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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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ABSTRACT

Objective 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 January 2006 and 31 December 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.

Results 60 studies met the inclusion criteria, of which 53 studies focused on medication errors, 3 on error-related adverse events and 4 on risk factors only. The prevalence of prescribing errors was reported in 46 studies: prevalence estimates ranged widely from 2% to 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-related adverse drug reactions 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.

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.

INTRODUCTION

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

Since the release of *To Err is Human: Building a Safer Health System* by the Institute of Medicine (now the National Academy of Medicine), which focused on acute care settings, most patient safety research has been conducted in hospital settings. 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, there is an increased sense of urgency to further focus attention on community care contexts, particularly in relation to medication safety. With an ageing 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.

### Box 1 Key definitions

- **Adverse drug event (ADE):** Bates et al define ADE as ‘an injury resulting from medical intervention related to a drug’. 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 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’. 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.
- **Non-prescription drugs:** Medicines that can be sold legally without a prescription.
- **Over-the-counter (OTC) drug:** The Food and Drug Administration 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’.
- **Prescription drug:** Drugs that cannot be sold legally without a prescription.

### METHODS

#### Protocol and reporting

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

#### 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 inpatients or in emergency departments (ED) were excluded. Randomised controlled trials 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, for example, 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. The search terms and detailed search strategies are presented in online supplementary 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 the following: for the outcome: medication safety, medication error, preventable adverse drug event and 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, EMBASE, Eastern Mediterranean Regional Office of the WHO, MEDLINE, PsycINFO and Web of Science, between 1 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 (online supplementary appendix 1). The reference list of all included studies was further reviewed for additional possible eligible studies.

The databases were searched by GAA. The title and abstracts were then independently screened for eligible studies according to the above detailed selection criteria by GAA and a second reviewer, NAS. 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, 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 (GAA and NAS, or GAA and MAM). 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, was extracted.

The risk of bias assessment was independently carried out on each study by two reviewers (GAA and NAS, or GAA and NA) using the Critical Appraisal Skills Programme (CASP) quality assessment tool for cohort and case-control studies, and cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for descriptive studies. 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 ORs, together with 95% CIs, for each study (where available). A descriptive and narrative synthesis of the extracted data was undertaken.

The following is the definition of incidence rate used in this review: ‘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)’. The following is the definition of prevalence rate used in the data extraction: ‘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)’. 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. Medication errors were described according to (1) the stage in the medicines’ management process when the error occurred, that is, prescribing, dispensing, administration and monitoring; and (2) 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). 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 protocol12: (1) 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: 1 January 2006–31 December 2015; (2) only studies with the incidence or prevalence rate per number of patients were included; and (3) 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 tables 2A and 2B.

Nine studies were conducted in Asia, 4 in Australia, 32 in Europe, 8 in North America, 5 in South America and 2 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 Nineteen 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, 5 studies in community pharmacies and 2 studies in post-discharge settings, while 3 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 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 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 ten 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 3 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 are 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 et al, Lu and Roughhead, Sears et al,1 and Mira et al,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 et al’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 et al’s study population comprised older polymedicated 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

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 et al23 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 (GP), but not mentioned in the indication of the UpToDate.25

Drug–disease interactions or contraindications
Drug–disease interactions were measured in one study by Mand et al25 with a prevalence of 10%.33

Drug–drug interactions

The prevalence of DDIs was measured in 11 studies and ranged from 2% to 58%.25 26 27 30 34–39 This could in part have been due to the fact that different DDI screening tools were used, namely DDI compendia and ePocrates RX, Thomson Micromedex program, Pharmavista database, BotPlus program 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% to 94%.18 19 20 21 23 25 26 29 37 40–70 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, improved prescribing in the elderly tool, Medication Appropriateness Index, PRISCUS and Screening Tool of Older

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**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. Adam et al, 2009 | Australia | Cross-sectional | Analysis of data from 3522 adults participating in stage 2 of the North West Adelaide Health Study aged ≥18 years | | | Self-reported adverse event (medication, diagnosis and other). | 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% to 5.0%). Medication error. | Medication error prevalence: 69/3522=1.9% | Subjective data rather than objective |
| 2. Lu and Roughead, 2013 | Australia, Canada, New Zealand, UK, USA, Germany, and the Netherlands | Cross-sectional (secondary analysis) | 11910 adult respondents 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 seven countries. Using survey. | Self-reported medication error's prevalence: 752 respondents had medication error (Australia=7.4%; Canada=6.7%; New Zealand=0.9%; UK=6.2%; USA=7.1%; Germany=3.2%; The Netherlands=9.1%). Risk factors across all seven countries included seeing multiple specialists, multiple chronic conditions, hospitalisation and multiple emergency room visits. | Medication error prevalence: 712/1910=3.8% | Prevalence for medication error alone from table 1, while the risk factors for both medical and medication error. |
| 3. Sorensen et al, 2006 | Australia, Canada, France, Germany, the Netherlands, New Zealand, UK, and USA | Descriptive (secondary retrospective analysis) | 9944 adults aged ≥18 years | Tasting medication regularly | Patient-related risk factors associated with self-reported medication errors. | 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: 570/9944=5.7% | Risk factors for both hospital and community setting |
| 4. Miss et al, 2013 | Alicante, Spain | prospective cross-sectional | 382 elderly aged ≥65yrs from primary care. Patients on polypharmacy (five or more drugs) and with comorbidity cardiovascular (37.8%), 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 patients reported having made at least one mistake with the medication in the last year. Risk factors: Prevalence of self-reported 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=45 (21%). 4. Hearing of medications=43 (21%). 5. Therapeutic duplication present=50 (45%). Administration error: No medication administration routine=56 (27.5%). Poor adherence=23 (11.3%). Confused by generic and trade names=114 (55.9%). | Medication error prevalence: 207/380=75% | Consequence* |
| 5. Sorensen et al, 2006 | 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’ visits 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=45 (21%). 4. Hearing of medications=43 (21%). 5. Therapeutic duplication present=50 (45%). Administration error: No medication administration routine=56 (27.5%). Poor adherence=23 (11.3%). Confused by generic and trade names=114 (55.9%). | Medication error prevalence: 16/87=18% | |
| 6. Vuong and Marriott, 2006 | Melbourne, Australia | Descriptive | 142 discharged adults aged ≥65yrs who were returning to independent care at home. Patients 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%. | Unnecessary medicine stored at home prevalence: 85/142=60% | |
| 7. Pit et al, 2008 | New South Wales, Australia | Cross-sectional study | 849 elderly aged ≥65yrs from general practice | Self-medications | Prevalence of self-reported risk factors for medication misadventures. Test used Medication Risk Assessment Form (patient survey) | Risk factors: Using at least one medication for more than 6 months (93%). 2. More than one doctor involved in their care (99%). 3. Had three or more health conditions (79%). 4. Used five or more medications (54%). 5. ADRs, in the last month 39% of patients had ADRs, of which 20% was moderate and 6% was severe. 6. Poor adherence=97 (52.5%). | No information on how many patients had unnecessary medicine. Information available is on the patient allowed to remove unnecessary medicine. |
| 8. Musher et al, 2013 | Iowa, USA | Cohort prospective | 310 elderly aged ≥65yrs who were cognitively intact from a Veterans Administration primary care clinic | Tasting five 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 increased the risk of ADEs. | |
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. Mandel et al., 2014

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%.

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Prescribing error prevalence:
Indication: 158 of the 169 patients (93.5%) had at least one non-evidence-based prescription.

Contraindication or drug–disease interaction prevalence: 10.4% of elderly were exposed to at least one PDDI.

Risk factors:
1. Patients over 75 years (OR 1.10, CI 1.05 to 1.15).
2. Number of drugs prescribed (>4 drugs: OR 1.91, CI 1.83 to 2.00).
3. Blood clotting disorders/receiving anticoagulant therapy (OR 2.38, CI 2.15 to 2.64) showed the strongest association with PDDI.

11. Gagne et al., 2008

Clinically significant ADI.
Prescription review.
DDI screening tool: (DrugDigest, Medscape and Micromedex). PIM using Beers criteria 2003.

Risk factors:
Female sex (OR=2.49 (95% CI 2.29 to 2.75)), diagnosis of ≥3 diseases (OR=6.43 (95% CI 3.25 to 12.44)) and diagnosis of hypertension (OR=1.68 (95% CI 1.23 to 2.24)) were associated with potential DDIs.

12. Dallenbach et al., 2007

Prescription of drugs commonly associated with DDI: Metformin and Statins; Metformin and PPIs; Metformin and diuretics; Metformin and thiazolidinediones; and Metformin and statins.

Risk factors:
Total=1195.

13. Obreli Neto et al., 2011

Prescribing error: DDI prevalence: 47.4% Risk factors: Female sex (OR=2.49 (95% CI 2.29 to 2.75)), diagnosis of ≥3 diseases (OR=6.43 (95% CI 3.25 to 12.44)) and diagnosis of hypertension (OR=1.68 (95% CI 1.23 to 2.24)) were associated with potential DDIs.

14. Scolari et al., 2010

Prescribing error: DDI prevalence: 568/2143=26.5%. Risk factors: 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.

15. Obreli Neto et al., 2012

Prescribing error: DDI prevalence: 5855/12349=47.4% Risk factors: 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.

