 50 to (human and yr="1990 -2015")

D. Web of Science

#5	#4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#4	TS=(follow up) OR TS=(cross sectional) OR TS=(cohort) OR TS=(case control) OR TS=(observational study) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#3	TS=(epidemiology) OR TS=(incidence) OR TS=(prevalence) OR TS=(risk factor*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#2	**TOPIC:** (household) *OR* **TOPIC:** (residence) *OR* **TOPIC:** (ambulatory) *OR* **TOPIC:** (community) *OR* **TOPIC:** (outpatient) *OR* **TOPIC:** (general practice) *OR* **TOPIC:** (family practice) *OR* **TOPIC:** (primary health care) *OR* **TOPIC:** (patient centered care) *OR* **TOPIC:** (self care) *OR*

	TOPIC: (self manage*) *OR* **TOPIC:** (self medication*) *OR* **TOPIC:** (after hours care) *OR* **TOPIC:** (after hospital discharge) *OR* **TOPIC:** (post hospital discharge) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#1	**TOPIC:** (medication error*) *OR* **TOPIC:** (adverse drug event*) *OR* **TOPIC:** (drug related adverse event*) *OR* **TOPIC:** (medication related adverse event*) *OR* **TOPIC:** (patient safety) *OR* **TOPIC:** (drug safety) *OR* **TOPIC:** (patient error*) *OR* **TOPIC:** (drug related problem*) *OR* **TOPIC:** (preventable adverse drug event*) *OR* **TOPIC:** (potential adverse drug event*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015

E. CINAHL

S25	S21 AND S22 AND S23 Limiters – Published Date: 19900101-20151031

S24	S21 AND S22 AND S23
S23	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S22	S8 OR S9 OR S10 OR S11 OR S12 OR S13
S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S20	(MH "Case Control Studies")
S19	"cohort"
S18	(MH "Cross Sectional Studies")
S17	(MH "Prospective Studies")
S16	(MH "Risk Factors")
S15	(MH "Incidence")
S14	(MH "Prevalence")
S13	(MH "Family Practice") OR "general practice"
S12	(MH "Primary Health Care")
S11	(MH "Self Care")
S10	(MH "Ambulatory Care")
S9	(MH "Outpatients")

S8	"household*"
S7	"medication therapy management"
S6	"drug related problem*"
S5	"over the counter medication*"
S4	"prescribed medication*"
S3	"drug safety"
S2	(MH "Adverse Drug Event")
S1	(MH "Medication Errors")

F. Global Health Library (EMRO)

(Adverse drug event* OR medication error* OR patient error*) AND (outpatient OR ambulatory OR general practice OR family practice OR household OR community OR home visit OR after hospital discharge) AND (prevalence OR incidence OR risk factor* OR cross sectional OR cohort OR case control)

G. Google scholar

(Medication error* OR adverse drug event*) AND (home* OR ambulatory OR community OR outpatient OR general practice OR after discharge) AND (prevalence OR incidence OR risk factor* OR Cross sectional OR cohort OR case control)

2- Experts in the field was contacted by email:

	Date	Replay or not	Result
1- Tahir M khan from Malaysia	11/8/2015	Yes	(Medication error in the Southeast Asian countries) systematic review study
2- Azmi Hassali from Malaysia	11/8/2015	Yes	Referred to Tahir M khan
3- Izham M Ibrahim from Malaysia	11/8/2015	No	-
4- David Bates	11/8/2015	No	-

5- Tejal Gandhi	11/8/2015	No	-
6- Kathleen Walsh	11/8/2015	Yes	Published papers

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	0
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	49(table2)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10, 27(table 1)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: **www.prisma-statement.org**.