Table 1 Continued

| Author, year | Country/city | Study design/type | Population of interest | Exposure of interest | Outcome of interest | Main finding | Conclusion, n/N (%) | Additional notes |
|--------------|--------------|-------------------|------------------------|---------------------|-------------------|-------------|---------------------|------------------|
| 9. Koper et al., 2013 | Austria | Descriptive | 169 patients from general practice taking five or more medications. Mean age: 76.4±8.5 SD years. Of the 169 patients, 158 were elderly ≥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 patients according to the PRAGUE list. Using case report form filled in by the GPs. | Prescribing error prevalence: Indication: 118 of the 169 patients (69.5%) had at least one non-evidence-based medication. Dosing error: 74 of the 169 patients (44.8%) had at least one dosing error. 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: 118/169=69.5%. 2. Dosing error: 74/169=44.8%. 3. Category D drug interaction: 99/169=58%; category X drug interaction: 4/169=2.4%. 4. PMs: 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. Mandel et al., 2014 | Germany | Descriptive retrospective | 244/19 elderly aged ≥85 years from family practice with at least one diagnosis named in the Beers list. | Prescribed drug | PDDI frequency and whether there are gender-related or age-related differences. Analysis from electronic patient records. | Prescribing error: Contraindication or drug–disease interaction prevalence: 16.4% of elderly were exposed to at least one PDDI. Risk factors: 1. Patients over 75 years (OR 1.10, CI 1.05 to 1.15). 2. Number of drugs prescribed (>4 drugs: OR 1.91, CI 1.83 to 2.00). 3. Blood clotting disorders/receiving anticoagulant therapy (OR 2.38, CI 2.15 to 2.64) showed the strongest association with PDDI. | PDDI prevalence: 2390/2491=99.6% |
| 11. Gagne et al., 2008 | Region Emilia-Romagna, Italy | Cohort retrospective | 4221/4165 adults ≥85 years excluded. Outpatient aged from 0 to ≥85 years. | Prescribed drug | Clinically important potential DDI. | Prescribing error: DDI prevalence: 135/591=23%; DDI screening tool: a list of clinically important potential DDIs included 12 drug pairs that could be captured using the regional Emilia-Romagna database. | DDI prevalence: 7893/14906=53% Risk factors for all age groups including paediatrics. All age groups included so results should be considered cautiously. |
| 12. Dallenbach et al., 2007 | Geneva, Switzerland | Descriptive, retrospective file review | 591 outpatients, mean age 65 years | Prescription drug and drug currently taking | Clinically significant ADI. | Prescribing error: DDI prevalence in 135 of the 591 patients (23%), a potentially clinically significant ADI was identified. | DDI prevalence: 135/591=23% |
| 13. Obreli Neto et al., 2010 | 3 cities of Brazil | Cross-sectional | 2687 elderly aged 60–88 years from the primary healthcare | Prescribed drug | Potential risks in drug prescriptions: DDI and PIM. Using prescription review, and DDI screening tool: (DrugDigest, Medscape and Micromedex) with clinical decision support. | Prescribing error: DDI prevalence: 568/2143=26.5%. Risk factors: 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: 568/2143=26.5% Risk factors: 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. |
| 14. Scolari et al., 2010 | Sao Paulo, Brazil | Cross-sectional | 2143 community-dwelling elderly aged ≥60 years. Data were obtained from the SABE (Health, Well-Being and Ageing) survey. | >2 prescribed drug use | Potential DDIs and identify associated factors. Using home interview. DDI screening tool: Micromedex Healthcare Series. | Prescribing error: DDI prevalence: 5855/12349=47.4%. Risk factors: The use of six or more medications (OR 3.37, 95% CI 2.08 to 5.48) or having hypertension (OR 2.56, 95% CI 1.73 to 3.79), diabetes (OR 1.73, 95% CI 1.22 to 2.46) or heart problems (OR 3.36, 95% CI 2.11 to 5.34) significantly increased the risk of potential DDI. | DDI prevalence: 5855/12349=47.4% |
| 15. Obreli Neto et al., 2012 | 5 cities of Brazil | Cross-sectional | 12349 elderly aged ≥60 years from the primary public health system | Prescription for two or more drugs (prescribed both within and across prescriptions) | Potential DDIs (prevalence of a minimum of 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 programmes (DrugDigger, Drugs, Micromedex and Medscape). | 12349 patients (9959 exposed, 6488 unexposed) | Prescribing error: DDI prevalence: 5855/12349=47.4% Risk factors: Using medical prescriptions and patients’ medical records review. DDI screening tool: DDI checker programmes (DrugDigger, Drugs, Micromedex and Medscape). | DDI prevalence: 5855/12349=47.4% |

Continued
Table 1 Continued

| Author, year | Country/city | Study design/type | Population of interest | Exposure of interest | Outcome of interest | Main finding | Conclusion, n/N (%) | Additional notes |
|--------------|--------------|-------------------|------------------------|---------------------|-------------------|-------------|--------------------|-----------------|
| 16. Mahmood et al, 2007 | Switzerland | Descriptive | 1183 passer-by customers aged ≥18 years from community pharmacies | Prescription-only medicines and OTC drug | Potential drug interactions: Observation of passer-by customers. Of 1183 passer-by customers observed, 164 purchased at least one of the selected OTC drugs, 102 (62.3%) of these subjects were interviewed. | DDI prevalence: Observation of passer-by customers. Of 1183 passer-by customers observed, 164 purchased at least one of the selected OTC drugs, 102 (62.3%) of these subjects were interviewed. | DDI prevalence: 3/102=3%, 69/434=16%, 116/434=26.7% | |
| 17. Indermitte et al, 2007 | USA | Cross-sectional, retrospective | 2531 patients who filled prescriptions for medications involved potential DDI from 12 Veterans Affairs medical centres, Ambulatory clinics | Prescribed drug | Clinically important DDI. Database analysis of pharmacy records. | DDI screening tool: Pharmavista database. | 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% |
| 18. Lapi et al, 2009 | Dicomano, Italy | Cohort, a two-wave, population-based survey | 5868 community-dwelling elderly aged ≥65 years | Prescription and non-prescription drugs used at least 1 week before enrolment | Suboptimal prescribing: Inappropriate medication. Suboptimal appropriateness of prescription was significantly higher in 1999 compared with 1995 (p<0.001). | DDI screening tool: Micromedex Drug-Reax system. Using population-based survey. | Prescribing error: Potential DDI prevalence was significantly higher in 1999 compared with 1995 (30.5% vs 20.1%; p<0.001). Inappropriate prescriptions were significantly higher in 1995 compared with 1999 (9.1% vs 5.1%; p<0.001). | Potentially severe DDI prevalence: 30.5%, p<0.001 |
| 19. Nobili et al, 2009 | Lecce, Italy | Cross-sectional, retrospective | 58400 community-dwelling elderly aged ≥65 years registered under the local health authority of Lecce | Receiving at least two coadministered prescriptions | DDIs and associated risk factors (age, sex and number of prescribed drugs). | DDI screening tool: Italian computerised interaction database. Analyzed all prescriptions dispensed from 1 January 2003 to 31 December 2003. | Prescribing error: Potential DDI prevalence was 94.7 elderly people (16%) were exposed to drug combinations with the potential for 13932 DDIs. Mean number of DDIs per patient was 0.2 (range 0–9). Risk factors: Age and number of chronic drugs were associated with an increasing risk of DDIs. | Potentially severe DDI prevalence: 94.7/58400=16% |
| 20. Guthrie et al, 2015 | Scotland, UK | Cross-sectional | 31181 residents aged ≥65 years from the community-dispensed prescribing data of a general practice | Living in own home | DDIs and associated risk factors. | DDI screening tool: Analysis of community-dispensed prescribing data using British National Formulary 2010. | Prescribing error: Potential DDI prevalence: 40469 adults (13%) had potentially serious DDI in 2010 for both residents living in own home and care home. Number of patients with potentially serious DDI for residence living in own home in 2010=13.6% | DDI prevalence: 13.6/1000=0.4% |
| 21. Malo et al, 2006 | Emilia-Romagna, Italy | Cohort retrospective | 6495 elderly outpatients aged ≥65 years from the Emilia-Romagna outpatient prescription claims database | Prescribed drugs | Using the 2002 Beers criteria and factors associated with PIM. | Prescription review | Prescribing error: PIM prevalence: A total of 102641 (8.0%) elderly had one or more occurrences of PIM prescribing. Risk factors: 1. Older age (65–85 years) (OR 1.18, 95% CI 1.16 to 1.2, p<0.05); 2. ≥10 drugs prescribed (OR 7.33, 95% CI 7.15 to 7.51, p<0.05); 3. ≥4 chronic conditions (OR 1.76, 95% CI 1.72 to 1.81, p<0.05). | PIM prevalence: 152/6495=4.5% |

Continued
### Table 1 Continued

| Author, year | Country/city | Study design/type | Population of interest | Exposure of interest | Outcome of interest | Main finding | Conclusion, n/N (%) | Additional notes |
|--------------|--------------|-------------------|------------------------|---------------------|-------------------|-------------|-------------------|------------------|
| 22. de Oliveira Martins et al, 2007 | Lisbon, Portugal | Cross-sectional | 213 elderly aged ≥65 years from 12 community pharmacies | Prescription and home medications | IDU by 1997 Beers and 2003 Beers criteria. Using survey. | Prescribing error: PM prevalence. Using the 1997 Beers criteria, 72 cases of inappropriate medicines were detected in 93 patients (77.3%). Using the 2003 Beers criteria inappropriate medication was detected in 62 patients (88.5%). Risk factors: Male gender, excessive number of drugs. Occurrence of inappropriate medicines was significantly associated with the consumption of a high number of drugs. | IDU prevalence: 82/213=38.5% using 2003 Beers |
| 23. Pugh et al, 2006 | Austin, Texas, USA | Cross-sectional, retrospective | 1 096 361 outpatient elderly aged ≥65 years using national data from the Veterans Health Administration | Prescribed drug only | Potentially IP included in the 2006 HEDIS criteria and to determine if patient risk factors are similar to those found using Beers criteria. | Prescribing error: IP prevalence. Overall, 19.6% of older veterans were exposed to HEDIS 2006 drugs. Risk factors: 1. Older patients receiving ≥3 medications were at greater risk of exposure in men (OR 8.2, 95% CI 8.6 to 8.8, and women (OR 9.6, 95% CI 8.2 to 11.3). 2. Patients with more outpatient clinic visits (≥10) were at greater risk regardless of gender (OR 1.4, 95% CI 1.3 to 1.6). 3. Diagnosis with other mental illness (eg, depression, anxiety) alone or in combination with serious mental illness was associated with higher risk of potentially IP by women (OR 1.3, 95% CI 1.1 to 1.6). | Potentially IP prevalence: 23.4% using Beers criteria |
| 24. Saab et al, 2006 | Lebanon | Descriptive | 277 elderly aged ≥65 years from 10 community pharmacies | Prescription and/or OTC medications | IDU (Beers criteria, missing doses, inappropriate frequency of administration, poor memory, drug-disease interaction, DDI, inappropriate dose, duplication 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. | Insufficient information to determine conclusions. | Just extracted the IDU by Beers criteria because the IDU includes 5 cases of ADR and some patients had more than one IDU. Risk factors for all types of IDU. |
| 25. Zudekerman et al, 2006 | USA | Cohort/retrospective | 487 383 community-dweller elderly aged ≥65 years. Data from MarketScan Medicare Supplemental and Coordination of Benefits database. | Prescribed drug | Inappropriate medication use using Beers criteria. | Prescribing error: PM prevalence. The prevalence of elderly outpatient with at least one inappropriate medication: 160 077 (69.6%) (include five patients with ADR). Inappropriate medication use was most frequently identified in terms of Beers criteria (22.4%), missing doses (8.8%) and incorrect frequency of administration (13%). Drug-disease interaction in 28 patients (10.1%), DDI (9.1%), duplicate therapy 12 (4.3%). | Inappropriate medication prevalence: 62/272=22.4% using Beers criteria |
| 26. Bregnhøj et al, 2007 | Copenhagen, Denmark | Cross-sectional | 212 elderly aged ≥65 years with polypharmacy (>3 drugs) from primary care | Subsidised and non-subsidised medications prescribed | IP measured by the MAI: 10 criteria are indication effectiveness, dosage, directions, practicality, directions correctness, DDI, drug-disease interaction, duplication, duration and frequency. | Prescribing error: IP prevalence. The majority of the patients, namely 94.3%, had one or more inappropriate ratings among their medications. | IP prevalence: 200/121=16.3% |
| 27. Johnell and Fastbom, 2008 | Sweden | Cross-sectional | 731 105 people aged ≥75 years from the Swedish Prescribed Drug Register (secondary data analysis) | Prescribed drug only and multidose drug dispensing | Whether the use of multidose drug dispensing is associated with potential IDU. | Prescribing error: PM prevalence. Prevalence of potential IDU in multidose dispensing users: 40.3% (women: 41%, men: 38.8%). Prevalence of potential IDU in prescription users: 13.6% (women: 15%, men: 11.5%). The multidose users had higher prevalence of all indicators of inappropriate drug use compared to prescription users. 1. The younger elderly (aged 75–79 years) who used multidose drug dispensing had the highest percentage of all indicators of potential IDU. 2. Most indicators of IDU were more common in women than men. 3. Multidose drug dispensing among those aged 75–79 years old 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. | Multidose drug dispensing means that patients get their drugs machine-dispensed into one unit for each dose occasion and packed in disposable bags. |
## Table 1 Continued

### 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 |
|--------------|--------------|-------------------|------------------------|----------------------|---------------------|--------------|---------------------|-----------------|
| 28. Bendit et al, 2009 | Dijon, Bourgogne, Montpellier, France | Cohort prospective | 6343 community-dwelling elderly aged ≥65 years | Prescribed drug | PM using 1997 and 2003 Beers criteria, risk and inappropriateness, face-to-face interview using standardized questionnaire. | Prescribing error: | PM prevalence: One-third (31.6%) of the study participants reported using at least one inappropriate medication at study entry. | |
| 29. Haidar et al, 2009 | Sweden | Cross-sectional, register-based study | 626 258 people aged 75–89 years from the Swedish Prescribed Drug Register (secondary data analysis) | Prescribed drug | If low education associated with potential IDU (ie, anticholinergic drugs, long-acting benzodiazepines, concurrent use of 3 psychotropic drugs) and clinically relevant potential DDI. Information from the Swedish Prescribed Drug Register. | Precribing error: | PM 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 to 1.17). Older age, being a woman and higher CCI were associated with the highest frequencies of potential IDU. | |
| 30. Lai et al, 2009 | Taiwan | Descriptive | 2 133 864 patients aged ≥65 years between 2001 and 2004 from ambulatory care National Health Insurance claim database | Prescribed drug | PM prescribing using updated 2003 Beers criteria and the characteristics of and risk factors for such prescribing | Precribing error: | PM prevalence: A mean of 63.8% of the older population received a PM at least once a year in 2001-2004. Details: 2001: 1,974 689 patients of whom 1,297 425 had inappropriate prescription (65.7); 2002: 2,026 737 patients of whom 1,312 147 had inappropriate prescription (64.7); 2003: 2,077 677 patients of whom 1,298 377 had inappropriate prescription (62.3); 2004: 2,133 864 patients of whom 1,333 792 had IP (62.5). Risk factors: The only patient characteristic associated with an increased likelihood of the prescribing of PM was female sex (male sex; OR 0.982 (95% CI 0.980 to 0.983) and when ≥4 drugs were prescribed (p<0.001). The following are physician characteristics associated with a greater likelihood of the prescribing of PM: 1. Male sex (OR 1.256, 95% CI 1.253 to 1.259, p<0.001); 2. Older age (43–50 years: OR 1.021, 95% CI 1.018 to 1.025, p<0.001; ≥51 years: OR 1.238, 95% CI 1.235 to 1.242, p<0.001); 3. Family medicine/general practice (OR 1.267, 95% CI 1.265 to 1.269, p<0.001). | |
| 31. Ryan et al, 2009 | Ireland | Cohort prospective | 500 patients aged ≥65 years from primary care | Prescribed drug | IP using 2003 Beers criteria and IPET. Screening patients’ medical records (electronic and paper). | Prescribing error: | PM prevalence: 65 patients (13%) and 52 patients (10.4%) had at least one medicine prescribed inappropriately using 2003 Beers and IPET criteria, respectively. | |
| 32. Ryan et al, 2009 | Cork, Southern Ireland | Descriptive case record review | 1 329 elderly aged ≥65 years from primary care | Prescribed drugs | A–1. PM using 2003 Beers and STOPP criteria. 2. IPET using START criteria. B–Relationship between age and number of prescription drugs and IP. Case record through paper and electronic record review. | Prescribing error: | PM prevalence: IP rate identified by Beers criteria in 18.3% (243) of patients. IP rate identified by STOPP was 21.4% (284). IP rate identified by START was 23.7% (302) of patients using the START tool. Risk factors: A significant correlation was found between the occurrence of PM and the following: 1. The number of medicines prescribed when calculated using Beers criteria (OR=0.99, p=0.01) and STOPP (OR=0.95, p=0.01) using Spearman’s r correlation test. 2. Age using Beers criteria (OR=0.99, p=0.01) and STOPP (OR=0.97, p=0.01). More outpatient visit days (1.18-fold) and higher medical costs (33% increase) than did non-users. | |
| 33. Akazawa et al, 2010 | Tokyo, Japan | Cohort retrospective | 628 elderly patients aged ≥65 years from health insurance claim data (secondary data analysis) | Prescribed drugs | PM using modified Beers criteria in Japan. Drug utilization review using medical and pharmacy claim from database of Japan Medical Data Center. | Prescribing error: | PM prevalence: 43.6% (286/6628) were prescribed at least one PM. Risk factors: Factors positively associated with PM prescriptions at a significance level of 5% included the following: hospital admission (OR=3.35, 95% CI 2.43 to 4.62), polypharmacy (OR=4.09, 95% CI 2.56 to 6.48) prescriptions from a hospital (OR=1.18), general medicine practitioner (OR=1.46) or psychiatrist/neurologist (OR=2.39), and comorbid conditions including peptic ulcer disease without bleeding (OR=4.19, 95% CI 3.52 to 4.97), depression (OR=3.38), cardiac arrhythmias (OR=1.93), other neurological disorders (Parkinson’s disease, multiple sclerosis and epilepsy, OR=1.88) and congestive heart failure (OR=1.46). PM users had significantly higher hospitalisation risk (6.89-fold), more outpatient visit days (1.18-fold) and higher medical costs (33% increase) than did non-users. | |

Continued
Table 1 Continued

| Author(s), year | Country/city | Study design/type | Population of interest | Exposure of interest | Outcome of interest | Main finding | Conclusion, n/N (%) | Additional notes |
|-----------------|--------------|-------------------|------------------------|---------------------|-------------------|-------------|---------------------|-----------------|
| 34. Zavari et al., 2010<sup>26</sup> | Ahmedabad city, India | Descriptive prospective | 40-year-old men aged ≥85 years from medicine outpatient department | Prescribed drug | Using 2003 Beers criteria. Using prospective proforma data collection. | Prescribing error: PM prevalence: Out of 437 patients, 96 patients (22.1%) received at least one drug that was potentially inappropriate. Risk factors: There was a highly significant association between the number of drugs prescribed and frequency of use of PIMs (p=0.0002). | | |
| 35. Barnett et al., 2011<sup>24</sup> | Tayside, Scotland, UK | Cohort | 65-74 years of age | Prescribed drug | Using 2003 Beers criteria and the association between exposure to PM and mortality. Using discerning and prescribing database and medical record. | Prescribing error: PM prevalence: PM found in 2003 (30.9%) patients living at home. Risk factors: After adjustment for age, sex, and polypharmacy. | | Risk factors for both care home and home | |
| 36. Cheng et al., 2011<sup>18</sup> | Taipei, Taiwan | Cohort | 1,054 community-dwelling elderly patients aged ≥65 years | Prescribed drugs and dietary supplement excluding herbs | Using six different criteria and drug-related problems: the 2003 version of the Beers criteria (from the USA), the Raccoon (from Canada), the Lanzarote (from Spain), STOPP from Ireland, the Whitt-Wajima (from Thailand) and the NORGEP criteria (from Norway). Analyse baseline data from the MSRC-Taiwan study. Secondary data analysis. | Prescribing error: PM prevalence: The proportion of patients who had at least one PM varied from 24% (the NORGEP criteria) to 73% (the Whitt-Wajima criteria). Approximately 31% (the STOPP criteria) to 42% (the NORGEP criteria) of PIMs identified were considered drug-related problems by the medication review team experts. Risk factors: In the binary and logistic regression the common characteristics associated with having at least one PM were age, having a higher number of chronic conditions and a high number of chronic medications. | | |
| 37. Leloka et al., 2011<sup>14</sup> | Finland | Cross-sectional | 841 non-institutionalized elderly patients aged ≥65 years from Finland’s Social Insurance Institution prescription register of all reimbursed drugs for outpatients | Prescribed and OTC medications that are reimbursed and 2003 Beers criteria | | Prescribing error: PM prevalence: 14.7% (n=123/45) had received PIMs according to the Beers 2003 criteria. | | |
| 38. Lin et al., 2011<sup>11</sup> | Taiwan | Cross-sectional, retrospective analysis | 1,738 elderly patients aged ≥65 years from outpatient clinic of a community health centre | Prescribed drugs | Using 2003 Beers criteria and risk factors of PM use. Using data review. | Prescribing error: PM prevalence: The prevalence of patients having at least one PM was 27.5% (95% CI 20.3% to 37.5%). Risk factors: Independent risk factors for PIMs are older age (OR=1.05, 95% CI 1.01 to 1.09), higher number of prescribed medications (OR=1.06, 95% CI 1.00 to 1.11), and a worse health status (OR=1.42, 95% CI 1.00 to 1.98, p<0.01) and diagnosis of acute disease (OR=1.68, 95% CI 1.17 to 2.41, p<0.05). | | |
| 39. Woelfel et al., 2011<sup>17</sup> | California, USA | Cross-sectional | 2,151 elderly aged ≥65 years from ambulatory population of Medicare beneficiaries | Prescribed drug | Using 2003 Beers criteria. Using medication review. | Prescribing error: PM prevalence: 54 (8.3%) beneficiaries were taking at least one PIM. Risk factors: The number of medications was significantly greater in the PIM than the non-PIM group (p<0.001). | | |
| 40. Zhang et al., 2011<sup>11</sup> | USA | Cohort retrospective | 3,570 elderly community-based respondents aged ≥65 from the 2007 MEPS, a nationally representative survey of the US community-dwelling population | Prescribed drug | Using Zhan criteria and risk factors for PIM use. Information from MEPS database. | Prescribing error: PM prevalence: PM prevalence in 2007: 13.8% (CI 12.52 to 15.17). PM prevalence in 1996: 21.3% (CI 19.5 to 23.1). Risk factors: Older women, people taking ≥25 medications, 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. | | |
| 41. Haasum et al., 2010<sup>28</sup> | Sweden | Cross-sectional, retrospective | 1,360-600 home-dwelling elderly aged ≥65 years from the Swedish Prescribed Drug Register | Prescribed drug only | Potentially IDU (use of anticholinergic drugs, long-acting benzodiazepines, concurrent use of ≥2 psychopharmacics and potentially serious DDIs). Information from the Swedish Prescribed Drug Register. | Prescribing error: PM prevalence: 11.6% of the home-dwelling elderly were exposed to potentially IDU. | | Information on both institutionalized and home-dwelling. Extracted home-dwelling information only | |
| 42. Candés Marquó et al., 2012<sup>12</sup> | Cáceres, Spain | Descriptive | 471 patients aged ≥65 years from six centres | Consumed medications | Potentially IP using STOPP/START criteria. Using patient interview and medical chart review. | Prescribing error: PM prevalence: 369 patients (52.8%, 95% CI 48.3 to 57.3) had potentially IP according to STOPP/START criteria. STOPP: 162 patients (22.4%, 95% CI 16.6 to 24.3%), START: 207 patients (28.5%, 95% CI 23.8 to 33.1%). | | |

*STOPP*: Stepping Outside Prescribed Therapy Program; *START*:Screening Tool to Alert Doctors to Right Treatment; *IP*: Inappropriate Prescriptions; *PIM*: Potentially Inappropriate Medication; *PM*: Potentially Medication.
| Author, year | Country/city | Study design/type | Population of interest | Exposure of interest | Outcome of interest | Main finding | Conclusion, n/N (%) | Additional notes |
|--------------|--------------|-------------------|------------------------|---------------------|-------------------|-------------|---------------------|-----------------|
| Nyborg et al. 2012 | Norway | Cross-sectional, retrospective | 445 home-dwelling elderly aged ≥70 years from the Norwegian Prescription Database | Prescribed drug | Prevalence of and predictors for PIM use by the 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 to 3.60 for those with ≥5 compared with those with 1 or two prescribers). Women were at higher risk for PIMs (OR 1.6, 99% CI 1.58 to 1.64). | PIM prevalence: 155/445 (34.8%) | Additional notes |
| Yasein et al. 2012 | Jordan | Cross-sectional | 400 elderly aged ≥65 years from family practice clinic | Prescribed drug | Polypharmacy (≥5 drugs) and IP using 2003 Beers criteria | Prescribing error: Inappropriate medications as determined by Beers criteria independent of diagnosis accounted for 118/400 (29.5%) patients. | IP prevalence: 118/400 (29.5%) | Additional notes |
| Block et al. 2012 | Switzerland | Cohort | 2008: 1 059 495 2009: 1 047 939 2010: 929 791 Community-dwelling adults aged ≥65 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 prescription which is PIM, and according to the PRISCUS list, 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 at least one PIM according to 2003 Beers, 20.2% according to PRISCUS and 26.6% of either definition. | PIM prevalence: 21.1% | Additional notes |
| Cahill et al. 2013 | Ireland | Cohort | 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 (AODEs, HROQOL, and hospital accident and ED). Using patient self-report and medical record. | Prescribing error: PIM prevalence: Prevalence of potentially IP was 40.5% (n=377). AODE prevalence: In total, 214 of 899 participants (24%) were classified as having at least one AOE 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 to 4.83, p=0.05). 2. Significantly lower mean HROQOL utility (adjusted coefficient -0.09, SE 0.02, p<0.001). 3. A substantial increased risk in the expected rate of ED visits (adjusted incidence rate ratio 1.85, 95% CI 1.52 to 2.28, p<0.001). | Potentially IP prevalence: 377/931 (40.5%) ADE prevalence: 674/899 (78%) | Additional notes |
| Weng et al. 2013 | Taiwan | Cross-sectional, retrospective | 760 older patients aged ≥65 years from the outpatient geriatric clinic | Long-term prescribed drugs (≥28 days for chronic disease, 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=0.005). Patients prescribed ≥5 drugs (adjusted OR=5.4) had significantly higher PIM risk than those prescribed ≤2 drugs. | PIM prevalence: 302/760 (39%) | Additional notes |
| Zimmermann et al. 2013 | Germany | Cohort | Follow-up: 3: n=5942 Baseline: n=3131 1865 elderly aged ≥70 years from primary care. Data from the prospective multicenter, observational study 'German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe)'. | Prescribed drug using Beers, PRISCUS list. By checking medications during visits to patients’ homes. | PM using Beers, PRISCUS list. By checking medications during visits to patients’ homes. | Prescribing error: PIM prevalence: 23% (848) according to the PRISCUS list, which decreased to 25% (620) at baseline, decreasing after 4.5 years to 17.1% (310) (χ² 10.77, p=0.001). Risk factors: By PRISCUS list: The risk for PIM increased with: 1. Increasing age of the patients (OR: 1.06, CI 1.00 to 1.13, p=0.03). 2. The presence of depression (OR: 2.42, CI 1.85 to 3.27, p=0.003). 3. Increasing number of prescription drugs (OR: 1.99, CI 1.90 to 2.18, p=0.003). By contrast, the risk of taking PIM decrease by using PRISCUS list with the number of present illnesses (OR: 0.88, CI 0.80 to 0.97, p=0.03). As the growing number of ingested prescription drugs increased the risk for the ingestion of PIM from the Beers list(OR: 1.69, CI 1.50 to 1.94, p=0.00). | Prescribing error: PIM prevalence: 17% (23%) | Additional notes |
### Table 1 Continued

| Author, year                       | Country/city       | Study design/type | Population of interest                                                                 | Exposure of interest                                | Outcome of Interest                                                                 | Main finding                                                                                                                                                                                                 | Conclusion, n/N (%)                                                                 | Additional notes |
|-----------------------------------|--------------------|-------------------|----------------------------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------|
| 49. Baldoni et al, 2014           | Ribeirao Preto, Brazil | Cross-sectional   | 1200 elderly aged ≥60 years from outpatient pharmacy                                    | Prescribed drug, self-medication (309 users) and OTC (802 users) | 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 1 to 5. According to Beers criteria 2012, 538 (62.9%) participants used at least one PIM, the mean being 2.10 (SD=0.48) PIMs/person, ranging from 1 to 8. 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 were female gender, self-medication, use of OTC medications, complaints related to ADEs, psychotropic medication and more than five medications. | PIM prevalence by Beers criteria 2003: 480 (48.0%) PIM prevalence by Beers criteria 2012: 538 (62.9%) | *Error-related adverse event* |
| 50. Castillo-Páramo et al, 2014   | Spain              | Cross-sectional   | 272 electronic records 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 (misprescribing and overprescribing) using the STOPP original criteria was 37.5% (95% CI 31.7 to 43.2), and 50.7% (95% CI 44.7 to 56.6) using the STOPP Spanish AP2012 version and the prevalence of underprescribing was 46.3% (95% CI 40.5 to 51.8) with the START original criteria, and 43.5% (95% CI 37.1 to 48.9) with the START AP2012 version. Risk factors: A significant correlation was found between the number of STOPT 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 to 43.2), 138/272 (STOPP AP2012)=50.7% (95% CI 44.7 to 56.6), 125/272 (START)=45.9%, 117/272 (START AP2012)=43% |                           |
| 51. Vavlar Kovačević et al, 2014  | Serbia             | Cross-sectional, prospective | 508 elderly aged ≥65 years from five community pharmacies                                | Prescribed drugs                                      | PIM and PPO using STOPP/START criteria. Using patient interview and medical, biomedical record. | Prescribing error: PIM prevalence: There were 164 PIMs identified in 139 patients (27.3%) by STOPP and 439 PPOs identified in 257 patients (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 to 4.14, p<0.001) and ≥9 medications (OR 7.43, 95% CI 3.20 to 17.23, p=0.003). Patients older than 74 years were more likely to have a PPO (75–84 years: OR 1.47, 95% CI 1.01 to 2.13, p=0.041; and ≥85 years: OR 1.79, 95% CI 1.19 to 2.83, p<0.009). | PIM prevalence: 164/508 (STOPP)=32.3% PPO prevalence: 439/508 (STOPP)=86.4% |                           |
| 52. Amos et al, 2015              | Emilia-Romagna, Italy | Cohort retrospective | 865 354 elderly aged ≥85 years community-dwelling from administrative care data         | Prescribed drug only                                    | Using updated Maio criteria and patient characteristics related to PI. 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 65–74 years old, respectively. OR=1.53; 95% CI 1.41 to 1.61; OR=1.25; 95% CI 1.19 to 1.33. These odds of exposure to any PIM were slightly lower among men than women (OR=0.98; 95% CI 0.96 to 1.00). An increase in the number of medications prescribed to the patient corresponded with higher odds of PIM exposure. Older GPs (≥56), male GPs and solo practice GPs were more likely to prescribe PIMs to their older patients. | PIM prevalence: 240 310/865 (28%) |                           |
| 53. Hadha et al, 2015             | 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 to 3.68), p<0.001, compared with those in persons without potentially IP. | Potentially IP prevalence: 226/542=42% |                           |
### Table 1  Continued

| Author, year | Country/city | Study design/type | Population of interest | Exposure of interest | Outcome of interest | Main finding | Conclusion, n/N (%) | Additional notes |
|--------------|--------------|-------------------|-----------------------|---------------------|--------------------|--------------|---------------------|------------------|
| Moriarty et al., 2015 | Ireland | Cohort prospective | 2051 elderly aged ≥65 years from The Irish Longitudinal Study on Ageing, Community-dwelling elderly. | Prescribed drug only | PM and PPO using STOPP, Beers criteria, ACOVE indicators and START. Using face-to-face interview, then follow-up after 1 and 2 years. | Prescribing error: PM prevalence | Baseline N (%) (95% CI) Follow-up N (%) (95% CI) |
| | | | | | | | Any PM using STOPP, Beers, ACOVE | 129 (61.4%) (CI 59.3 to 63.5) 1330 (64.8%) (CI 62.8 to 66.9) |
| | | | | | | | Any PPO using START, ACOVE | 1094 (53.3%) (CI 51.2 to 55.5) 1161 (56.6%) (CI 54.5 to 58.8) |
| | | | | | | | Both PM and PPO | 753 (36.7%) 843 (41.1%) |
| | | | | | | | Risk factors: Female sex, age and higher number of medicines were significantly associated with change in PM prevalence. Age and higher numbers of medicines and chronic conditions were found to be significantly associated with change in PPO prevalence. |
| Ramia and Zeenny, 2014 | Lebanon | Cross-sectional | 284 outpatients aged ≥18 years visiting community pharmacy | Patients on ≥1 of the chronic medications mentioned in the study | Monitoring error: 1. 185 of the patients (65%) were found to complete some, but not all, of the recommended therapeutic/safety monitoring tests. 2. 23 of the patients (8%) did not complete any of the recommended monitoring tests. | Incomplete therapeutic/safety laboratory-test monitoring prevalence: 208/284=73% |
| Tulner et al., 2009 | Amsterdam, The Netherlands | Descriptive prospective | 130 elderly aged ≥65 years from Dutch geriatric outpatient | Using more than one prescribed or OTC medications | Frequency and relevancy of discrepancies in drug use. Frequency of MDAPEs. 2. Frequency of MDAPEs. Contributing factors such as increasing age, cognitive status and depressive symptoms, the number of medications used, and 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 (80.7%) involving 396 drugs. MDAPEs: MDAPEs were identified in 29 patients (24.2%). 7 patients had undertreatment due to omissions. 9 patients had ADR due to additions. 13 patient had OD. Risk factors: Patients with ≥1 discrepancy reported using a higher mean number of drugs (5.9 vs 4.1; p<0.05) and had more prescribing physicians in addition to their GP (1.1 vs 0.3; p<0.05). Both the presence of discrepancies (Pearson's r 0.29, p=0.05) and MDAPEs (Pearson's r 0.23, p=0.01) were significantly correlated with the number of medications reported by the patient. *The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (62.9%) and formulations for dermatological or ophthalmological diseases (81.3%). |

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 (80.7%) involving 396 drugs. MDAPEs: MDAPEs were identified in 29 patients (24.2%). 7 patients had undertreatment due to omissions. 9 patients had ADR due to additions. 13 patient had OD. Risk factors: Patients with ≥1 discrepancy reported using a higher mean number of drugs (5.9 vs 4.1; p<0.05) and had more prescribing physicians in addition to their GP (1.1 vs 0.3; p<0.05). Both the presence of discrepancies (Pearson's r 0.29, p=0.05) and MDAPEs (Pearson's r 0.23, p=0.01) were significantly correlated with the number of medications reported by the patient. *The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (62.9%) and formulations for dermatological or ophthalmological diseases (81.3%). |

**Error-related adverse event:**
- MDAPEs: 29/120=24.2%
| Author, year          | Country/city | Study design/type | Population of interest                                                                 | Exposure of interest | Outcome of interest | Main finding                                                                                                                                  | Conclusion, n/N (%) | Additional notes |
|----------------------|--------------|-------------------|----------------------------------------------------------------------------------------|----------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------|
| Cornu et al., 2012   | Brussels, Belgium | Cohort retrospective | 189 elderly aged ≥65 years discharged from acute geriatric department of a Belgian 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), discordant dose, missing dose, and 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 to 54.7) had one 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 (discontinued the prescriped 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 hospitalisation. 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 five drugs, the likelihood of experiencing one or more drug discrepancies was 3.22 (95% CI 1.40 to 7.42, p=0.009) times higher than when five or fewer drugs were mentioned. Increasing numbers of drugs in the discharge medication list (OR 1.18, 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 to 54.7) | *Error-related adverse event |
| Field et al., 2007   | 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 of medical records, reports from clinicians, hospital discharge summaries and ED visit. | Preventable ADE: ADE resulting from patients’ error prevalence: 113 individuals experienced ADE and potential ADE. Risk factor: In a multivariate analysis, there was a dose-response association between patient errors leading to ADEs and potential ADEs: for zero to two medications, the OR for three to four medications was 2.06 (95% CI 0.9 to 4.3); for five to six medications was 3.18 (95% CI 1.5 to 7.0); and for seven or more medications was 3.95 (95% CI 1.5 to 7.0). The strongest association was with the CCI compared to a score of 1, the OR for a score of 2–3 was 3.98 (95% CI 2.1 to 7.0); for a score of 4–6 was 4.9 (95% CI 4.3 to 7.0); and for a score of 7 or more was 15.0 (95% CI 6.5 to 34.5). | ADE resulting from patients’ error prevalence: 113/30 000 = 0.38% | ADE resulting from patients’ error |
| Gandhi et al., 2010  | Boston and Indianapolis, USA | Cross-sectional | 68 013 outpatients, mean age 48 and 47 years | Prescribed drug | ADE: Using electronic health record screening, chart review and ADE monitor. | Preventable ADE: The overall rate was 1.38 ADEs/1000 person-years across the two sites. Preventable ADE rate 15/1000 person-years across two sites. | Preventable ADE incidence: The overall rate was 1.38 ADEs/1000 person-years across the two sites. Preventable ADE rate 15/1000 person-years across two sites. | Preventable ADE rate 15/1000 person-years across two sites | Preventable ADE |
| Obreli-Neto et al, 2012 | 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 interviews. DDI screening tool: DDI checker programmes (DrugDigNet, Drugs, Micromedex and MedicAdapt). | Preventable ADE: DDI-related ADR incidence: occurred in 30 patients (6.9%). | Prevalent ADE: DDI-related ADR incidence occurred in 30 patients (6.9%). Geometric mean bleeding occurred in 37% of the DDI-related ADR cases, followed by hyperkalaemia (17%) and myopathy (16%). 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 (97% of cases), followed by aspirin (22%), digoxin (17%), and antibiotics (17%). Risk factors: The multiple logistic regression showed that the following were associated with the occurrence of DDI-related ADRs: 1. Age ≥80 years (OR 4.4, 95% CI 2.1 to 9.1, p=0.001); 2. CCI ≥ 3 (OR 3.9, 95% CI 1.1 to 13.3, p=0.004); 3. Consumption of five or more drugs (OR 2.7, 95% CI 1.9 to 3.6, p<0.001); 4. Use of warfarin (OR 1.7, 95% CI 1.1 to 2.5, p<0.001); 5. Use of prednisone (OR 1.7, 95% CI 1.1 to 2.5, p<0.001). | Incidence of DDI-related ADR: 30/433=6.9% | *Error-related adverse event |
### Table 2A

Systematic review quality assessment: Joanna Briggs Institute Critical Appraisal Checklist for descriptive/case series and cross-sectional studies.

| Study | Adult | Elderly-PIM | Adult-DDI | Overall appraised |
|-------|-------|-------------|-----------|-------------------|
| 1 | Ramia and Zeenny, 2014 | Y | N | N | NA | NA | Y | Y | High | Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring, may cause recall bias. |
| 2 | Sorensen et al, 2006 | Y | Y | N, risk factors related to patient not studied | Y | NA | NA | Y | Y | High |
| 3 | Vuong and Marriott, 2006 | U | Y | N | Y | NA | NA | N | Y | Y | High | Unclear sampling strategy. |
| 4 | Adams et al, 2009 | Y | Y | Y (but for all types 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. |
| 5 | Gandhi et al, 2010 | U | Y | N | Y | Y | NA | NA | Y | Y | High |
| 6 | Lu and Roughead, 2011 | Y | Y | Y (subjective patient-reported medication error) | N | NA | NA | (secondary analysis) | N | (telephone survey, self-reported) | Y | High | Risk of recall bias with patient-reported medication error. |
| 7 | Sears et al, 2012 | Y | Y | Y (subjective self-reported medication error) | N | NA | NA | (secondary analysis) | N | (telephone survey, self-reported) | Y | High | Risk of recall bias with patient self-reported medication error. |
| 8 | Koper et al, 2013 | N (convenience) | Y | N | Y | NA | NA | N (100% participants) | Y | Y | High | Selection bias. |
| 9 | Dallenbach et al, 2007 | N (consecutive) | N | N | Y | NA | NA | NA (retrospective) | Y | Y | Moderate |
| 10 | Indermette et al, 2007 | Y (pharmacy choose); N (first 12 customers) | Y | N | Y | NA | NA | Y | Y | High |
| 11 | Mahmood et al, 2007 | 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 et al, 2015 | Y | Y | Y (but for both own home and care home) | Y | Y | NA | (secondary analysis) | Y | Y | High | Risk factors for both own home and care home. |
| 13 | de Oliveira Martins et al, 2006 | N (first came to pharmacy carrying prescription for two 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 et al, 2006 | Y | Y | Y | NA | NA | NA (secondary data analysis) | Y | Y | Y | High | May underestimate the exposure because they do not account for OTC. |
| 15 | Saab et al, 2006 | Y | Y | Y | NA | NA | N | Y | Y | Y | High | Self-reported data from elderly concerning drug use may decrease accuracy. |

Continued
### Table 2A Continued

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Overall appraised |
|---|---|---|---|---|---|---|---|---|------------------|
| 16 | Bregnhøj et al., 2007<sup>46</sup> Elderly-PIM | N (each GP was asked to recruit six patients who were randomly selected) | Y | N | Y | NA | NA | Y | Y | High | Selection bias. |
| 17 | Johnell and Fastbom, 2008<sup>47</sup> Elderly-PIM | Y | Y | Y | Y | NA | Y | Y | Y | High | Did not look for comorbidity as a risk factor because data were from Swedish Prescribing Drug Register. |
| 18 | Haider et al., 2009<sup>39</sup> Elderly-PIM | Y | Y | Y | Y | NA | NA | NA | Y | Y | High |
| 19 | Lai et al., 2009<sup>48</sup> Elderly-PIM | Y | Y | Y | Y | NA | NA | NA | Y | Y | High |
| 20 | Ryan et al., 2009<sup>49</sup> Elderly-PIM | Y | Y | Y | Y | NA | NA | N | Y | Y | High |
| 21 | Zaveri et al., 2010<sup>50</sup> Elderly-PIM | U | Y | Y | Y | NA | NA | N | Y | Y | High |
| 22 | Leikola et al., 2011<sup>51</sup> Elderly-PIM | Y | Y | N | Y | NA | NA | NA | Y | Y | High |
| 23 | Lin et al., 2011<sup>52</sup> Elderly-PIM | U | Y | Y | Y | NA | NA | NA | Y | Y | High |
| 24 | Weetel et al., 2011<sup>53</sup> Elderly-PIM | Y | Y | Y | Y | NA | NA | NA | Y | Y | High |
| 25 | Haasum et al., 2012<sup>54</sup> Elderly-PIM | Y | Y | N | Y | Y | NA | NA | Y | Y | High |
| 26 | Nyborg et al., 2012<sup>55</sup> Elderly-PIM | Y | Y | Y | Y | NA | NA | NA | Y | Y | High |
| 27 | Yasein et al., 2012<sup>56</sup> Elderly-PIM | N | Y | N | Y | Y | NA | N | Y | Y | Moderate |
| 28 | Candela Marroquín et al., 2012<sup>57</sup> Elderly-PIM | N (convenience sample) | Y | N | Y | NA | NA | N | Y | Y | Moderate |
| 29 | Weng et al., 2013<sup>58</sup> Elderly-PIM | Y | Y | Y | Y | NA | N | Y | Y | High |
| 30 | Baldoni et al., 2014<sup>59</sup> Elderly-PIM | U | Y | Y | Y | Y | NA | Y | Y | Y | High |

Moderate Sampling strategy. Subjective information on socioeconomic and clinical variables may decrease accuracy.

High Sampling strategy.
### Table 2A Continued

|   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Overall appraised |
|---|---|---|---|---|---|---|---|---|---|------------------|
| 31 | Castillo-Páramo et al., 2014<sup>31</sup> | Y | Y | Y | Y | NA | Y | Y | Y | High |
|   | Elderly-PIM | | | | | | | | | Electronic health record use limitations (incomplete record and quality of data). |
| 32 | Vezmar Kovacevic et al., 2014<sup>32</sup> | Y | Y | Y | Y | NA | N | Y | Y | High |
| 33 | Nobili et al., 2009<sup>33</sup> | Y | Y | Y | Y | NA | NA | NA | Y | High |
|   | (administrative database) | | | | | | | | | The use of administrative database limits looking for comorbidity as a confounder. |
| 34 | Secoli et al., 2010<sup>34</sup> | U | Y | Y | Y | NA | NA | NA | Y | High |
|   | Elderly-DDI | | | | | | | | | May underestimate the true DDI prevalence because they do not account for OTC. |
| 35 | Obrelli Neto et al., 2012<sup>35</sup> | Y | Y | Y | Y | NA | NA | NA | Y | High |
|   | (data from primary healthcare system) | | | | | | | | | May underestimate 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 et al., 2008<sup>36</sup> | Y | Y | Y | Y | NA | NA | Y | Y | High |
| 37 | Tulner et al., 2009<sup>37</sup> | Y | Y | Y | Y | NA | NA | Y | Y | High |
|   | (consecutive) | | | | | | | | | Information on medication described by the patient and caregivers may not always be accurate. |
| 38 | Obrelli Neto et al., 2011<sup>38</sup> | Y | Y | N | Y | NA | NA | NA | Y | High |
| 39 | Mira et al., 2013<sup>39</sup> | Y | Y | Y | Y | NA | NA | Y | Y | High |
|   | Elderly-DDI | | | | | | | | | Self-reported medication error from elderly concerning drug use may have recall bias. |
| 40 | Mand et al., 2014<sup>40</sup> | Y | Y | Y | Y | NA | NA | NA | Y | High |

1 Was study based on a random or pseudo-random sample?  
2 Were the criteria for inclusion in the sample clearly defined?  
3 Were confounding factors identified and strategies to deal with them stated?  
4 Were outcomes assessed using objective criteria?  
5 If comparisons are being made, was there sufficient descriptions of the groups?  
6 Was follow-up carried out over a sufficient time period?  
7 Were the outcomes of people who withdrew described and included in the analysis?  
8 Were outcomes measured in a reliable way?  
9 Was appropriate statistical analysis used?  

DDI, drug-drug interaction; GP, general practitioner; N, no; NA, not applicable; OTC, over-the-counter; PIM, potentially inappropriate medication; U, unclear; Y, yes.
### Table 2B: Systematic review quality assessment: Critical Appraisal Skills Programme for cohort study

| 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 |
|---------------------|-----------|----------------|----|----|----|----|------|------|------|------|----|----|----|----|----|-------|----------------|
|                     |           |                | 1  | 2  | 3  | 4  | 5(a) | 5(b) | 6(a) | 6(b) | 7  | 8  | 9  | 10 | 11 | 12 |                  |
| 1 Maio et al., 2006  | Y Y Y Y Y  | Y, age, gender, geographical location, number of medication, number of chronic condition and income None | N  | Y  | Y (1year) retrospective | PIM prevalence: 18%. Older age, polypharmacy and greater number of chronic conditions were significant predictors of PIM use. | P<0.05, 95% CI | Y  | Y  | Y – | Moderate |
|                     | 2006      | PIM            |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| 2 Zuckerman et al., 2006 | Y Y Y Y Y  | Y, but used for irrelevant outcome - | Y  | Y  | Y (2years) | Inappropriate medication use prevalence: 41.9% | P=0.01, 99%CI | Y  | Cannot tell (generalisability) | Y | Limited information from the database. Confounding factors were for the nursing home admission rather than for PIM. | Moderate |
|                     | 2006      | PIM            |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| 3 Field et al., 2007  | Y Y Y Y Y  | Y, age, gender, comorbidity, number of medications None | Y  | Y  | Y (1year) | ADE resulting from patients' error prevalence: 0.38% | P<0.05 | Y  | Y  | Y | Possible drug-related incidence for which necessary information was not documented in the medical record was not considered. | High |
|                     | 2007      | Elderly        |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| 4 Gagne et al., 2008  | Y Y Y Y Y  | Y, age, gender, geographical location, comorbidity, number of medication prescribed None | Y  | Y  | Y (1year) | 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 is for all age groups. | High |
|                     | 2008      | DDI            |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| 5 Berdot et al., 2009 | Y Y Y Y Y  | Y, but for irrelevant outcome - | Y  | Y  | Y (4years) | PMI prevalence: 31.6% | 95% CI, p<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 |
|                     | 2009      | Elderly-PIM    |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| 6 Lapi et al., 2009   | Y Y Y Y Y  | Y, comorbidity, polypharmacy, stroke, heart failure Age, gender | Y  | Y  | Y (1year) | 1999: IP prevalence: 5.1%. Potential DDI prevalence: 30.5%. Potential major DDI: 5.6% Polypharmacy was a predictor of PIM use. | P<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 reflects US drug market. | Moderate |
|                     | 2009      | Elderly-PIM    |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| 7 Ryan et al., 2009   | Y Y Y N N   | Cannot tell Y (6months) | Y  | Y  | Cannot tell | Medicine prescribed inappropriately. Beers 2003: 13% IPET: 10.4% | Cannot tell | Y  | Y  | Y – | Low |
|                     | 2009      | Elderly-PIM    |     |    |    |    |      |      |      |      |    |    |    |    |    |       |                  |
| Study design: cohort | Reference | Quality domains | Overall quality |
|----------------------|-----------|----------------|----------------|
|                      | 1 2 3 4 5(a) 5(b) 6(a) 6(b) 7 8 9 10 11 12 | | |
| 8 Akazawa et al, 2010 Elderly-PIM | Y Y Y Y | 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<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 et al, 2011 Elderly-PIM | Y Y Y | Y Y Y (2 years) | PIM prevalence: 30.9%. Patients 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 et al, 2011 Elderly-PIM | Y Y Y | Y Y Y (12, 24 weeks) | PIM: 24%–73% Number of chronic drugs and number of chronic conditions were a common risk factor in all criteria. | P<0.05 Y Y | Y May underestimate the prevalence because several drugs in Taiwan were not available in the sex criteria. | High |
| 11 Zhang et al, 2011 Elderly-PIM | Y Y Y | Y Cannot tell | Prevalence of PIM was from 13.84% (95% CI 12.52 to 15.17) to 21.3% (95% CI 19.5 to 23.1). | 95% CI, p<0.05 Y Y | Y Recall bias due to self-reported survey. Did not assess DDI and underuse so may underestimate the prevalence. | Moderate |
| 12 Cornu et al, 2012 Elderly | Y Y Y | Y Y (from admission to discharge) | Almost half of these patients (47.6% [95% CI 40.5 to 54.7]) had one or more discrepancies in medication information at discharge. | 95% CI, p<0.05 Y | Y Cannot tell | Moderate |
| Study design: cohort | Reference | Quality domains | Overall quality |
|---------------------|-----------|----------------|----------------|
|                     |           | 1 2 3 4 5(a) Y 5(b) 6(a) 6(b) 7 | 8 9 10 11 12 |  |
|                     |           | Y Y Y Y, health literacy | Y Y Y (3 and 12 months) | P<0.05 | Y Cannot tell | Y Results may be biased due to sampling strategy. | Moderate |
| 13 Mosher et al., 2012 | Elderly | Y Y Y Y | 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. |  |
| 14 Obreli-Neto et al., 2012 | DDI | Y Y Y Y | Incidence of DDI-related ADR (6.9%) | 95% CI, p<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 Blozik et al., 2013 | Adult | Y Y Y Y, gender | Y Y Y (3 years) | Prevalence of PIM: 21.1% 95% CI | Y Y | Y – | High |
| 16 Cahir et al., 2014 | Elderly-PIM | Y Y Y Y, age, gender, socioeconomic status, private health insurance, comorbidity, number of repeat drug, social support and network, adherence | 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 et al., 2013 | Elderly-PIM | Y Y Y Y, gender age, number of medications, number of disease, depression, education | Y Y Y (4.5 years) | At baseline PIM prevalence is 29% (848) according to the PRISCUS list, which decreased to 25.0% (464) 4.5 years later and 21% according to the Beers list decreasing after 4.5 years to 17.1% (317). 95% CI, p<0.05, OR and CI for risk factors | Y Y | Y – | High |  |
| Reference | Study design: cohort | Quality domains | Overall quality |
|-----------|----------------------|-----------------|-----------------|
| Amos et al, 2015 | Y Y Y Y Y age, gender, geographical 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<0.05 | Y Cannot tell Y May underestimate the true PIM prevalence because they do not account for OTC. Moderate |
| Hedna et al, 2015 | Y Y Y Y N age, 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<0.05 | Y Cannot tell Y Undetected confounders Moderate |
| Moriarty et al, 2015 | 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 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. 95% CI | Y Y Y Lack of information on OTC from the pharmacy claim data. High |

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?

ADE, adverse drug event; ADR, adverse drug reaction; ATC, Anatomical Therapeutic Chemical; DDI, drug–drug interaction; ED, emergency department; IP, inappropriate prescribing; IPET, improved prescribing in the elderly tool; N, no; OTC, over-the-counter; PIM, potentially inappropriate medication; PPO, potential prescribing omission; U, unclear; Y, yes.
Person’s Prescriptions criteria. Johnell and Fastbom and Haider et al mentioned two other specific criteria. B. The prevalence of potential prescribing omission (PPO) was measured in five studies for the elderly age group only (≥65 years), ranging from 23% to 57%. PPO was detected by the Screening Tool to Alert doctors to Right Treatment and Assessing Care of Vulnerable Elders.

Dosing errors
Koper et al found that overdosing and/or underdosing was found in 44% of patients.

Monitoring errors
Monitoring errors were measured in one study by Ramia and Zeenny, who found that 73% of patients had incomplete therapeutic/safety laboratory-test monitoring tests.

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

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% to 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. 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, of which 18 mentioned the estimated OR ranging from 1.06 to 11.45. Older age (≥75 years) was associated with medication errors in 13 studies, of which 10 mentioned the OR ranging from 1.02 to 4.03.

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 specialty, 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).

Figure 2: Medication errors prevalence estimates according to settings.
### Table 3: Medication errors patient-related risk factors

| Risk factor                       | Studies with positive association (n) | Controlled studies (n) | Controlled for                                                                 | Specific information                  | OR or RR (95% or 99% CI) | p values |
|-----------------------------------|--------------------------------------|------------------------|--------------------------------------------------------------------------------|---------------------------------------|--------------------------|----------|
| 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 to 1.023) | p<0.001  |
|                                  |                                      |                        | Adjusted for age, sex, number of regular medicines and diagnosed chronic condition | Older age                             | OR 1.03 (95% CI 1.02 to 1.04) | p<0.05   |
|                                  |                                      |                        | NA                                                                              | Older age                             | OR 1.05 (95% CI 1 to 1.09)     | p=0.046    |
|                                  |                                      |                        | NA                                                                              | ≥75 years                             | OR 1.10 (95% CI 1.05 to 1.15) | p<0.001  |
|                                  |                                      |                        | NA                                                                              | ≥85 years                             | OR 1.18 (95% CI 1.16 to 1.20) | p<0.05   |
|                                  |                                      |                        | Adjusted for sex, age and number of chronic drugs                             | ≥85 years                             | OR 1.52 (95% CI 1.46 to 1.6)  | p<0.05    |
|                                  |                                      |                        | NA                                                                              | ≥85 years                             | OR 1.53 (95% CI 1.5 to 1.55) | p<0.01    |
|                                  |                                      |                        | NA                                                                              | ≥85 years                             | OR 1.79 (95% CI 1.19 to 2.83) | p=0.009   |
| 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 to 1.56) | p<0.05   |
|                                  |                                      |                        | NA                                                                              | CCDG score ≥4                         | OR 1.76 (95% CI 1.72 to 1.81) | p<0.05   |
|                                  |                                      |                        | Adjusted for age and sex                                                       | Diagnosed disease ≥3                  | OR 6.43 (95% CI 3.25 to 12.44) | p<0.001  |
| CCI                              | 3 (52, 55, 69)                        | 1                      | NA                                                                              | CCI <2                                | RR 2.885 (95% CI 1.972 to 4.22) | p<0.05   |
| Female gender                    | 10 (33, 35, 47, 52, 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 to 1.5) | p<0.05   |
|                                  |                                      |                        | Adjusted                                                                           |                                      | OR 1.6 (99% CI 1.58 to 1.64)   | p<0.05   |
|                                  |                                      |                        | Adjusted for age, sex, education level, partnership, per capita income and occupation |                                      | Beers 2003: OR 2.5 (95% CI 1.9 to 3.5) |        |
|                                  |                                      |                        | Adjusted for sex and age                                                          |                                      | Beers 2012: OR 1.8 (95% CI 1.3 to 2.5) |        |
| 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 to 1.17) | p<0.05   |
| Hospital admission               | 2 (26, 56)                            | 1                      | NA                                                                              |                                      | OR 3.35 (95% CI 2.43 to 4.62) | p<0.05   |
| Middle family income             | 1 (62)                                | NA                     | NA                                                                              |                                      |                          |  

Continued
| Risk factor                                      | Studies with positive association (n) | Controlled studies (n) | Controlled for                                                                 | Specific information                                                                 | OR or RR (95% or 99% CI) p values |
|------------------------------------------------|--------------------------------------|------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------|
| 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                                         | PIM: OR 1.2 (95% CI 1.17 to 1.24) p<0.05                                             | NA                                |
|                                                |                                      |                        | Higher number of prescribed medications                                         | PPO: OR 1.04 (95% CI 1.01 to 1.07) p<0.05                                           | NA                                |
|                                                |                                      |                        | ≥4 medications                                                                 | OR 1.91 (95% CI 1.83 to 2.0) p<0.00                                                 | NA                                |
|                                                |                                      |                        | Higher number of prescribed medications                                         | OR 1.99 (95% CI 1.80 to 2.18) p=0.00                                                  | NA                                |
|                                                |                                      |                        | ≥5 medications                                                                 | Beers 2003: OR 2.9 (95% CI 2.1 to 3.8)                                               | NA                                |
|                                                |                                      |                        | ≥5 medications                                                                 | Beers 2012: OR 2.7 (95% CI 2 to 3.8)                                                 | NA                                |
|                                                |                                      |                        | ≥3 medications                                                                 | OR 3.21 (95% CI 2.78 to 3.59) p<0.00                                                 | NA                                |
|                                                |                                      |                        | ≥5 medications                                                                 | OR 3.22 (95% CI 1.40 to 7.42) p=0.00                                                  | NA                                |
|                                                |                                      |                        | ≥6 medications                                                                 | OR 3.37 (95% CI 2.08 to 5.48) p<0.00                                                 | NA                                |
|                                                |                                      |                        | ≥7 medications                                                                 | OR 4.528 (95% CI 4.52 to 4.54) p<0.00                                                 | NA                                |
|                                                |                                      |                        | ≥5 medications                                                                 | OR 5.4 (95% CI 3 to 9.7) p=0.00                                                      | NA                                |
|                                                |                                      |                        | ≥6 medications                                                                 | OR 5.59 (95% CI 5.39 to 5.80)                                                       | NA                                |
|                                                |                                      |                        | ≥5 medications                                                                 | OR 5.69 (95% CI 5.0 to 6.48) p<0.05                                                 | NA                                |
|                                                |                                      |                        | ≥6 medications                                                                 | STOPP: RR 6.837 (95% CI 4.155 to 11.247) START: RR 2.051 (95% CI 1.25 to 3.367)     | NA                                |
|                                                |                                      |                        | ≥10 medications                                                               | OR 7.33 (95% CI 7.15 to 7.51) p<0.05                                                 | NA                                |
|                                                |                                      |                        | ≥9 medications                                                                 | OR 7.43 (95% CI 3.20 to 17.23) p<0.00                                                 | NA                                |
|                                                |                                      |                        | ≥10 medications                                                               | Male: OR 8.2 (95% CI 8 to 8.4) Female: OR 9.6 (95% CI 8.2 to 11.2)                   | NA                                |
|                                                |                                      |                        | ≥10 medications                                                               | OR 11.45 (95% CI 11.2 to 11.7) p<0.01                                                 | NA                                |
Table 4  Medication errors healthcare professional-related risk factors

| Risk factor | Studies with positive association (n) | Controlled studies (n) | Adjusted for | OR or RR or beta (95% or 99% CI) p values |
|-------------|--------------------------------------|------------------------|--------------|------------------------------------------|
| Age ≥51 years | 2 (53, 71) | 2 | NA | OR 1.03 (95% CI 1.01 to 1.06) p<0.0167 |
| | | | | OR 1.238 (95% CI 1.235 to 1.242) p<0.001 |
| More than one physician involved in their care | 5 (22, 33, 64, 77, 78) | 3 | NA | Beta 0.7 (95% CI 0.5 to 1.0) p=0.034 |
| | | | Adjusted for age, sex, number of chronic conditions and number or drug consumed | OR 1.39 (95% CI 1.17 to 1.67) p<0.001 |
| | | | Adjusted for age and number of prescriber | OR 3.52 (99% CI 3.44 to 3.60) |
| Male general practitioner | 2 (53, 71) | 2 | NA | OR 1.07 (95% CI 1.05 to 1.10) p<0.0167 |
| | | | | OR 1.267 (95% CI 1.265 to 1.269) p<0.001 |
| Frequent changes in prescription | 1 (77) | 1 | NA | Beta 0.4 (95% CI 0.2 to 0.9) p=0.0173 |
| Not considering the prescription of other physicians | 1 (77) | 1 | NA | Beta 1.9 (95% CI 1.1 to 3.2) p=0.013 |
| Inconsistency in the information | 1 (77) | 1 | NA | Beta 4.4 (95% CI 1.3 to 14.8) p=0.013 |
| Outpatient clinic visit | 1 (46) | 1 | NA | 1.4 (male 95% CI 1.3 to 1.4) (female 95% CI 1.3 to 1.6) |
| Family medicine/general practice specialty | 3 (53, 56, 71) | 3 | NA | OR 1.06 (95% CI 1.03 to 1.10) p<0.0167 |
| | | | | OR 1.267 (95% CI 1.265 to 1.269) p<0.001 |
| | | | | OR 1.46 (95% CI 1.28 to 1.65) p<0.05 |

CI, Charlson Comorbidity Index; IP, inappropriate prescribing; NA, not applicable; PIM, potentially inappropriate medication; PPO, potential prescribing omission; START, Screening Tool to Alert doctors to Right Treatment; STOPP, Screening Tool of Older Person’s Prescriptions.

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, no medication administration routine, poor adherence and patients confused by generic and trade names. In one study by Johnell and Fastbom, multidose drug dispensing users (ie, medicines machine-packed into unit-dose bags for each time of administration) were more exposed to all indicators of potentially inappropriate drug.

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

The use of OTC and/or prescribed drugs was a risk factor in two additional studies. 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 to 3.6) using Beers 2003 and 1.8 (95% CI 1.2 to 2.5) using Beers 2012.

ERROR-RELATED ADVERSE EVENTS
Error-related adverse events or preventable ADEs were mentioned in six studies. The most frequently reported consequences were ED visits and hospitalisation.

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

Incidence and/or prevalence
One study estimated preventable ADE incidence as 15/1000 person-years. ACE inhibitors and beta-blockers
were the most common medications associated with preventable ADE. The estimate of the prevalence of preventable ADE was calculated from five studies as detailed below.  

All stages of medicines’ management process
Field et al found the prevalence of error caused by patients leading to an adverse event to be 0.38%, that is, less than 1% of the overall population experienced a medication-related adverse event. They 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%). The medications associated with more than 10 preventable ADEs were anti-coagulants/antiplatelets, cardiovascular drugs, diuretics, hypoglycaemics and non-opioid analgesics.

ERROR-RELATED ADVERSE EVENTS ACCORDING TO MEDICINES’ MANAGEMENT PROCESS
Prescribing errors
Drug–drug interaction
Obreli-Neto et al found that DDI-related adverse drug reaction (ADR) occurred in 7% of patients. Warfarin, digoxin, spironolactone and acetylsalicylic acid were the drugs most commonly associated with DDI-related ADRs.

Potentially inappropriate medication
Forty-six per cent of participants reported complaints related to ADEs by interview; 95% of these were caused by prescribed medications.

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.

Other errors
Adverse events (undertreatment 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. Two discrepancies were categorised as having the potential to cause severe patient harm.

RISK FACTORS
Risk factors for the error-related adverse events were discussed in three studies only.

Patient-related risk factors
Field et al found that the number of regularly scheduled medications (seven or more medications) (OR 3.3, 95% CI 1.5 to 7.0) and a Charlson Comorbidity Index (CCI) score of 5 or more (OR 15.0, 95% CI 6.5 to 34.5) were both associated with higher risk of patient error leading to preventable ADE. Obreli-Neto et al found that an age of 80 years or more (OR 4.4, 95% CI 3.0 to 6.1, p<0.01), a CCI of 4 or more (OR 1.3, 95% CI 1.1 to 1.8, p<0.01) and consumption of five or more medications (OR 2.7, 95% CI 1.9 to 3.1, p<0.01) were associated with the occurrence of DDI-related ADRs. In addition, Tullner et al found that the number of medications was significantly positively correlated with medication discrepancy adverse patient events.

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

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 (ie, 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. 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 strength of this systematic review is 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, 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. First, 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. Second, no data were found regarding the administration error stage. However, 14 studies on administration errors were also excluded for the same previous reason. Third, this systematic review had different outcomes reported in a variety of ways using different tools and methodology, which 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. 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.

Implications for research, policy and practice
There is a need for (1) 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; (2) training and monitoring of healthcare professionals with the involvement of medication safety pharmacists in the community; (3) 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; (4) patient use of tools and technology particularly for monitoring and follow-up; and (5) encourage the reporting of medication errors, administration errors and dispensing errors. 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, that is, 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-income and middle-income countries, particularly give the WHO’s recent launch of a Global Medication Safety Challenge. 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 factor 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 ADEs 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 *BMJ Open* on 31 August 2016 and is registered with PROSPERO, an international prospective register of systematic reviews. It is reported using PRISMA. Trial registration number: CRD42016048126.

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

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